

SCREENING-LEVEL HAZARD CHARACTERIZATION

Substituted *p*-Phenylenediamines Category

SUB-CATEGORY I: N-ALKYLATED *p*-PHENYLENEDIAMINES

SPONSORED CHEMICALS

<i>p</i> -Phenylenediamine, N,N-di- <i>sec</i> -butyl	CASRN 101-96-2
<i>p</i> -Phenylenediamine, N,N-bis(1,4-dimethylpentyl)	CASRN 3081-14-9

SUB-CATEGORY II: 4-AMINODIPHENYLAMINE DERIVATIVES

SPONSORED CHEMICALS

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives	CASRN 68953-84-4
<i>p</i> -Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl-	CASRN 3081-01-4
<i>p</i> -Phenylenediamine, N-(1-methylheptyl)-N'-phenyl-	CASRN 15233-47-3

SUPPORTING CHEMICALS

<i>p</i> -Phenylenediamine, N-isopropyl-N'-phenyl-, [CA Index Name: 1,4-Benzenediamine, N1-(1-methylethyl)-N4-phenyl-]	CASRN 101-72-4
<i>p</i> -Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl [CA Index Name: 1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl-]	CASRN 793-24-8

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

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

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>.

The evaluation is performed according to established EPA guidance³ and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

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

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

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

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p style="text-align: center;"><u>Sponsored Chemicals</u> Subcategory I</p> <p style="text-align: center;">101-96-2 3081-14-9</p> <p style="text-align: center;">Subcategory II</p> <p style="text-align: center;">68953-84-4 3081-01-4 15233-47-3</p> <p style="text-align: center;"><u>Supporting Chemicals</u> 101-72-4 793-24-8</p>
<p>Chemical Abstract Index Name</p>	<p style="text-align: center;"><u>Sponsored Chemicals</u> <u>Subcategory I</u></p> <p style="text-align: center;">1,4-Benzenediamine, N1,N4-bis(1-methylpropyl)- 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)-</p> <p style="text-align: center;">Subcategory II</p> <p style="text-align: center;">1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives 1,4-Benzenediamine, N1-(1,4-dimethylpentyl)-N4-phenyl- 1,4-Benzenediamine, N1-(1-methylheptyl)-N4-phenyl-</p> <p style="text-align: center;"><u>Supporting Chemicals</u> 1,4-Benzenediamine, N1-(1-methylethyl)-N4-phenyl- 1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl-</p>
<p>Structural Formula</p>	<p style="text-align: center;">See Appendix</p>
<p style="text-align: center;">Summary</p> <p>The p-Phenylenediamines Category comprises five substituted p-phenylenediamines that are used as antioxidants/antiozonants in rubber, fuel additives, or in monomer distillation. For human health effects, the category is divided into two subcategories. The Subcategory I contains two dialkyl substituted p-phenylenediamines; the Subcategory II contains one diaryl substituted p-phenylenediamine and two mixed alkyl/aryl substituted p-phenylenediamines. The two supporting chemicals are mixed alkyl/aryl substituted phenylenediamines.</p> <p>The members of this category are solids or liquids possessing low to moderate vapor pressure and low to moderate water solubility. Category members are expected to possess low to moderate mobility in soil. Volatilization is expected to be moderate to low. Due to their antioxidant properties, members of this category react rapidly with oxygen. Abiotic transformation in water, sometimes characterized as hydrolysis, is likely to be a chemical</p>	

oxidation process and occurs at a moderate-to-rapid rate. The rate of atmospheric photooxidation is rapid. The members of the p-phenylenediamines category are expected to possess low persistence (P1) and low to moderate bioaccumulation potential (B1–B2).

Human Health Hazard

Subcategory I: N-Alkylated p-Phenylenediamines

The acute oral toxicity of CASRN 101-96-2 to rats is moderate while that for CASRN 3081-14-9 is low. The acute dermal toxicity of CASRN 101-96-2 and 3081-14-9 to rabbits is low. The acute inhalation toxicity of CASRN 101-96-2 to rats is low.

