SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME
Diethylbenzene-rich Streams

Mixed Diethylbenzenes **(CAS No. 25340-17-4)**
[9th CI Name: Benzene, diethyl-]

Polyethylbenzenes **(CAS No. 68608-82-2)**
[9th CI Name: Benzene, ethylenated, by-products from]

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INTERIM

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program[1] is 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 sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do 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 1,400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website[3].

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to "bin" chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance[2,4] and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA[2] and OECD[5] guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT's existing chemicals review process. These hazard characterizations are technical documents intended to support 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. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations[4,6]. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

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[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. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[4] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[5] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[6] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

SCREENING-LEVEL HAZARD CHARACTERIZATION
Diethylbenzene-Rich Streams Category

Introduction

The sponsor, the American Chemistry Council Ethylbenzene Panel HPV Task Group, submitted a Test Plan and Robust Summaries to EPA for the Diethylbenzene-Rich Streams Category on October 26, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 12, 2001 (http://www.epa.gov/chemrtk/pubs/summaries/diethbnz/c13272tc.htm). EPA comments on the original submission were posted to the website on July 17, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on October 3, 2002 and May 3, 2004 which were posted to the ChemRTK HPV Challenge website on October 17, 2002 and August 26, 2004. The diethylbenzene-rich streams category consists of the following chemicals:

Mixed diethylbenzenes (diethylbenzenes) [9th CI name: Benzene, diethyl-)]	(CAS No. 25340-17-4)
Polyethylbenzenes (by-products from ethylenated benzene) [9th CI name: benzene, ethylenated, by-products from]	(CAS No. 68608-82-2)

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor 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. The composition of the two category members and structures of predominant constituent chemicals are presented in the Appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Category Justification

The diethylbenzene-rich streams category consists of two streams produced during ethylbenzene manufacture that contain predominantly diethylbenzene isomers (87.6 – 98.8 wt %). Ethylbenzene is produced through alkylation of benzene with ethylene. In addition to the production of ethylbenzene, there are side reactions of ethylene with ethylbenzene to produce diethylbenzene, and, to a much lesser extent, further alkylations to produce triethylbenzene and polyethylbenzene. After the ethylbenzene is removed, the remaining stream is separated into a diethylbenzene-rich stream and a bottoms stream. Diethylbenzene-rich streams may be further processed to increase the diethylbenzene content. The composition for both diethylbenzene-rich streams (CAS Nos. 25340-17-4 and 68608-82-2) is very similar (see Appendix) and therefore, the two mixtures can be evaluated in a single category.

For physical-chemical properties and aquatic toxicity testing conducted under the HPV program, equal quantities of the streams from each of the three current manufacturers were combined to form a representative test sample of diethylbenzene-rich streams (diethylbenzene blend).

Supporting Chemical Justification

The constituent chemicals 1,2-diethylbenzene, 1,3-diethylbenzene and 1,4-diethylbenzene were used as supporting evidence for several endpoints. These constituents are suitable supporting chemicals because diethylbenzenes comprise a large portion of the category members' composition. Estimations from these three compounds are used as read across to the category members (represented by the diethylbenzene blend) for the octanol-water partition coefficient and indirect photodegradation. The constituents also provide support for other physical-chemical properties. For human health endpoints, 1,4-diethylbenzene and 1,2-diethylbenzene support reproductive and developmental toxicity conclusions, respectively.

Summary-Conclusion

The Log K_{ow} values of constituent chemicals in the diethylbenzene-rich streams category indicate that their potential to bioaccumulate is expected to be high. Mixed diethylbenzenes is not readily biodegradable, indicating that the category members have the potential to persist in the environment.

The evaluation of available toxicity data indicates that the potential acute hazard of diethylbenzene-rich streams category members to fish is high and to aquatic invertebrates and aquatic plants is moderate.

