SCREENING LEVEL HAZARD CHARACTERIZATION FOR HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME
Substituted Diphenylamines

SPONSORED CHEMICALS

Benzenamine, 4-octyl-N-(4-octylphenyl) **[9th CI Name: Benzeneamine, 4 octyl-N-(4-octylphenyl)]**	**CAS No. 101-67-7**
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-phenylethyl) phenyl]- **[9th CI Name: Benzeneamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-pehylethyl) phenyl]-]**	**CAS No. 10081-67-1**
Benzenamine, ar-nonyl-N-nonylphenyl **[9th CI Name: Benzeneamine, AR-nonyl-N-(nonylphenyl)-]**	**CAS No. 36878-20-3**
Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene **[9th CI Name: Benzeneamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene]**	**CAS No. 68411-46-1**
Benzenamine, N-phenyl-, styrenated **[9th CI Name: Benzeneamine, N-phenyl-, styrenated]**	**CAS No. 68442-68-2**
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives **[9th CI Name: Benzeneamine, 2-ethyl-N-(2-ethylphenyl)-(tripropynyl) derivatives]**	**CAS No. 68608-77-5**
Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene **[9th CI Name: Benzeneamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene]**	**CAS No. 68921-45-9**
Benzenamine, N-phenyl- reaction products with 2,4,4-trimethylpentene and isobutylene **[9th CI Name: Benzeneamine, N-phenyl- with 2,4,4-trimethylpentene and isobutene]**	**CAS No. 184378-08-3**

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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 1400 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
Substituted Diphenylamines Category

Introduction

The sponsor, the American Chemistry Council, Rubber and Plastic Additives (RAPA) Panel, submitted a Test Plan and Robust Summaries to EPA for the Substituted Diphenylamines Category on December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 15, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/subdipha/c13378tc.htm). EPA comments on the original submission were posted to the website on December 3, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 25, 2003 and November 17, 2006, which were posted to the ChemRTK website on October 24, 2003 and January 19, 2007 respectively.

The substituted diphenylamines category consists of the following chemicals:

Benzenamine, 4-octyl-N-(4-octylphenyl) [9th CI Name: Benzeneamine, 4 octyl-N-(4-octylphenyl)]	CAS No. 101-67-7
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-phenylethyl) phenyl]- [9th CI Name: Benzeneamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-pehylethyl) phenyl]-]	CAS No. 10081-67-1
Benzenamine, ar-nonyl-N-nonylphenyl [9th CI Name: Benzeneamine, AR-nonyl-N-(nonylphenyl)-]	CAS No. 36878-20-3
Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene [9th CI Name: Benzeneamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene]	CAS No. 68411-46-1
Benzenamine, N-phenyl-, styrenated [9th CI Name: Benzeneamine, N-phenyl-, styrenated]	CAS No. 68442-68-2
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives [9th CI Name: Benzeneamine, 2-ethyl-N-(2-ethylphenyl)-(tripropynyl) derivatives]	CAS No. 68608-77-5
Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene [9th CI Name: Benzeneamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene]	CAS No. 68921-45-9
Benzenamine, N-phenyl- reaction products with 2,4,4-trimethylpentene and isobutylene [9th CI Name: Benzeneamine, N-phenyl- with 2,4,4-trimethylpentene and isobutene]	CAS No. 184378-08-3

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. Structures of the sponsored and supporting chemicals are included 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 eight members of the substituted diphenylamines category are diphenylamines with various degrees of phenyl or alkyl substitution; some of which are complex mixtures, also called Class 2 substances. Class 2 substances are composed of several chemicals whose concentration is variable depending on the degree of their synthesis. All substances in the category share a common starting material, diphenylamine (benzenamine, N-phenyl-; CAS No. 122-39-4) and a common synthetic pathway. The sponsor grouped the chemicals into one category based on the similarities in structure, physical-chemical and environmental fate properties and aquatic and mammalian toxicities. The sponsor replaced one of the original substances (CAS No. 15721-78-5) with another substance, benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (CAS No. 10081-67-1).

In comments on the original test plan (dated November 27, 2002), EPA found the category approach reasonable for ecological effects, but the data for the supporting chemical, diphenylamine, was deemed inappropriate for these endpoints due to differences in physical-chemical properties. EPA noted that there were differences in the toxicity of unsubstituted diphenylamine and the substituted category members suggesting that these substitutions affect toxicity; therefore, EPA did not consider that the category had been adequately justified for the human health endpoints and found the proposed supporting data for diphenylamine of limited utility. EPA further suggested that the sponsor needed to provide a strong showing that significant substitution on the parent substance would not alter its toxicity.

In its revised submission, the sponsor submitted new data for some of the category members to further support the category justification and address SIDS data gaps. EPA finds the inclusion of the new substance, benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (CAS No. 10081-67-1) reasonable for the purposes of the HPV Challenge Program. However, the limited submitted data still suggest that the differences in substitution alter the toxicity of the category members, e.g. 10- to 50-fold differences in repeated-dose, reproductive/ developmental toxicity values. These differences do not necessarily negate the category justification, but indicate there may be a pattern of toxicity based on molecular weight and substituted functional groups.

The sponsor's approach to arraying the category chemicals is not transparent, i.e. it does not seem to follow patterns in physical-chemical properties and/or toxicity. For several physical-chemical properties, a "range for components" is provided by the sponsor, but information regarding the identity of these components is not provided. Without information on the composition of each of the category members it is difficult to evaluate robustness of these data as well as the sponsor's proposed read-across proposals. Therefore, EPA has arrayed the category chemicals roughly according to trends in the submitted physical-chemical properties, because they are expected to correlate with ecotoxicity. However, for human health endpoints it is not clear that this represents a sound rationale and proportional composition information on each category members would strengthen the evaluation.

Summary-Conclusion

The log K_{ow} values of the substituted diphenylamines category members are high. However, the low water solubility for many of the category members suggests the potential for these chemicals to bioaccumulate is low. The substituted diphenylamines category members are not readily biodegradable, indicating that they have the potential to persist in the environment.