Repeated administration of CASRN 101-96-2 via oral gavage to rats for 28 days resulted in increased liver weights and elevation of serum enzymes with a dose-dependent increase in the incidence of hepatocellular lesions indicative of hepatocellular damage at 10 mg/kg bw/day; the NOAEL is not determined. Following 90 days of dietary exposure of CASRN 3081-14-9 to rats, adverse effects included reduced mean body weight and body weight gain at ≥ 22.82 mg/kg-bw/day in males and at all doses in females. Increased alkaline phosphatase levels at high doses in males and females and decreased serum glutamic pyruvic transaminase levels in females were seen at ≥ 45.65 mg/kg-bw/day; however, there were no accompanying histopathological changes. For females, the LOAEL is ~ 22.82 mg/kg-bw/day; NOAEL is not established. For males, the NOAEL is ~ 9.13 mg/kg-bw/day (lowest dose tested).

There was no adequate reproductive toxicity study; however, no effects were reported on reproductive organs in the 90-day repeated exposure study, mentioned above, and no developmental effects were reported in the pre-natal developmental toxicity study.

A prenatal developmental toxicity study in rats of CASRN 3081-14-9 resulted in no adverse fetus effects; the NOAEL is 150 mg/kg-bw/day (highest dose tested). In this study the maternal toxicity NOAEL is 25 mg/kg-bw/day, based on effects seen at ≥ 75 mg/kg/day (survival, behavior and body weight gain). CASRN 3081-14-9 did not induce gene mutations in bacteria and mammalian cells *in vitro*. No data are available on chromosomal aberrations. CASRN 101-96-2 is corrosive to the rabbit skin and eyes and sensitizing to guinea pigs, while CASRN 3081-14-9 is irritating to the rabbit skin and eyes and sensitizing to guinea pigs.

The genetic toxicity (chromosomal aberrations) endpoint was identified as a data gap for subcategory I under the HPV Challenge Program.

Subcategory II: 4-Aminodiphenylamine Derivatives

The acute oral toxicity of CASRN 68953-84-4 and 3081-01-4 to rats is low, while the acute oral toxicity of CASRN 15233-47-3 to rats is high. The acute inhalation toxicity of CASRN 3081-01-4 to rats is high. The acute dermal toxicity of CASRN 68953-84-4, 3081-01-4 and 15233-47-3 to rabbits is low.

Repeated administration of CASRN 68953-84-4 to rats via the diet for 28 days resulted in

macrocytic anemia at ≥ 30 mg/kg-bw/day; the NOAEL is 7.5 mg/kg-bw/day. Repeated administration of CASRN 3081-01-4 to rats via the diet for 28 days resulted in no adverse effects; the NOAEL is ~ 273.89 mg/kg-bw/day (highest dose tested).

In a two generation reproductive toxicity study, dietary administration of CASRN 68953-84-4 to rats resulted in increased dystocia, perinatal deaths, decreased live births and increased pup weights at $\geq \sim 8.78$ mg/kg-bw/day; a NOAEL for reproductive toxicity is not established. In this study, exposure at $\geq \sim 8.78$ mg/kg-bw/day resulted in polycystic kidney lesions in parental animals; NOAEL for systemic toxicity is not established.

A prenatal developmental toxicity of CASRN 68953-84-4 in rats resulted in no treatment-related effects on pregnancy rates, litter sizes, number of live fetuses, uterine implantation or any gestational parameters. A linear dose-related trend for decreased fetal body weight was observed with an approximate 5% decrease at the highest dose, 200 mg/kg-bw/day; the NOAEL for developmental toxicity is not established. In maternal rats, exposure to 200 mg/kg-bw/day resulted in reduced body weight and food consumption; the maternal toxicity NOAEL is 70 mg/kg-bw/day.