Acute oral toxicity of diethylbenzene-rich streams category members to rats and acute dermal toxicity to rabbits and rats is low. Mixed diethylbenzenes are irritating to rabbit skin and eyes. Repeated exposures to these category chemicals via inhalation resulted in decreased mean body weights at high concentrations and decreased total white cell and lymphocyte counts. In a repeated-exposure study, no effects were seen on reproductive organs (ovaries, pituitary, prostate, seminal vesicles, testes with epididymides and uterus (corpus and cervix)) except for an abnormal blue-gray color of the tissues/organs in the high exposure group. In a developmental toxicity study with mixed diethylbenzene and the constituent chemical, 1,2-diethylbenzene, maternal toxicity was evidenced by reduced mean body weight gains and reduced food consumption. Greenish-blue discoloration of the amniotic sac was observed in the study with mixed diethylbenzenes. Mean fetal body weights were lower than the control group; however, there were no malformations or skeletal variations. Mixed diethylbenzenes did not induce gene mutation or chromosomal aberrations. Mixed and individual diethylbenzenes showed evidence of neurotoxicity when administered via oral and inhalation routes of administration. In a minimally documented test, mixed diethylbenzenes showed carcinogenic potential in mice administered via dermal route of administration.

The potential health hazard of chemicals in the diethylbenzene-rich streams category is moderate based on repeated-dose and developmental toxicity. Available data indicate that diethylbenzenes show evidence of neurotoxicity.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in Table 1. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indictors of bioaccumulation and persistence, respectively. Physical-chemical and environmental fate properties are available for the diethylbenzene blend, which represents both category members.

Octanol-water Partition Coefficient

The octanol/water partition coefficient of the streams was not evaluated because it was technically infeasible. The octanol/water partition coefficient values for the constituent isomers (1,2-diethylbenzene, 1,3-diethylbenzene and 1,4-diethylbenzene) were used as supporting data.

1,2-Diethylbenzene (CAS No. 135-01-3, supporting chemical)
Log K_{ow}: 3.72 (estimated)

1,3-Diethylbenzene (CAS No. 141-93-5, supporting chemical)
Log K_{ow}: 4.44 (estimated)

1,4-Diethylbenzene (CAS No. 105-05-5, supporting chemical)
Log K_{ow}: 4.45 (estimated)

Biodegradation

Mixed Diethylbenzenes (CAS No.25340-17-4)
In an aerobic CO_2 evolution test using activated sludge as inoculum, 4.7% of mixed diethylbenzenes had degraded after 28 days.
Mixed Diethylbenzenes is not readily biodegradable.

Conclusion: The Log K_{ow} values of constituent chemicals in the diethylbenzene-rich streams category indicate that their potential to bioaccumulate is expected to be high. Mixed diethylbenzenes are not readily biodegradable, indicating that the category members have the potential to persist in the environment.

Table 1. Summary of Physical-Chemical Properties and Environmental Fate Data

Endpoints	**Diethylbenzene Blend [1]**	**1,2-Diethylbenzene, supporting chemical (CAS No. 135-01-3)**	**1,3-Diethylbenzene, supporting chemical (CAS No. 141-93-5)**	**1,4-Diethylbenzene, supporting chemical (CAS No. 105-05-5)**
Melting Point (ºC)	**< -75 (m)**	**-31.2 (m)**	**-83.9 (m)**	**-42.83 (m)**
Boiling Point (ºC)	**180.8 (m)**	**184 (m)**	**181.1 (m)**	**183.7 (m)**
Vapor Pressure (hPa)	**3.1 (m) @ 20°C**	**1.40 (m)**	**1.60 (m)**	**1.37 (m)**
Log K_{ow}	3.72 – 4.45 (RA)	3.72 (e)	4.44[2]	4.45[2]
Water Solubility (mg/L)	**15.7 (m) @ 20°C**	**71.1 (m)**	**24.0 (m)**	**24.8 (m)**
Direct Photodegradation (cm^3/molecule-sec)	Will not undergo direct photolysis	—*	—*	—*
Indirect (OH^-) Photodegradation $t_{1/2}$ (h)	9.0 – 15.8 (RA)	15.8 (e)	9.0 (e)	15.8 (e)
Stability in Water (Hydrolysis)	Unlikely to hydrolyze	Unlikely to hydrolyze	Unlikely to hydrolyze	**> 5 days at 50 ºC (m)**
Fugacity (Level III Model) **Air (%)** **Water (%)** **Soil (%)** **Sediment (%)**	—	 1.14 51.4 45.5 1.9	 0.54 31.2 61.7 6.6	 0.56 31.0 61.8 6.7
Biodegradation at 28 days (%)	**4.7 (m) Not Readily Biodegradable**	—*	—*	—*