The aquatic toxicity data submitted were difficult to interpret because they were generated in the presence of solvent(s), the concentration of chemical in the test water was not measured and/or effects concentrations reported were above the chemical's water solubility limit. The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that for most category members acute hazard is expected to be low based on observed effects occurring at concentrations in great excess of the water solubility limit. However, a fish test conducted with the most soluble category member and without solvents indicates that some of the category members that are soluble or miscible in water may have the potential to cause chronic effects. Subsequent consideration of environmental fate and exposure information will inform a determination of the need to obtain the chronic aquatic toxicity data.

The acute oral toxicity of substituted diphenylamines category members to rats and acute dermal toxicity to rabbits is low; acute dermal toxicity to rats is moderate. The category members are not irritating to the skin but, slightly irritating to the eyes. Category members, benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene and benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, are not dermal sensitizers. Repeated oral exposures of benzenamine, N-phenyl-, styrenated to rats for 43-54 days resulted in increased activity of alkaline phosphatase and increased liver and adrenal weights in both sexes. Centrilobular hepatocyte hypertrophy in both sexes and follicular cell hypertrophy in thyroid glands of males were seen during histopathological examination. Repeated exposures to rats via the oral route of exposure to benzenamine, N-phenyl-, 2,4,4-trimethylpentene reaction products with styrene and isobutylene resulted in increased activities of aspartate aminotransferase and alkaline phosphatase activities; elevated activated partial thromboplastin time in both sexes; decreased platelet count in both sexes prior to mating; a reduction in total plasma protein, albumin and the albumin/globulin ratio in females in both sexes. Decreased gestation length and pre-implantation losses were seen

in rats exposed to benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, and benzenamine, N-phenyl-, styrenated, respectively. For developmental toxicity, oral exposures of rats to benzenamine, N-phenyl-, styrenated and benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, resulted in mortality, decreased offspring weights and/or reduced surface righting response. Six category members were tested for mutagenicity in bacteria; none were mutagenic. Benzenamine, 4-octyl-N-(4-octylphenyl) did not induce chromosomal aberrations tested *in vitro*. Benzenamine, 4-octyl-N-(4-octylphenyl) and benzenamine, N-phenyl-, styrenated did not induce chromosomal aberrations *in vivo*.

The potential health hazard of the substituted diphenylamines category is moderate based on the repeated-dose, reproductive and developmental toxicity of two category members.

No data gaps have been identified for 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.

Octanol-Water Partition Coefficient

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
Log K_{ow} = 11.26 (estimated)

The model used to estimate the K_{ow} submitted (KOWWIN v.1.66) has been demonstrated to be accurate in predicting log K_{ow} between -4 and 10. Given the estimate for benzenamine, 4-octyl-N-(4-octylphenyl) is outside this range indicates that the absolute value may not be accurate. Nonetheless, it is reasonable to conclude that this prediction is indicative that the log K_{ow} for this chemical is high (> 4).

Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene (CAS No. 68411-46-1)
Log K_{ow} > 6 (estimated)

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
Log K_{ow} = 4.64 (measured)

Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (CAS No. 68608-77-5)
Log K_{ow} = 9.84 (estimated)

Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (CAS No. 68921-45-9)
Log K_{ow} = 5.2 (measured)

Benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
Log K_{ow} = 3.13 to > 6.20 (measured)

Biodegradation

Benzenamine, ar-nonyl-N-nonylphenyl (CAS No. 36878-20-3)
In a manometric respirometry test using activated sludge from a domestic wastewater treatment plant as inoculum, 8% of benzenamine, ar-nonyl-N-nonylphenyl had degraded after 28 days.
Benzenamine, ar-nonyl-N-nonylphenyl is not readily biodegradable.

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
In a manometric respirometry test using predominantly domestic sewage as inoculum, 9% of benzenamine, N-phenyl-, styrenated had degraded after 28 days.
Benzenamine, N-phenyl-, styrenated is not readily biodegradable.

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
Biodegradation was estimated to be 0.78% using the EPISUITE/EPIWIN modeling program; BIOWIN v4.00. Based on data read-across from benzenamine, N-phenyl-, styrenated and benzenamine, ar-nonyl-N-nonylphenyl, this substance is not considered readily biodegradable.
Benzenamine, 4-octyl-N-(4-octylphenyl) is not readily biodegradable.

Conclusion: The log K_{ow} values of the substituted diphenylamines category members are high. However, the low water solubility for many of the category members suggests the potential for these chemicals to bioaccumulate is low. The substituted diphenylamines category members are not readily biodegradable, indicating that they have the potential to persist in the environment.

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

Endpoints	**Benzenamine, N-phenyl-, styrenated (68442-68-2)**	**Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethyl-pentene (68921-45-9)**	**Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethyl-pentene (68411-46-1)**	**Benzenamine, N-phenyl-reaction product with 2,4,4-trimethyl-pentene and isobutylene (184378-08-3)**	**Benzenamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)**	**Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7)**	**Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)**	**Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)**
Melting Point (°C)	**~ 6 (m)**	< 0 (e)[1]	**44 – 107 (m)**	**7 (m)**	**98.5 (m)**	**87 – 95 (m)**	< 0 (e)	< 0 (e)[1]
Boiling Point (°C)	**> 300 (m)**	**175 – > 198 (m)**	370 (e)	**275 (m)**	N/A	**200 (m)**	**258 (m) degradation at 260**	**221 (e)**
Vapor Pressure (hPa at 25°C)	**< 100 (m) (at 100 °C)**	9.99×10^{-7} – 1.9×10^{-15} (e)	2.66×10^{-5} (e)	**9.4×10^{-7} (m)**	—	< 0.13332 (e)	—	2.35×10^{-8} – 9.18×10^{-12} (e)
Log K_{ow}	**4.64 (m)**	**5.2 (m)**	6 (e)	**3.13 – > 6.20 (m)**	—	11.26 (e)	—	9.84 (e)
Water Solubility (mg/L at 25°C)	**0.41 (m) (at 20 °C)**	0.3889 – 1.869 $\times 10^{-11}$ (e)	**< 0.01 (m) (at 20 °C)**	**9.09×10^{-2} – 5.93×10^{-5} (m) (at 20 °C)**	Insoluble	4.215×10^{-7} (e)	—	2.35×10^{-5} – 5.85×10^{-10} (e)
Direct Photodegradation (cm^3/molecule-sec)	—	—	—	—	—	2.19×10^{-14} (e)	—	—
Indirect (OH^-) Photodegradation ($t_{1/2}$)	—	1.3 (e)	1.27 (e)	1.27 (e)	—	0.586 (e)	—	1.2 (e)
Stability in Water (Hydrolysis) ($t_{1/2}$)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Fugacity (Level III Model) **Air (%)** **Water (%)** **Soil (%)** **Sediment (%)**	—	 0.057 – 0.010 13.5 – 1.26 44.0 – 28.6 42.5 – 69.0	 0.07 – 0.01 17.4 – 1.27 49.6 – 32.0 33.0 – 66.7	 0.07 – 0.01 17.4 – 1.27 49.6 – 32.0 33.0 – 66.7	—	 0.03 3.49 27.1 69.3	—	 0.04 4.34 – 4.31 56.1 – 56.4 39.5 – 39.2
Biodegradation at 28 days	**9 (m) Not readily biodegradable**	No Data 8 – 9 (RA) Not readily biodegradable	No Data 8 – 9 (RA) Not readily biodegradable	No Data 8 – 9 (RA) Not readily biodegradable	No Data 8 – 9 (RA) Not readily biodegradable	No Data 8 – 9 (RA) Not readily biodegradable	**8 (m)**	No Data 8 – 9 (RA) Not readily biodegradable

2. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
(1) Bluegill sunfish (*Lepomis macrochirus*) were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at a nominal concentration range of 100 – 1000 mg/L, in a closed system under static conditions for 96 hours. Acetone was used as the solvent and solvent control. Although not specifically stated, it appears that there were no mortalities and the sponsor reported a 96-h LC_{50} of > 1000 mg/L. The results of this test are difficult to interpret because the substance was tested above its water solubility limit and in the presence of solvent. Therefore, EPA considers the no effect concentration to be the water solubility limit (saturation), which for benzenamine, 4-octyl-N-(4-octylphenyl) would be approximately 4.215×10^{-7} mg/L.
No effects at saturation

(2) Rainbow trout (*Salmo gairdneri*) were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at a nominal concentration range of 100 – 1000 mg/L, in a closed system under static conditions for 96 hours. Acetone was used as the solvent and solvent control. Although not specifically stated, it appears that there were no mortalities and the sponsor reported a 96-h LC_{50} of > 1000 mg/L. The results of this test are difficult to interpret because the substance was tested above its water solubility limit and in the presence of solvent. Therefore, EPA considers the no effect concentration to be the water solubility limit (saturation), which for benzenamine, 4-octyl-N-(4-octylphenyl) would be approximately 4.215×10^{-7} mg/L.
No effects at saturation

Benzenamine, ar-nonyl-N-nonylphenyl (CAS No. 36878-20-3)
Fathead minnows (*Pimephales promelas*) were exposed to benzenamine, ar-nonyl-N-nonylphenyl at a nominal concentration range of 1000 – 10,000 mg/L, under semi-static conditions for 96 hours. Benzenamine, ar-nonyl-N-nonylphenyl was renewed after 48 hours. A sheen of insoluble material was observed in all treated vessels except the control. No mortality was observed at the highest concentration tested. The results of this test are difficult to interpret because the substance was tested above its water solubility limit. Therefore, EPA considers the no effect concentration as the water solubility limit (saturation).
No effects at saturation

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
Zebrafish (*Brachydanio rerio*) were exposed to benzenamine, N-phenyl-, styrenated at nominal concentrations (not stated) under static conditions for 96 hours. The benzenamine, N-phenyl-, styrenated was dispersed in water by means of an Ultra-Turrax. Mortality increased with increasing concentration of benzenamine, N-phenyl-, styrenated added to the test solution and the sponsor reported 96-h LC_{50} of 920 mg/L. The results of this test are difficult to interpret because the substance was tested above its water solubility limit, but indicate there were effects at or below the water solubility limit (saturation) which for benzenamine, N-phenyl-, styrenated is 0.41 mg/L.
Effects at or below water solubility limit

Acute Toxicity to Aquatic Invertebrates

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
Daphnia magna were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at a nominal concentration range of 1.8 – 32 mg/L, in a closed system under static conditions for 48 hours. DMF was used as the solvent and solvent control. Mortality increased with increasing concentration of benzenamine, 4-octyl-N-(4-octylphenyl) added to the test solution and the sponsor reported 48-h EC_{50} of 7.7 mg/L. The results of this test are difficult to interpret because the substance was tested above its water solubility limit and in the presence of solvent, but are likely due to physical effects because tested concentrations vastly exceeded the water solubility limit (saturation), which for benzenamine, 4-octyl-N-(4-octylphenyl) is approximately 4.215×10^{-7} mg/L.
No effects at saturation

Benzenamine, ar-nonyl-N-nonylphenyl (CAS No. 36878-20-3)
Crustacea (*Mysidopsis bahia*) were exposed to benzenamine, ar-nonyl-N-nonylphenyl as water accommodated fractions (WAFs) under semi-static conditions for 96 hours. The loading rates were 0, 150, 250, 400, 600 or 1000 mg/L and no analytical measurements were made on the WAFs. At 600 mg/L, mysids were lethargic and exhibited erratic swimming from 48 to 96 hours. No other sublethal effects were observed in any test vessel during the 96-hour exposure. EPA does not consider the loading rate as the no effect concentration when the concentration exceeds the water solubility of the test substance. The results of this test are difficult to interpret because the substance was tested above its water solubility limit, but are likely due to physical effects because the tested concentrations vastly exceeded the water solubility limit (saturation).
No effects at saturation

Toxicity to Aquatic Plants

Benzenamine, ar-nonyl-N-nonylphenyl (CAS No. 36878-20-3)
Algae (*Pseudokirchneriella subcapitata*) were exposed to benzenamine, ar-nonyl-N-nonylphenyl as water accommodated fractions (WAFs) under static conditions for 96 hours. The loading rates were 0, 0.3, 3.3, 33, 330 or 3300 mg/L and no analytical measurements were made on the WAFs. Effects observed at 330 mg/L were determined to be algistatic based on the rapid re-growth of an aliquot of cells taken from 500 mg/L cultured in fresh control media. EPA does not consider the loading rate as the no effect concentration when the concentration exceeds the water solubility of the test substance. The results of this test are difficult to interpret because the substance was tested above its water solubility limit, , but are likely due to physical effects because the tested concentrations vastly exceeded the water solubility limit (saturation),
No effects at saturation

Conclusion: The aquatic toxicity data submitted were difficult to interpret because they were generated in the presence of solvent(s), the concentration of chemical in the test water was not measured and/or effects concentrations reported were above the chemical's water solubility limit. The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that for most category members acute hazard is expected to be low based on observed effects occurring at concentrations in great excess of the water solubility limit. However, a fish test conducted with the most soluble category member and without solvents indicates that some of the category members that are soluble or miscible in water may have the potential to cause chronic effects. Subsequent consideration of fate and exposure information will inform a determination of the need to obtain the chronic aquatic toxicity data.