CASRN 68953-84-4 induced gene mutation in bacteria *in vitro*, but CASRNs 3081-01-4 and 15233-47-3 did not. CASRN 3081-01-4 was weakly positive in mammalian cells *in vitro*. CASRNs 68953-84-4 and 3081-01-4 did not induce chromosomal aberrations in bone marrow erythrocytes mice or rats *in vivo*. CASRN 3081-01-4 is not irritating to rabbit skin. CASRN 68953-84-4 and CASRN 15233-47-3 are irritating to the rabbit skin. CASRNs 68953-84-4, 3081-01-4 and 15233-47-3 are irritating to rabbit eyes. CASRN 68953-84-4 is a contact sensitizer in guinea pigs.

No data gaps were identified for subcategory II under the HPV Challenge Program.

Environmental Effects – Aquatic Toxicity

The 96-hour LC₅₀ of CASRN 101-96-2 for fish ranges from 0.13 to 0.18 mg/L. The 96-hour LC₅₀ of CASRN 3081-14-9 for fish ranges from 0.032 to 0.28 mg/L. The 96-hour LC₅₀ for CASRN 3081-01-4 for fish ranges from 0.06 to 1.10 mg/L.

The 48-hour EC₅₀ of CASRN 3081-14-9 for aquatic invertebrates is 0.37 mg/L. The 48-hour EC₅₀ of CASRN 68953-84-4 for aquatic invertebrates is 0.36 mg/L.

The 96-hour EC₅₀ of CASRN 68953-84-4 for aquatic plants is 0.018 mg/L (biomass) and 0.079 mg/L (growth rate). The 96-hour EC₅₀ for CASRN 3081-01-4 for aquatic plants is 0.7 mg/L (biomass and growth rate). The 28-day LC₅₀ of CASRN 793-24-8 for fish ranges from 0.15 to 0.067 mg/L.

No data gaps were identified for environmental effects under the HPV Challenge Program.

The sponsor, Rubber and Plastic Additives Panel of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the substituted *p*-phenylenediamines category on December 13, 2001. EPA comments on the original submission were posted to the website on November 21, 2002. The sponsor submitted updated/revised documents on July 17, 2003 and EPA posted the submission on the ChemRTK HPV Challenge website August 7, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/sbphnyld/c13383tc.htm>). The sponsor submitted further updated/revised documents on July 17, 2003, which were posted to the ChemRTK website on October 29, 2003. The members of the category are listed in the Appendix.

Category Justification

The five members of the substituted *p*-phenylenediamines category have been defined by the sponsor based on the physicochemical properties and structural similarities. All materials in this category are phenylenediamines with various substituent groups that are always in the para position of the aromatic ring. The substituent groups may be all alkyl, all aryl or mixed alkyl/aryl. All category members are highly-colored (dark brown, purple, reddish or black) solids or semi-viscous liquids intended for use as antidegradants in dark-colored or black finished rubber articles or functional fluids. The use of these materials requires that they be stable under high temperatures. Their low volatility is due to their low vapor pressure and semi-viscous or solid form. The existing information for these materials indicates that they have very low water solubility and high flash points.

The category was further divided into two subcategories: subcategory I, N-alkylated *p*-phenylenediamines, which contains compounds with alkyl substituents only, and subcategory II, 4-aminodiphenylamine derivatives, which contains either a mixture of alkyl/aryl or aryl-only substituents. The N-alkylated *p*-phenylenediamines subcategory includes *p*-phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2) and *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9). The 4-aminodiphenylamine derivatives subcategory includes 1,4-benzenediamine, N,N'-mixed phenyl and tolyl derivatives (CASRN 68953-84-4), *p*-phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4) and *p*-phenylenediamine N-(1-methylheptyl)-N'-phenyl- (CASRN 15233-47-3).

Justification for Supporting Chemicals

Although the sponsor included data on two chemicals, *p*-phenylenediamine, N-isopropyl-N'-phenyl-, (CASRN 101-72-4) and *p*-phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8), to support the 4-aminodiphenylenediamine derivative subgroup category members for ecotoxicity and mammalian toxicity endpoints; only CASRN 793-24-8 was used to support the chronic value for ecotoxicity. The supporting chemicals are similar in structure and exhibit physicochemical properties and toxicity similar to the sponsored chemicals. EPA considered them appropriate for use as supporting chemicals.