(m) = measured data (i.e. derived from experiment); (e) = estimated data (i.e. derived from modeling); — indicates endpoint was not addressed for this chemical; *indicates data is not necessary for supporting chemical; [1]Equal portions of 3 commercial producers' mixed diethylbenzene products; all measured data were tested using this diethylbenzene blend except the biodegradation endpoint, which was tested using one company's mixed diethylbenzene stream (CAS No. 25340-17-4). [2]Unclear whether endpoint was measured or estimated

2. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. Data are available for the diethylbenzene blend, which represents both category members.

Acute Toxicity to Fish

Diethylbenzene Blend
Rainbow trout (*Oncorhynchus mykiss*) were exposed to diethylbenzene blend at nominal concentrations of 0 (control), 0 (vehicle control; 0.1mL/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 LC_{50} was based on mean measured concentrations.
96-h LC_{50} = 0.673 mg/L

Acute Toxicity to Aquatic Invertebrates

Diethylbenzene Blend
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 EC_{50} was based on mean measured concentrations.
48-h EC_{50} = 2.01 mg/L

Toxicity to Aquatic Plants

Diethylbenzene Blend
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 EC_{50} (growth) = 1.21 mg/L
72-hr EC_{50} (biomass) = 1.00 mg/L

Conclusion: The evaluation of available toxicity data indicates that the potential acute hazard of diethylbenzene-rich streams category members to fish is high and to aquatic invertebrates and aquatic plants is moderate.

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	Diethylbenzene Blend [1]
Fish **96-h LC_{50} (mg/L)**	**0.673 (m)**
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	**2.01 (m)**
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)** **(biomass)**	 **1.21 (m)** **1.00 (m)**

(m) = measured data (i.e. derived from testing)
[1]Equal portions of 3 commercial producers' mixed diethylbenzene products

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

Mixed Diethylbenzenes (CAS No.25340-17-4)
(1) Sprague-Dawley rats (5/sex/dose) were administered mixed diethylbenzenes via gavage at 1700, 2500, 3500 and 5000 mg/kg-bw and observed for 14 days. Signs of toxicity include hypoactivity, red nasal discharge, urinary staining, partially closed eyes, prostration and decreased food consumption, ataxia, tremors, clear nasal and oral discharge, wet rales, soft stool, fecal staining, abdominal griping, blue pigmentation and hypothermia. Necropsy of decedents showed blue pigmentation of all/most soft tissues and/or blue fluid in the gastrointestinal tract and urinary bladder, irritation or corrosive effects in the stomach, intestine and urinary bladder.
LD_{50} = 2050 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered mixed diethylbenzenes via gavage at 3400, 4300, 5000 and 7700 mg/kg-bw and observed for 14 days. Signs of toxicity included awkward gait, splayed fore- and hind-limbs and tremors. All animals showed reductions in spontaneous motor activity, abnormal righting reflexes, decreases in responsiveness to extraneous sensory stimuli; some were found comatose or unable to maintain normal posture, reductions in the rate and depth of breathing, red nasal discharge, ocular and anogenital discharge, diarrhea, reduced pupil response, mydriasis, lacrimation, partial palpebral closure, cyanosis and green urine. At necropsy, dark fluid was found in the bladders of some animals treated with > 3400mg/kg-bw.
LD_{50} (males) = 6900 mg/kg-bw
LD_{50} (females) = 4700 mg/kg-bw