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	Benzenamine, N-phenyl-, styrenated (68442-68-2)	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethyl-pentene (68921-45-9)	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethyl-pentene (68411-46-1)	Benzenamine, N-phenyl-reaction products with 2,4,4-trimethyl-pentene and isobutylene (184378-08-3)	Benzenamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7)	Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)
Fish 96-h LC_{50} (mg/L)	**Effects at or below water solubility**	No Data Effects at or below water solubility (RA)	No Data Effects at or below water solubility (RA)	No Data NES (RA)	No Data NES (RA)	**NES**	**NES**	No Data NES (RA)
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No Data Effects at or below water solubility (RA)	No Data Effects at or below water solubility (RA)	No Data Effects at or below water solubility (RA)	No Data NES (RA)	No Data NES (RA)	**NES**	No Data NES (RA)	No Data NES (RA)
Aquatic Plants 72-h EC_{50} (mg/L)	No Data NES (RA)	No Data NES (RA)	No Data NES (RA)	No Data NES (RA)	No Data NES (RA)	No Data NES (RA)	No Data NES (RA)	No Data NES (RA)

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

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
Sprague-Dawley rats (5/sex/dose) were administered benzenamine, 4-octyl-N-(4-octylphenyl) as a 20.0% suspension in corn oil at 6310 or 7940 mg/kg-bw and observed for 14 days. The only clinical signs noted were a slightly reduced appetite and activity for 1– 2 days. At necropsy, all viscera appeared normal.
LD_{50} > 7940 mg/kg-bw

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
(1) Rats (5/dose, strain not stated) were administered benzenamine, N-phenyl-, styrenated as a 20% solution in corn oil via gavage at doses of 2500, 5000, 10,000, 20,000 and 40,000 mg/kg-bw and were observed for 14 days. At each of the two highest doses, two animals died. Clinical observations were not reported.
LD_{50} > 20,000 mg/kg-bw

(2) Rats (5/sex/dose, strain not stated) were administered benzenamine, N-phenyl-, styrenated dispersed in corn oil via gavage at 500 mg/kg-bw and observed for 14 days. No animals died and no clinical signs or changes in body weight were observed. At necropsy, no abnormal tissues were noted.
LD_{50} > 500 mg/kg-bw

Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (CAS No. 68608-77-5)
Charles River Rats (2/dose) were administered benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives via gavage at 10,250, 15,380, 23,070 and 34,600 mg/kg-bw and were observed for 14 days. No mortality or adverse clinical findings were reported at any dose.
LD_{50} > 34,600 mg/kg-bw

Benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
Sprague-Dawley rats (3/sex/dose) were administered a solution of benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene in arachis oil via gavage as a single dose of 2000 mg/kg-bw and observed for 14 days. No deaths or clinical signs of toxicity were observed. Body weight gains were normal.
LD_{50} > 2000 mg/kg-bw

Acute Dermal Toxicity

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
New Zealand white rabbits (3/sex) were administered benzenamine, 4-octyl-N-(4-octylphenyl) dermally as a single application of 40.0% suspension in corn oil at 5010 or 7940 mg/kg-bw to the shaved skin under occlusive conditions for 24 hours or and observed for 14 days. Clinical signs of toxicity included slightly reduced appetite and activity for 1 – 2 days. All animals survived until sacrifice on day 14. At necropsy, all viscera appeared normal.
LD_{50} > 7940 mg/kg-bw

(2) Rats (6/sex/dose, strain not stated) were administered undiluted benzenamine, 4-octyl-N-(4-octylphenyl) dermally at 1200, 1483, 1833, 2265 and 2800 mg/kg-bw. Clinical signs of toxicity included black urine, loss of appetite, decreased activity and death.
LD_{50} = 1347 – 1915 mg/kg-bw

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
Rabbits (5/dose, strain not stated) were administered benzenamine, N-phenyl-, styrenated dermally at 10,000 mg/kg-bw. No mortality was reported.
LD_{50} > 10,000 mg/kg-bw

Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (CAS No. 68608-77-5)
New Zealand rabbits (4/dose) were administered benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives dermally to a shaved area on the backs under occlusive conditions for 4 hours and observed for 14 days. No mortality was observed and skin reactions were limited to mild erythema, desquamation and edema. On day 14, slight erythema and desquamation were still present.
LD_{50} > 3000 mg/kg-bw

Repeated-Dose Toxicity

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (10/sex/dose) were administered benzenamine, N-phenyl-, styrenated suspension in corn oil, via gavage at 0, 50, 250 and 600 mg/kg-bw/day for 43 (males) and 54 (females) days. No deaths or treatment-related changes in body weight, growth, food and water intake or behavioral assessments were seen in any treatment groups. An increased activity for alkaline phosphatase was noted in males at 600 mg/kg-bw/day. Absolute and relative (to body weights) liver and adrenal weights were increased in both sexes at the 600 mg/kg-bw/day. Histopathological examination of the liver revealed centrilobular hepatocyte enlargement in all treated females and at 250 and 600 mg/kg-bw/day males. In males, follicular cell hypertrophy in the thyroid glands was observed at 600 mg/kg-bw/day. The sponsor considered the observed changes as adaptive and suggested a NOAEL of 600 mg/kg-bw/day. However, given that this was the highest dose tested in this study, and is not the limit dose, this interpretation of the data cannot be substantiated.
LOAEL = 600 mg/kg-bw/day (based on increased liver enzyme activity and histopathological changes in the liver in both sexes and thyroid glands in the males)
NOAEL = 250 mg/kg-bw/day

Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (CAS No. 68921-45-9)
Carworth rats (25/sex/dose) were administered benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene in the diet at 2500, 5000 and 10,000 ppm (~ 125, 250 and 500 mg/kg-bw/day, respectively) for 64 weeks. Growth retardation was observed in all treated females. No growth retardation was observed in the males at 125 mg/kg-bw/day, but it is unclear if an effect was observed at higher doses. Hepatomegaly was observed in both sexes at all doses. Diffuse hepatic degeneration was observed in all animals, the severity of which was not treatment-related. The degenerative changes in the liver were described as diffuse cloudy swellings and fatty metamorphosis of the cytoplasm of the hepatocytes.
LOAEL ~ 125 mg/kg-bw/day (based on growth retardation in females and effect on liver)
NOAEL = Not established

Benzenamine, N-phenyl- reaction products with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley (10/sex/dose) were administered benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene and isobutylene via gavage at 0, 5, 25 and 125 mg/kg-bw/day for 43 (males) and 54 (females) days. No deaths or treatment-related signs of toxicity, behavioral assessments, functional performance or sensory reactivity were noted at any dose. At 125 mg/kg-bw/day, there was decreased food intake and body weight gain in females during lactation. There was also a decreased food intake at this treatment dose during lactation. Hematological evaluation indicated increased levels of activated partial thromboplastin time at 125 mg/kg-bw/day in both sexes. There was a decreased platelet count in both sexes prior to mating. Females at $\geq$ 25 mg/kg-bw/day had decreased total plasma protein, albumin and the albumin/globulin ratio and elevated aspartate aminotransferase and alkaline phosphatase activities. These effects were observed in males at 125 mg/kg-bw/day. At necropsy, two males treated with 125 mg/kg-bw/day had pale liver. At 125 mg/kg-bw/day, males had elevated liver weights (absolute and relative to terminal weight) and females had reduced spleen weights. Histopathological evaluation revealed centrilobular hepatocytes enlargement in both sexes of the 125 mg/kg-bw/day treatment group and the 25 mg/kg-bw/day treated females.
LOAEL (females) = 25 mg/kg-bw/day (based on changes in biochemical parameters)
NOAEL (females) = 5 mg/kg-bw/day
LOAEL (males) = 125 mg/kg-bw/day (based on changes in biochemical and hematological parameters and effects on liver)
NOAEL (males) = 25 mg/kg-bw/day

Reproductive Toxicity

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
In the combined repeated-dose/reproductive/developmental toxicity screening study described previously, no adverse effects on mating performance, fertility or gestation were observed. Females treated with 600 mg/kg-bw/day had a higher percentage of pre-implantation losses compared to controls, resulting in less offspring/litter when compared to controls and lower total litter weights.
LOAEL (reproductive toxicity) = 600 mg/kg-bw/day (based on higher pre-implantation losses)
NOAEL (reproductive toxicity) = 250 mg/kg-bw/day

Benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
In the combined repeated-dose/reproductive/developmental toxicity screening study described previously, shorter gestation length, lower viability indices and lower total litter weights were seen at 125 mg/kg-be/day.
LOAEL (reproductive toxicity) = 125 mg/kg-bw/day (based on shorter gestation lengths and a higher incidence of offspring mortality)
NOAEL (reproductive toxicity) = 25 mg/kg-bw/day

Developmental Toxicity

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
In the combined repeated-dose/reproductive/developmental toxicity screening study described previously, no clinical signs of toxicity were observed in the offspring. The mean offspring weights of treated animals were comparable to controls. Offspring from the 600 mg/kg-bw/day treated animals showed less successful completion of surface righting assessments. No treatment-related macroscopic abnormalities were observed at necropsy.
LOAEL (maternal toxicity) = 600 mg/kg-bw/day (based on effects on the liver)
LOAEL (developmental toxicity) = 600 mg/kg-bw/day (based on diminished surface righting assessments)
NOAEL (maternal/developmental toxicity) = 250 mg/kg-bw/day

Benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
In the combined repeated-dose/reproductive/developmental toxicity screening study described previously, the number of interim deaths at 125 mg/kg-bw/day was considerably higher than that observed for controls. At the same dose, the mean offspring body weights were also slightly lower. No other treatment-related effects were observed on offspring development.
LOAEL (maternal toxicity) = 25 mg/kg-bw/day (based on biochemical parameters)
NOAEL (maternal toxicity) = 5 mg/kg-bw/day
LOAEL (developmental toxicity) = 125 mg/kg-bw/day (based on mortality and decreased offspring body weights)
NOAEL (developmental toxicity) = 25 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
(1) *Salmonella typhimurium* strains were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at concentrations up to 500 μg/plate with and without metabolic activation. Positive and negative controls were used; however, their responses were not provided.
Benzenamine, 4-octyl-N-(4-octylphenyl) was not mutagenic in this assay.

(2) *Saccharomyces cerevisiae,* D4, were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at concentrations up to 500 μg/plate with and without metabolic activation. Positive and negative controls were used; however, their responses were not provided..
Benzenamine, 4-octyl-N-(4-octylphenyl) was not mutagenic in this assay.

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
S. typhimurium and *Escherichia coli* were exposed to benzenamine, N-phenyl-, styrenated at concentrations up to 5000 µg/plate with and without metabolic activation. The vehicle and positive controls responded appropriately.
Benzenamine, N-phenyl-, styrenated was not mutagenic in this assay.

Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (CAS No. 68608-77-5)
S. typhimurium and *E. coli* were exposed to benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives in two separate assays at concentrations up to 5000 µg/plate with and without metabolic activation. The positive controls responded appropriately. A precipitate was observed at concentrations ≥ 1500 µg/plate.
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives was not mutagenic in these assays.

Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (CAS No. 68921-45-9)
S. typhimurium and *E. coli* were exposed to benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene at concentrations up to 5000 µg/plate with and without metabolic activation. The vehicle and positive controls responded appropriately. No cytotoxicity was observed to any of the strains. Precipitates were observed at 1500 and 5000 µg/plate, but did not interfere with the scoring.
Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene was not mutagenic in this assay.

Benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
S. typhimurium strains were exposed to benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene and isobutylene at concentrations up to 5000 µg/plate with and without metabolic activation. The vehicle and positive controls responded appropriately. No toxicity was observed to any of the strains. No precipitation was observed.
Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene and isobutylene was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
Chinese hamster ovary (CHO) and lung (CHL) cells were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at concentrations up to 4.45 mg/mL and 0.5 mg/mL, respectively, with and without metabolic activation. The controls responded appropriately.
Benzenamine, 4-octyl-N-(4-octylphenyl) did not induce chromosomal aberrations in this assay.

In vivo
Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
CD-1 mice (5 males/dose) were administered single doses of benzenamine, N-phenyl-, styrenated in corn oil, via gavage at 0, 500, 1000 and 2000 mg/kg-bw/day. Bone marrow cells were harvested 24 and 48 hours after dosing. Slides were prepared from the bone marrow extracts and 2000 micronucleated polychromatic erythrocytes were evaluated for the presence of micronuclei. The ratio of polychromatic erythrocytes (PCE) to nonchromatic erythrocytes (NCE) cells was determined. Low PCE:NCE ratios indicated that benzenamine, N-phenyl-, styrenated was cytotoxic to bone marrow.
Benzenamine, N-phenyl-, styrenated did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
In a sister chromatid exchange assay, CHO cells were exposed to benzenamine, 4-octyl-N-(4-octylphenyl) at concentrations up to 5 mg/L with and without metabolic activation. The controls responded appropriately.
A precipitate was observed at 855 µg/mL.
Benzenamine, 4-octyl-N-(4-octylphenyl) did not induce sister chromatid exchange in this assay.

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
In an *in vitro* DNA damage and repair assay, *E. coli* strains W3110 and p3478 were exposed to benzenamine, N-phenyl-, styrenated up to 5000 µg/L with and without metabolic activation. Negative and positive controls were used.
Benzenamine, N-phenyl-, styrenated did not damage cellular DNA in this assay.

Additional Information

Eye Irritation

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
New Zealand White rabbits (6/dose) were instilled in one eye with 100 mg of benzenamine, 4-octyl-N-(4-octylphenyl) as a finely ground powder moistened with water. The other eye was not treated and served as the control. Slight discomfort was noted immediately following instillation. At 10 minutes, slight erythema and slight discharge were noted. At 24 hours, there was slight erythema and moderate discharge in all test animals. At 48 hours, two of the six had slight erythema and slight discharge. All signs of irritation had subsided by the third day post-exposure.
Benzenamine, 4-octyl-N-(4-octylphenyl) was slightly irritating to rabbit eyes in this study.

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
Albino rabbits (6, sex not stated) were instilled into in one eye with benzenamine, N-phenyl-, styrenated; the other eye was not treated and served as the control. Three rabbits had the test substance rinsed out of the eye with water and three rabbits did not. Mild eye irritation was noted in the eyes that were not rinsed.
Benzenamine, N-phenyl-, styrenated was slightly irritating to rabbit eyes in this study.

Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (CAS No. 68608-77-5)
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives was slightly irritating to the eye when tested in New Zealand white rabbits. Additional information was not provided.
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives was slightly irritating to rabbit eyes in this study.

Skin Irritation

Benzenamine, 4-octyl-N-(4-octylphenyl) (CAS No. 101-67-7)
New Zealand White rabbits (6/dose) were applied 0.5 g benzenamine, 4-octyl-N-(4-octylphenyl) as a finely ground powder moistened with water to the shaved dorsal area under occlusive conditions for 24 hours. Dermal irritation was scored by the Draize method and results were recorded 24, 48, 72 and 168 hours after application. No irritation was noted.
Benzenamine, 4-octyl-N-(4-octylphenyl) was not irritating to rabbit skin in this study.

Benzenamine, N-phenyl-, styrenated (CAS No. 68442-68-2)
Benzenamine, N-phenyl-, styrenated is not irritating to the skin. Study details were not provided.
Benzenamine, N-phenyl-, styrenated was not irritating to rabbit skin in this study.

Skin Sensitization

Benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene (CAS No. 184378-08-3)
In a guinea pig maximization test, Dunkin Hartley guinea pigs (10/dose) were administered benzenamine, N-phenyl-reaction product with 2,4,4-trimethylpentene and isobutylene as a 25% solution in either arachis oil BP or 25% in arachis oil BP in a 1:1 preparation of Freund's Complete Adjuvant in water via intradermal injection during the induction phase. .The application sites were evaluated at 24 and 48 hours. After 7 days, induction was initiated by applying undiluted test substance was applied to the same area as the previous injections on the clipped shoulder region and covered by an occlusive patch. On day 21, topical challenge proceeded with application of an undiluted test substance and a 75% solution (in arachis oil BP) to a clipped area and covered with an occlusive patch for 24 hours. No sensitization was observed.
Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene was not sensitizing in this test.

Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (CAS No. 68921-45-9)
In a patch test, volunteers (25/sex) were treated with benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene on the identical spots on the back for 24 hours every other day for 15 applications. Two weeks after the induction period, the sites were challenged with test material for 24 hours. A minimal transitory reaction was noted in three males and four females. No depigmentation was noted.
Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene was not considered to be a primary irritant, fatiguing agent or sensitizer in this test.

Conclusion: The acute oral toxicity of substituted diphenylamines category members to rats and acute dermal toxicity to rabbits is low; acute dermal toxicity to rats is moderate. The category members are not irritating to the skin but, slightly irritating to the eyes. Category members, benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene and benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, are not dermal sensitizers. Repeated oral exposures of benzenamine, N-phenyl-, styrenated to rats for 43-54 days resulted in increased activity of alkaline phosphatase and increased liver and adrenal weights in both sexes. Centrilobular hepatocyte hypertrophy in both sexes and follicular cell hypertrophy in thyroid glands of males were seen during histopathological examination. Repeated exposures to rats via the oral route of exposure to benzenamine, N-phenyl-, 2,4,4-trimethylpentene reaction products with styrene and isobutylene resulted in increased activities of aspartate aminotransferase and alkaline phosphatase activities; elevated activated partial thromboplastin time in both sexes; decreased platelet count in both sexes prior to mating; a reduction in total plasma protein, albumin and the albumin/globulin ratio in females in both sexes. Decreased gestation length and pre-implantation losses were seen in rats exposed to benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, and benzenamine, N-phenyl-, styrenated, respectively. For developmental toxicity, oral exposures of rats to benzenamine, N-phenyl-, styrenated and benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, resulted in mortality, decreased offspring weights and/or reduced surface righting response. Six category members were tested for mutagenicity in bacteria; none were mutagenic. Benzenamine, 4-octyl-N-(4-octylphenyl) did not induce chromosomal aberrations tested *in vitro*. Benzenamine, 4-octyl-N-(4-octylphenyl) and benzenamine, N-phenyl-, styrenated did not induce chromosomal aberrations *in vivo*.