1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2003 Test Plan and Robust Summary. The materials within the Substituted p-Phenylenediamines category, for the purposes of the HPV Program, are defined as phenylenediamines with alkyl, aryl or mixed alkyl-aryl substitutions. Test substance purity, when noted in the Robust Summaries, is given usually as >95%.

1.2 Physical-Chemical Properties

The physical-chemical properties of the members of the p-phenylenediamines category are summarized in Table 1. The structures of the compounds are provided in the Appendix.

The members of p-phenylenediamines category are solids or liquids possessing low to moderate vapor pressure and low to moderate water solubility

Table 1. Physical-Chemical Properties of p-Phenylenediamines¹

Property	Subcategory I: N-Alkylated <i>p</i> -Phenylenediamines		Subcategory II: 4-Aminodiphenylamine Derivatives			SUPPORTING CHEMICAL 1,4- Benzenediamine, N1-(1-methylethyl)- N4-phenyl-	SUPPORTING CHEMICAL 1,4- Benzenediamine, N1-(1,3- dimethylbutyl)-N4- phenyl-
	SPONSORED CHEMICAL 1,4- Benzenediamine, N1,N4-bis(1- methylpropyl)-	SPONSORED CHEMICAL 1,4- Benzenediamine, N1,N4-bis(1,4- dimethylpentyl)-	SPONSORED CHEMICAL 1,4- Benzenediamine, N,N'-mixed Ph and tolyl derivs.	SPONSORED CHEMICAL 1,4- Benzenediamine, N1-(1,4- dimethylpentyl)- N4-phenyl-	SPONSORED CHEMICAL 1,4- Benzenediamine, N1-(1- methylheptyl)-N4- phenyl-		
CASRN	101-96-2	3081-14-9	68953-84-4	3081-01-4	15233-47-3	101-72-4	793-24-8
Molecular Weight	220.36	304.52	260.34–288.40	282.43	296.46	226.32	268.41
Physical State	Liquid	Liquid	Solid	Oil/low melting solid	Liquid	Solid	Solid
Melting Point	18°C (measured) ²	-36°C (measured)	90–105°C (measured)	29.8°C (measured)	<25°C (liquid)	75–80°C (measured)	46–50°C (measured)
Boiling Point	98°C at 0.2 mm Hg (measured) ² 307°C at 760 mm Hg (estimated) ³	377°C at 760 mm Hg (measured) ⁴ 183°C at 1 mm Hg (measured)	398°C at 760 mm Hg (estimated) ⁵	231°C at 3.5 mm Hg (measured) 406°C at 760 mm Hg (estimated) ³	431°C (measured)	161°C at 1 mm Hg (measured) ² 353°C at 760 mm Hg (estimated) ³	164°C at 1 mm Hg (measured) ⁶ 357°C at 760 mm Hg (estimated) ³
Vapor Pressure	6.6×10 ⁻⁴ mm Hg at 25°C (estimated) ³	1.1×10 ⁻⁵ mm Hg at 25°C (measured)	<1.1×10 ⁻⁷ mm Hg at 25°C (estimated) ⁵	7×10 ⁻⁷ mm Hg at 25°C (estimated) ³	1.4×10 ⁻⁷ mm Hg at 25°C (estimated) ³	3.2×10 ⁻⁵ mm Hg at 25°C (estimated) ³	2.4×10 ⁻⁵ mm Hg at 25°C (estimated) ³
Water Solubility	95.8 mg/L at 25°C (estimated) ⁵	0.148 mg/L at 25°C (estimated) ⁵ 21 mg/L at pH 5 at 22°C; 0.8 mg/L at pH 9 at 22°C (measured) ^{1,7}	0.50–7.35 mg/L at 25°C (estimated) ⁵	0.67 mg/L at 25°C (measured) ^{1,7}	0.163 mg/L at 25°C (estimated) ⁵	7.6 mg/L at pH 7 at 25°C (measured) ^{1,7}	1.9 mg/L at 25°C (measured) ^{1,7}
Dissociation constants (pK _a)	6.03 (estimated) ⁸	6.12 (estimated) ⁸	0.23–0.76 (estimated)	pK _{a1} = 1.73 pK _{a2} = 4.99 (estimated) ⁸	pK _{a1} = 1.74 pK _{a2} = 4.97 (estimated) ⁸	pK _{a1} = 1.74 pK _{a2} = 4.97 (estimated) ⁸	pK _{a1} = 1.73 pK _{a2} = 5.01 (estimated) ⁸