Acute Dermal Toxicity

Mixed Diethylbenzenes (CAS No.25340-17-4)
(1) New Zealand White rabbits (5/sex/dose) were administered mixed diethylbenzenes dermally at 5000 mg/kg-bw and observed for 14 days. Decreased food consumption was seen in all animals. There were no deaths.
LD_{50} > 5000 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered the test substance dermally at 2000 mg/kg-bw and observed for 14 days. Decreased mean body weight gain was seen in males. Skin irritation consisting of red, swollen and scabbed skin was more persistent and severe in treated animals. There were no deaths.
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

Mixed Diethylbenzenes (CAS No.25340-17-4)
Sprague-Dawley rats (10/sex/concentration) were exposed to mixed diethylbenzenes via inhalation (whole body) at 0, 200, 600 and 1200 mg/m^3 (mean analytical values of 0, 190, 610 and 1400 mg/m^3 or 0, 0.19, 0.61 and 1.4 mg/L) for 6 hours/day, 5 days/week for 8 weeks (isomers) and 10 weeks (mixture). Decreased mean body weights were seen at the high dose throughout the study. Decreases in total white cell and lymphocyte counts were observed in males at 600 and 1200 mg/m^3. Treatment-related changes in serum chemistry parameters included decreases in alanine aminotransferase, aspartate aminotransferase and creatinine phosphokinase activity in females at 1200 mg/m^3, increases in potassium in males at 1200 mg/m^3 and increases in phosphorus in males at 1200 mg/m^3 and females at 600 mg/m^3 and 1200 mg/m^3. An abnormal blue-gray color was observed in sera and in most tissues in most animals at 1200 mg/m^3. At 600 mg/m^3, the same color was observed in brains and urinary bladder of most animals. There were no other gross or microscopic changes attributed to the test substance.
LOAEL = 0.61 mg/L/day (based on effects on hematological parameters)
NOAEL = 0.19 mg/L/day

Reproductive Toxicity

The sponsor did not submit reproductive toxicity data. Evaluation of effects on reproductive organs in the repeated-dose toxicity study and the availability of a developmental toxicity study addressed the reproductive toxicity endpoint for the purposes of the HPV Challenge Program.

Mixed Diethylbenzenes (CAS No.25340-17-4)
In the inhalation repeated-dose study previously described, tissues, including ovaries, pituitary, prostate, seminal vesicles, testes with epididymides, and uterus (corpus and cervix), from the control and high-exposure groups were examined microscopically. At the high concentration (1200mg/m^3), mean body weights were decreased. At 1200mg/m^3, most tissues, including ovaries, pituitary, prostate, seminal vesicles, testes with epididymides and uterus (corpus and cervix) showed an abnormal blue-gray color. No other gross or microscopic changes in the reproductive tissues were attributed to the test substance.

1,4-Diethylbenzene (CAS No. 105-05-5, supporting chemical)
In a combined repeat dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/dose) were administered the supporting chemical, 1,4-diethylbenzene, via gavage at 0, 30, 150 or 750 mg/kg-bw/day. Males were dosed for 44 days, including 14 days before mating and females from 14 days before mating until Day 3 of lactation. Male and female copulation and fertility indices, pregnancy rates, and implantation sites were comparable among groups. The number of live and dead pups, the number of litters with live offspring, the mean litter size and the male-to-female ratio were comparable among the groups on lactation day 0. There were no differences in mean pup weights across groups. No differences were noted in external observations; and no remarkable findings were observed at necropsy in pups found dead prior to lactation day 4. Duration of gestation was slightly, but statistically significantly (p not stated), increased at 750 mg/kg-bw/day and there was a statistically significant (p not stated) decrease in pup survival on day 4 at 750 mg/kg-bw/day. (The investigators did not consider these findings treatment-related.)
NOAEL (systemic toxicity) = 750 mg/kg-bw/day (based on no effects at the highest dose tested)
LOAEL (reproductive toxicity) = 750 mg/kg-bw/day (based on increased duration of gestation and decrease in pup survival on day 4)
NOAEL (reproductive toxicity) = 150 mg/kg-bw/day