The potential health hazard of the substituted diphenylamines category is moderate based on the repeated-dose, reproductive and developmental toxicity of two category members.

Table 3. Summary of Human Health Data								
Endpoints	**Benzenamine, N-phenyl-, styrenated (68442-68-2)**	**Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethyl-pentene (68921-45-9)**	**Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethyl-pentene (68411-46-1)**	**Benzenamine, N-phenyl- reaction product with 2,4,4-trimethyl-pentene and isobutylene (184378-08-3)**	**Benzenamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)**	**Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7)**	**Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)**	**Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**> 500 – > 20,000**	No Data > 500 (RA)	No Data > 2000 (RA)	**> 2000**	No Data > 7940 (RA)	**> 7940**	No Data > 7940 (RA)	**> 34,600**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**> 10,000**	No Data > 7940 1347 - 1915 (RA)	No Data > 7940 1347 - 1915 (RA)	No Data > 7940 1347 - 1915 (RA)	No Data > 7940 1347 - 1915 (RA)	**> 7940** **1347 - 1915**	No Data > 7940 **1347 - 1915** (RA)	**> 3000**
Repeated-Dose Toxicity NOAEL/LOAEL (mg/kg-bw/day)	**NOAEL = 250** **LOAEL = 600**	**NOAEL = Not established** **LOAEL ~ 125**	No Data NOAEL(f) = 5 LOAEL(f) = 25 NOAEL(m) = 25 LOAEL(m) = 125 (RA)	**NOAEL(f) = 5** **LOAEL(f) = 25** **NOAEL(m) = 25** **LOAEL(m) = 125**	No Data NOAEL(f) = 5 LOAEL(f) = 25 NOAEL(m) = 25 LOAEL(m) = 125 (RA)	No Data NOAEL(f) = 5 LOAEL(f) = 25 NOAEL(m) = 25 LOAEL(m) = 125 (RA)	No Data NOAEL(f) = 5 LOAEL(f) = 25 NOAEL(m) = 25 LOAEL(m) = 125 (RA)	No Data NOAEL(f) = 5 LOAEL(f) = 25 NOAEL(m) = 25 LOAEL(m) = 125 (RA)
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)	**NOAEL = 250** **LOAEL = 600**	No Data NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 25 LOAEL = 125 (RA)	**NOAEL = 25** **LOAEL = 125**	No Data NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 25 LOAEL = 125 (RA)
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) **Maternal Toxicity** **Developmental Toxicity**	**NOAEL = 250** **LOAEL = 600** **NOAEL = 250** **LOAEL = 600**	No Data NOAEL = 5 LOAEL = 25 NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 5 LOAEL = 25 NOAEL = 25 LOAEL = 125 (RA)	**NOAEL = 5** **LOAEL = 25** **NOAEL = 25** **LOAEL = 125**	No Data NOAEL = 5 LOAEL = 25 NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 5 LOAEL = 25 NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 5 LOAEL = 25 NOAEL = 25 LOAEL = 125 (RA)	No Data NOAEL = 5 LOAEL = 25 NOAEL = 25 LOAEL = 125 (RA)
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**	**Negative**	No Data Negative (RA)	**Negative**	No Data Negative (RA)	**Negative**	No Data Negative (RA)	**Negative**

Table 3. Summary of Human Health Data								
Endpoints	**Benzenamine, N-phenyl-, styrenated (68442-68-2)**	**Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethyl-pentene (68921-45-9)**	**Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethyl-pentene (68411-46-1)**	**Benzenamine, N-phenyl- reaction product with 2,4,4-trimethyl-pentene and isobutylene (184378-08-3)**	**Benzenamine, 4-(1-methyl-1-phenylethyl)-N-4[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)**	**Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7)**	**Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)**	**Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)**
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	**Negative**	No Data Negative (RA)	No Data Negative (RA)
Genetic Toxicity – Other DNA damage and repair (*in vitro*)	**Negative**	**—***	**—***	**—***	**—***	**—***	**—***	**—***
Mouse micronucleus (*in vivo*)	**Negative**	**—***	**—***	**—***	**—***	**—***	**—***	**—***
Sister chromatid exchange	**—***	**—***	**—***	**—***	**—***	**Negative**	**—***	**—***
Additional Information Skin Irritation	**Slightly irritating**	**Not irritating**	**—***	**—***	**—***	**Not irritating**	**—***	**—***
Eye Irritation	**Slightly irritating**	**—***	**—***	**—***	**—***	**Slightly irritating**	**—***	**Slightly irritating**
Sensitization	**—***	**Negative**	**—***	**Negative**	**—***	**—***	**—***	**—***

Measured data in bold text; (RA) = Read Across; (f) = females; (m) = males; – indicates endpoint was not addressed for this chemical; * indicates endpoint is not included in the base data set under the HPV Challenge Program.

4. Hazard Characterization

The log K_{ow} values of the substituted diphenylamines category members are high. However, the low water solubility for many of the category members suggests the potential for these chemicals to bioaccumulate is low. The substituted diphenylamines category members are not readily biodegradable, indicating that they have the potential to persist in the environment.

The aquatic toxicity data submitted were difficult to interpret because they were generated in the presence of solvent(s), the concentration of chemical in the test water was not measured and/or effects concentrations reported were above the chemical's water solubility limit. The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that for most category members acute hazard is expected to be low based on observed effects occurring at concentrations in great excess of the water solubility limit. However, a fish test conducted with the most soluble category member and without solvents indicates that some of the category members that are soluble or miscible in water may have the potential to cause chronic effects. Subsequent consideration of fate and exposure information will inform a determination of the need to obtain the chronic aquatic toxicity data.