Property	Subcategory I: N-Alkylated p-Phenylenediamines		Subcategory II: 4-Aminodiphenylamine Derivatives			SUPPORTING CHEMICAL 1,4-Benzenediamine, N1-(1-methylethyl)-N4-phenyl-	SUPPORTING CHEMICAL 1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl-
	SPONSORED CHEMICAL 1,4-Benzenediamine, N1,N4-bis(1-methylpropyl)-	SPONSORED CHEMICAL 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)-	SPONSORED CHEMICAL 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs.	SPONSORED CHEMICAL 1,4-Benzenediamine, N1-(1,4-dimethylpentyl)-N4-phenyl-	SPONSORED CHEMICAL 1,4-Benzenediamine, N1-(1-methylheptyl)-N4-phenyl-		
Henry's Law constant	4.7×10^{-6} atm-m ³ /mole (estimated) ⁵	8.1×10^{-5} atm-m ³ /mole (estimated) ⁵	2.5×10^{-8} to 4.0×10^{-8} atm-m ³ /mole (estimated) ⁵	1.3×10^{-6} atm-m ³ /mole (estimated) ⁵	2.0×10^{-7} atm-m ³ /mole (estimated) ⁵	2.7×10^{-6} atm-m ³ /mole (estimated) ⁵	5.4×10^{-6} atm-m ³ /mole (estimated) ⁵
Log K _{ow}	3.50 (estimated) ⁵	5.34 (measured) ^{1,7}	3.37–4.28 (measured) ^{1,7}	5.17 (estimated) ⁵	5.74 (estimated) ⁵	3.88 (measured) ^{1,7}	4.77 (measured) ^{1,7}

¹The American Chemistry Council. 2003. Revised Test Plan and Robust Summary for p-Phenylenediamines. The Rubber and Plastic Additives Panel, American Chemistry Council. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/sbphnyld/c13383tc.htm> as of February 28, 2011.

²SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available online at <http://www.syrres.com/esc/physprop.htm> as of February 28, 2011.

³NOMO5. 1987. Programs to enhance PC-Gems estimates of physical properties for organic compounds. The Mitre Corp.

⁴Dorf Ketal Chemicals. 2004. Material Safety Data Sheet for UOP – 788 ANTIOZONANT. Available online at http://www.dorketal.com/MSDS/MSDS_UOP/MSDS_UOP788.pdf as of February 28, 2011.

⁵U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of February 28, 2011.

⁶National Institute of Technology and Evaluation. 2002. Chemical Risk Information Platform (CHRIP). Available online at <http://www.safe.nite.go.jp/english/db.html> as of February 28, 2011.

⁷The rapid rate of oxidation in water may interfere with the accuracy of these measurements.

⁸pK_a values were calculated for loss of a proton from the protonated amines using SPARC pKa/property server. Ver. 4.5 Sept. 2009 [available online at <http://ibmlc2.chem.uga.edu/sparc/> as of February 28, 2011]. In the case of multiple pK_a values, the lower values are for nitrogens between the two phenyl groups.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

The Phenylene diamines category chemicals had an aggregated production and/or import volume in the United States between 13 million pounds and 80 million pounds in calendar year 2005.

- CASRN 101-96-2: 1 million to <10 million pounds
- CASRN 3081-14-9: 1 million to <10 million pounds
- CASRN 68953-84-4: 10 million to <50 million pounds
- CASRN 3081-01-4: 1 million to <10 million pounds

CASRN 15233-47-3 was not reported in the 2006 IUR.