Developmental Toxicity

Mixed Diethylbenzenes (CAS No.25340-17-4)
Pregnant Sprague-Dawley rats (25/dose) were administered mixed diethylbenzenes in corn oil via gavage at 0, 20, 100 and 200 mg/kg-bw/day from gestation days 6 – 15. Maternal food consumption and mean body weight gains were reduced at 100 and 200 mg/kg-bw/day. Greenish-blue discoloration of the amniotic sac was also observed at the same doses. Mean fetal body weights were lower than control at 200 mg/kg-bw/day. No treatment-related malformations or developmental variations were observed.
LOAEL (maternal toxicity) = 100 mg/kg-bw/day (based on reduced food consumption and mean body weight gain)
NOAEL (maternal toxicity) = 20 mg/kg-bw/day
LOAEL (developmental toxicity) = 200 mg/kg-bw/day (based on reduced mean fetal body weights)
NOAEL (developmental toxicity) = 100 mg/kg-bw/day

1,2-Diethylbenzene (CAS No. 135-01-3, supporting chemical)
Pregnant Sprague-Dawley rats (25/dose) were administered the supporting chemical, 1,2-diethylbenzene in corn oil via gavage at 5, 15, 25, or 35 mg/kg-bw/day during gestation days 6 – 20. Maternal food consumption and body weight gains were reduced at 15, 25 and 35 mg/kg-bw/day. Mean fetal body weights were lower than control at ≥ 15 mg/kg-bw/day. No treatment-related malformations or developmental variations were observed.
LOAEL (maternal toxicity) = 15 mg/kg-bw/day (based on reduced food consumption and mean body weight gain)
NOAEL (maternal toxicity) = 5 mg/kg-bw/day
LOAEL (developmental toxicity) = 15 mg/kg-bw/day (based on fetal effects of reduced mean body weights)
NOAEL (developmental toxicity) = 5 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
Mixed Diethylbenzenes (CAS No.25340-17-4)
(1) In three separate assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, 1537 and TA1538 and/or *Escherichia coli* WP2 uvrA were exposed to mixed diethylbenzenes at 0.5 – 10 mg/plate in the presence and absence of metabolic activation. Mixed diethylbenzenes did not cause mutations in these bacterial strains.
Mixed Diethylbenzenes was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Mixed Diethylbenzenes (CAS No.25340-17-4)
Chinese Hamster Ovary (CHO) cells were exposed to mixed diethylbenzenes at 25, 40, 50, 60 and 75µg/mL in the presence and absence of metabolic activation. Mixed diethylbenzenes did not cause marked increase in the number of cells with structural aberrations or in the average structural aberrations per cells.
Mixed Diethylbenzenes did not induce chromosomal aberrations in this assay.

In vivo
Mixed Diethylbenzenes (CAS No.25340-17-4)
Male and female CD 1 mice were administered mixed diethylbenzenes (diluted with peanut oil) intraperitoneally at 1000, 2000 and 4000 mg/kg-bw as single doses. Bone marrow cells were evaluated for the presence of micronuclei in erythrocytes. No treatment-related increase in micronucleated polychromatic erythrocytes was seen in either sex. Evidence of toxicity was found at ≥ 2000 mg/kg-bw in both sexes. Clinical signs of toxicity observed were decreased motor activity, collapse, labored breathing, convulsions and weakness.
Mixed Diethylbenzenes did not induce chromosomal aberrations in this assay.

Additional Information

Eye Irritation (Information available in TSCATS)

Mixed Diethylbenzenes (CAS No.25340-17-4)
New Zealand White Albino rabbits (3/sex/dose) were instilled mixed diethylbenzenes into the lower conjunctival sac of the right eye of each animal and observed twice daily for 3 – 7 days. The contralateral eye served as the control. No wash was done after instillation of the test substance, but the treated eyes were rinsed to remove any residual test material after 24 hours. The test substance produced mild but reversible conjunctival irritation (redness, chemosis and discharge) and iridial changes.
Mixed Diethylbenzenes was irritating to rabbit eyes in this assay.