The acute oral toxicity of substituted diphenylamines category members to rats and acute dermal toxicity to rabbits is low; acute dermal toxicity to rats is moderate. The category members are not irritating to the skin but, slightly irritating to the eyes. Category members, benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene and benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, are not dermal sensitizers. Repeated oral exposures of benzenamine, N-phenyl-, styrenated to rats for 43-54 days resulted in increased activity of alkaline phosphatase and increased liver and adrenal weights in both sexes. Centrilobular hepatocyte hypertrophy in both sexes and follicular cell hypertrophy in thyroid glands of males were seen during histopathological examination. Repeated exposures to rats via the oral route of exposure to benzenamine, N-phenyl-, 2,4,4-trimethylpentene reaction products with styrene and isobutylene resulted in increased activities of aspartate aminotransferase and alkaline phosphatase activities; elevated activated partial thromboplastin time in both sexes; decreased platelet count in both sexes prior to mating; a reduction in total plasma protein, albumin and the albumin/globulin ratio in females in both sexes. Decreased gestation length and pre-implantation losses were seen in rats exposed to benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, and benzenamine, N-phenyl-, styrenated, respectively. For developmental toxicity, oral exposures of rats to benzenamine, N-phenyl-, styrenated and benzenamine, N-phenyl- reaction product with 2,4,4-trimethylpentene and isobutylene, resulted in mortality, decreased offspring weights and/or reduced surface righting response. Six category members were tested for mutagenicity in bacteria; none were mutagenic. Benzenamine, 4-octyl-N-(4-octylphenyl) did not induce chromosomal aberrations tested *in vitro*. Benzenamine, 4-octyl-N-(4-octylphenyl) and benzenamine, N-phenyl-, styrenated did not induce chromosomal aberrations *in vivo*.

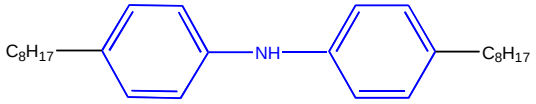
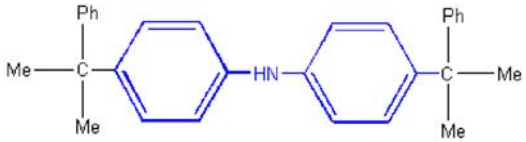
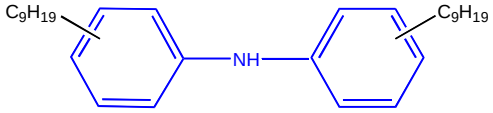
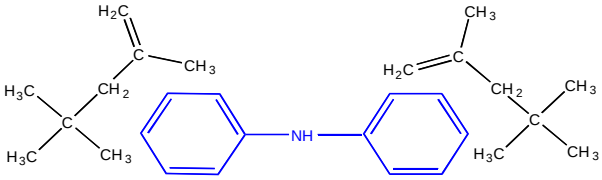
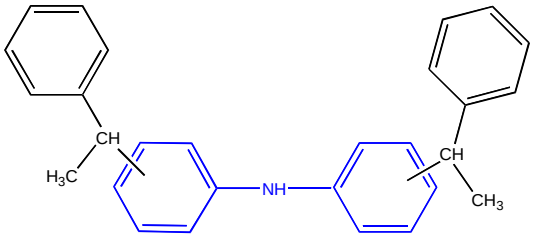
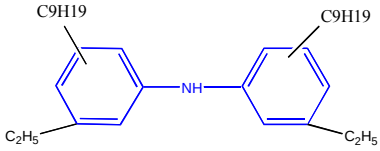
The potential health hazard of the substituted diphenylamines category is moderate based on the repeated-dose, reproductive and developmental toxicity of two category members.

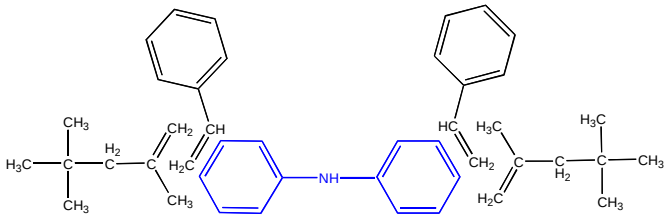
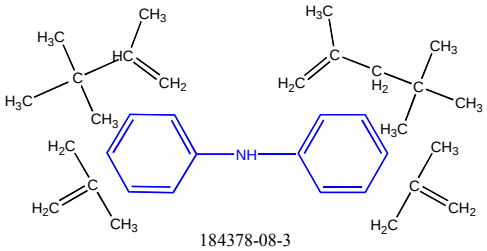
5. Data Gaps

No data gaps have been identified under the HPV Challenge Program.

Appendix

Mononitrogen (N) containing with various degrees of phenyl or alkyl substitution:
Ph-NH-Ph
R-Ph-NH-Ph-R'
Where:
Ph = phenyl;
R,R' =butyl derivatives, octyl-derivatives, nonyl-derivatives, styrenyl-derivatives

Substituted Diphenylamines Category Members		
CAS No.	**Chemical Name**	**Structure**
SPONSORED CHEMICALS		
101-67-7	**Benzenamine, 4-octyl-N-(4-octylphenyl)-**	 101-67-7
10081-67-1	**Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]-**	 10081-67-1
36878-20-3	**Benzenamine, ar-nonyl-N-(nonylphenyl)- mixed dinonyldiphenylamines**	 36878-20-3
68411-46-1	**Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene**	 68411-46-1 [Ring attachment at #2 carbon]
68442-68-2	**Benzenamine, N-phenyl-, styrenated**	 68442-68-2
68608-77-5	**Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives**	 68608-77-5 [alkylation reaction of diethydiphenylamine with propylene trimer]

Substituted Diphenylamines Category Members		
CAS No.	**Chemical Name**	**Structure**
SPONSORED CHEMICALS		
68921-45-9	**Benzenamine, N-phenyl, reaction products with Styrene and 2,4,4-trimethylpentene**	 68921-45-9 [Ring attachment at #2 carbon]
184378-08-3	**Benzenamine, N-phenyl, reaction products with 2,4,4-trimethylpentene and isobutylene**	 184378-08-3 [Ring attachment at #2 carbon]