Skin Irritation (Information available in TSCATS)

Mixed Diethylbenzenes (CAS No.25340-17-4)
New Zealand White Albino rabbits (3/sex/dose) were administered mixed diethylbenzenes dermally to clipped intact skin of the back with single 4- and/or 24-hour exposure and observed for 3 – 14 days. Irritation was mild and reversible at both sites. At the 4-hour exposure sites, very slight or slight erythema with moderate to severe edema was observed in all animals at 0.5 hours. Until the study termination on day 14, one animal was observed with very slight erythema. At the 24-hour exposure sites, slight erythema with slight to moderate edema were observed on all animals at 24.5 hours. Until the study termination on day 14, one animal was observed with sub-epidermal damage. The primary irritation index for the 24-hour exposures is 3.0.
Mixed Diethylbenzenes was irritating to rabbit skin in this assay.

Neurotoxicity (Information in the Test Plan)

Mixed Diethylbenzenes (mixture of 1,2-diethylbenzene, 1,3-diethylbenzene, and 1,4-diethylbenzene)
(1) Rats were administered mixed diethylbenzenes via gavage at 0, 500 or 750 mg/kg-bw/day, 5 days/week for 10 weeks. At both doses, rats exhibited a blue discoloration of the skin and urine and two animals in each group died during the study. A significant reduction in body weight gain was observed from the first week at the high dose. Rats in the treated groups developed severe weakness in hind limbs and disturbances in gait that resulted in a complete paralysis of the hind limbs for some rats. There was a time-dependent decrease in motor conduction velocity, sensory conduction velocity and amplitude of the sensory action potential.
LOAEL = 500 mg/kg-bw/day (based on neurotoxic effects).
NOAEL = Not established

(2) Rats were exposed to a commercial mixture of diethylbenzene isomers via inhalation at approximately 500, 600, 700, 800 or 900 ppm for 6 hrs/day, 5 days/week for 18 weeks. There was treatment-related weakness or paralysis of the hind limbs and disturbance of gait (not observed at 500 ppm), changes in motor and sensory nerve conduction velocities, changes in amplitude of the sensory action potential, and/or changes in parameters of the brainstem auditory evoked potential. Rats exhibited a blue discoloration of tissues and urine.
LOAEL = 600 ppm (based on neurotoxic effects)
NOAEL = 500 ppm

1,2-diethylbenzene, 1,3-diethylbenzene and 1,4-diethylbenzene (supporting chemicals)
(1) Rats were administered 1,2-diethylbenzene via gavage at 100 mg/kg-bw/day, 4 days/week for 8 weeks whereas 1,3-diethylbenzene and 1,4-diethylbenzene were each administered at 500 mg/kg-bw/day for 5 days/week for 8 weeks. There was an eight-week post-exposure observation period (recovery period). Rats given 1,2-diethylbenzene developed the same symptoms (decreased body weight, blue discoloration of the skin and urine, weakness of hind limbs, paralysis) as those described for the diethylbenzene mixture. Two rats died during the study. 1,3-Diethylbenzene and 1,4-diethylbenzene-treated rats did not display any signs of neurotoxicity or any other signs of systemic toxicity. During the recovery period, the 1,2-diethylbenzene treated rats regained weight and became more mobile, but presented trailing hind limbs when attempting to walk. On the 4th week of recovery, all animals treated with 1,2-diethylbenzene succeeded in standing up. A time-dependent decrease in motor conduction velocity, sensory conduction velocity and amplitude of the sensory action potential was observed in animals dosed with 1,2-diethylbenzene but not with 1,3-or 1,4-diethylbenzene.
LOAEL for 1,2-diethylbenzene = 100 mg/kg-bw/day (based on neurological effects at the only dose tested)
NOAEL for 1,3- and 1,4-diethylbenzene = 500 mg/kg-bw/day (based on no effects at the only dose tested)

(2) In another study, 1,2-diethylbenzene administered orally at 75 and 100 mg/kg/day, 4 days/week for 8 weeks and intraperitoneal injection of 1,2-diacetylbenzene at 10 or 15 mg/kg/day, 4 days/week for 8 weeks, produced time- and dose-dependent alteration in brainstem auditory evoked potentials which did not completely recover during an 8 or 10 week recovery period.

Carcinogenicity (Information available in TSCATS)

Mixed Diethylbenzenes (CAS No.25340-17-4)
C3H/HeJ male mice (40) were administered mixed diethylbenzenes dermally at 25µl of a10% (v/v) dilution in acetone three times a week until the deaths of the animals. A negative control group received acetone only. In the group receiving 10% (v/v) mixed diethylbenzenes, one squamous cell carcinoma was found in the application site of one mouse. Mixed diethylbenzenes treatment was associated with increases in hyperkeratosis, epidermal hyperplasia, surface crusting, dermatitis and dermal fibrosis. No significant difference in mortality rates was seen between the mixed diethylbenzenes-treated group and the acetone control group. The carcinoma in one treated mouse is considered to be treatment-induced because of a very low spontaneous incidence of squamous cell carcinoma in male C3H/HeJ mice, suggestive of oncogenic potential of test substance.

Conclusion: Acute oral toxicity of diethylbenzene-rich streams category members to rats and acute dermal toxicity to rabbits and rats is low. Mixed diethylbenzenes are irritating to rabbit skin and eyes. Repeated exposures to these category chemicals via inhalation resulted in decreased mean body weights at high concentrations and decreased total white cell and lymphocyte counts. In a repeated-exposure study, no effects were seen on reproductive organs (ovaries, pituitary, prostate, seminal vesicles, testes with epididymides and uterus (corpus and cervix)) except for an abnormal blue-gray color of the tissues/organs in the high exposure group. In a developmental toxicity study with mixed diethylbenzene and the constituent chemical, 1,2-diethylbenzene, maternal toxicity was evidenced by reduced mean body weight gains and reduced food consumption. Greenish-blue discoloration of the amniotic sac was observed in the study with mixed diethylbenzenes. Mean fetal body weights were lower than the control group; however, there were no malformations or skeletal variations. Mixed diethylbenzenes did not induce gene mutation or chromosomal aberrations. Mixed and individual diethylbenzenes showed evidence of neurotoxicity when administered via oral and inhalation routes of administration. In a minimally documented test, mixed diethylbenzenes showed carcinogenic potential in mice administered via dermal route of administration.

The potential health hazard of chemicals in the diethylbenzene-rich streams category is moderate based on repeated-dose and developmental toxicity. Available data indicate that diethylbenzenes show evidence of neurotoxicity.

Table 3. Summary of Human Health Data				
Endpoints	**Mixed Diethylbenzenes (25340-17-4)**	**Polyethylbenzenes (68608-82-2)**	**1,2 Diethylbenzene, (supporting chemical) (135-01-3)**	**1,4-Diethylbenzene, (supporting chemical) (105-05-5)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**2050** **4700 - 6900**	No data 2050 4700 - 6900 (RA)	—*	—*
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**> 5000 (rabbit)** **> 2000 (rat)**	No data > 5000 (rabbit) > 2000 (rat) (RA)	—*	—*
Repeated-dose Toxicity Inhalation (mg/L/day)	**NOAEL = 0.19** **LOAEL= 0.61**	No data NOAEL = 0.19 LOAEL = 0.61 (RA)	—*	—*
Reproductive Toxicity-Inhalation (mg/L/day) **Systemic Toxicity** **Reproductive toxicity**	No data Repeated-dose toxicity study indicated no effects on reproductive organs.	No data Repeated-dose toxicity study indicated no effects on reproductive organs. (RA)	—*	**NOAEL = 750** **NOAEL = 350** **LOAEL = 750**
Developmental Toxicity (mg/kg bw/day) **Maternal Toxicity** **Developmental Toxicity**	**NOAEL = 20** **LOAEL = 100** **NOAEL = 100** **LOAEL = 200**	No data NOAEL = 20 LOAEL = 100 NOAEL = 100 LOAEL = 200 (RA)	**NOAEL = 5** **LOAEL = 15** **NOAEL = 5** **LOAEL = 15**	—*
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**	No data Negative (RA)	—*	—*
Genetic Toxicity – Chromosomal Aberrations *In vivo*	**Negative**	No data Negative (RA)	—*	—*
Additional Information **Skin Irritation** **Eye Irritation** **Neurotoxicity** **Carcinogenicity**	**Irritating** **Irritating** **Positive evidence** **Potential for carcinogenicity**	—**	—*	—*

(m) = measured data (i.e. derived from testing); (RA) = Read Across; — indicates endpoint was not addressed for this chemical; *indicates data is not necessary for supporting chemical; **indicates data not necessary for non-SIDS endpoint.

4. Hazard Characterization

The Log K_{ow} values of constituent chemicals in the diethylbenzene-rich streams category indicate that their potential to bioaccumulate is expected to be high. Mixed diethylbenzenes is not readily biodegradable, indicating that the category members have the potential to persist in the environment.

The evaluation of available toxicity data indicates that the potential acute hazard of diethylbenzene-rich streams category members to fish is high and to aquatic invertebrates and aquatic plants is moderate.

Acute oral toxicity of diethylbenzene-rich streams category members to rats and acute dermal toxicity to rabbits and rats is low. Mixed diethylbenzenes are irritating to rabbit skin and eyes. Repeated exposures to these category chemicals via inhalation resulted in decreased mean body weights at high concentrations and decreased total white cell and lymphocyte counts. In a repeated-exposure study, no effects were seen on reproductive organs (ovaries, pituitary, prostate, seminal vesicles, testes with epididymides and uterus (corpus and cervix)) except for an abnormal blue-gray color of the tissues/organs in the high exposure group. In a developmental toxicity study with mixed diethylbenzene and the constituent chemical, 1,2-diethylbenzene, maternal toxicity was evidenced by reduced mean body weight gains and reduced food consumption. Greenish-blue discoloration of the amniotic sac was observed in the study with mixed diethylbenzenes. Mean fetal body weights were lower than the control group; however, there were no malformations or skeletal variations. Mixed diethylbenzenes did not induce gene mutation or chromosomal aberrations. Mixed and individual diethylbenzenes showed evidence of neurotoxicity when administered via oral and inhalation routes of administration. In a minimally documented test, mixed diethylbenzenes showed carcinogenic potential in mice administered via dermal route of administration.

The potential health hazard of chemicals in the diethylbenzene-rich streams category is moderate based on repeated-dose and developmental toxicity. Available data indicate that diethylbenzenes show evidence of neurotoxicity.

5. Data Gaps

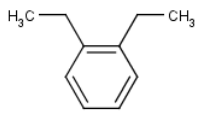
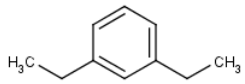
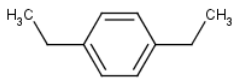
No data gaps were identified under the HPV Challenge Program.

APPENDIX

The composition of diethylbenzene-rich streams category members

	Mixed Diethylbenzenes **CAS No.25340-17-4** diethylbenzenes	Polyethylbenzenes **CAS No. 68608-82-2** by-products from ethylenated benzene
Component	**Wt %**	**Wt %**
Diethylbenzenes[1]	94.3 – 98.8	87.6 – 89.9
Triethylbenzenes	<0.1	4.9 -5.1
Polyethylbenzenes	<0.1	<0.1
Iso-/sec-butylbenzenes	0.6 – 0.8	1.1
Other alkylbenzenes	0.3 – 4.5	0.7 – 1.8
Ethylbenzene	<0.1	1.7 – 1.9
Benzene	<0.1	<0.1
Diphenylalkanes	<0.1	<0.1
Ethyl diphenylethanes and Diethyl biphenyls	<0.1	<0.1
PNAs (3-rings)	<0.1	<0.1
Paraffins/Naphthenes	<0.1	0.5 – 1.6
Total of unidentified components, each present at <0.1%	0.8 – 1.4	0.2 – 0.6

[1] n-butylbenzene co-eluted with 1,4-diethylbenzene

Supporting Chemicals		
CAS No.	**Chemical Name**	**Structure**
135-01-3	1,2-diethylbenzene	
141-93-5	1,3-diethylbenzene	
105-05-5	1,4-diethylbenzene