CASRN 101-96-2 and 3081-14-9:

Industrial processing and uses of these chemicals are claimed confidential. No commercial and consumer uses were reported for these chemicals.

CASRN 68953-84-4:

Non-confidential information in the IUR indicated that the industrial processing and uses for the chemical include rubber and plastics hoses and belting manufacturing, tire manufacturing, and resin and synthetic rubber manufacturing as stabilizers. Commercial and consumer uses of this chemical are claimed confidential.

CASRN 3081-01-4:

Industrial processing and uses, and commercial and consumer uses of this chemical are claimed confidential.

2.2 Environmental Exposure and Fate

The members of the p-phenylenediamines category and the supporting chemicals are expected to possess low to moderate mobility in soil. 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)- (CASRN 3081-14-9) was 50% biodegraded in 35 days in a carbon dioxide evolution shake flask procedure using an adapted sewage/soil/sludge mixture as inoculum. 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs. (CASRN 68953-84-4) achieved 0 and 0.64% degradation in separate manometric respirometry tests (OECD 301F) over 28 days. No mineralization of 1,4-benzenediamine, N1-(1,4-dimethylpentyl)-N4-phenyl- was observed over 35 days in a test identical to ASTM Draft 3 Proposed Standard Practice for the Determination of the Ultimate Biodegradation of Organic Chemicals (1980). 1,4-Benzenediamine, N1-(1-methylheptyl)-N4-phenyl- (CASRN 15233-47-3) was found to be not readily biodegradable in a MITI test (OECD 301C) after achieving only 4% of the theoretical biochemical oxygen demand (BOD) in 28 days. However, during the course of the MITI test, 1,4-benzenediamine, N1-(1-methylheptyl)-N4-phenyl- was observed to hydrolyze to 1-methylheptylamine, aniline, 4-hydroxydiphenylamine, and benzoquinoneimine-N-phenyl; these break-down products were not attributed to

biodegradation. In a similar MITI test involving supporting chemical 1,4-benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl- (CASRN 793-24-8), only 2% of the theoretical BOD was achieved, but the test substance was observed to breakdown to 1,3-dimethylbutylamine, aniline, 4-hydroxydiphenylamine, and benzoquinoneimine-N-phenyl during the course of the test. Supporting chemical 1,4-benzenediamine, N1-(1-methylethyl)-N4-phenyl- (CASRN 101-72-4) achieved only 18.9% of theoretical CO₂ evolution after 32 days in a shake flask procedure. Volatilization is expected to be low to moderate given the estimated Henry's Law constants for these substances and the fact that these substances will partially exist as cations under environmental conditions, which do not volatilize. The members of this category are antiozonants/antioxidants and react very quickly with oxygen. Therefore, fast oxidation in dilute solutions where oxygen is readily available occurs readily. The initial oxidation products are quinondiimines, which are very reactive species. The quinondiimine can hydrolyze or form a polymer by further oxidation, giving very complicated mixtures of products. 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)- (CASRN 3081-14-9) was degraded 97% in water after 24 hours at pH 7 at 25°C. 1,4-Benzenediamine, N1-(1,4-dimethylpentyl)-N4-phenyl- (CASRN 3081-01-4) underwent 96% degradation in 24 hours at pH 7 at 25°C. The hydrolysis half-lives for supporting chemical 1,4-benzenediamine, N1-(1-methylethyl)-N4-phenyl- (CASRN 101-72-4) in purified water, membrane-filtered river water, and unfiltered river water were reported as 11, 5, and 2 hours, respectively. Supporting chemical 1,4-benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl- (CASRN 793-24-8) underwent 93% degradation in water after 24 hours at pH 7 at 25°C. The members of the p-phenylenediamines category are expected to possess low persistence (P1) and low to moderate bioaccumulation potential (B1–B2).

The environmental fate properties are provided in Table 2.

Table 2. Environmental Fate Characteristics of p-Phenylenediamines¹							
Property	Subcategory I: N-Alkylated p-Phenylenediamines		Subcategory II: 4-Aminodiphenylamine Derivatives			SUPPORTING CHEMICAL 1,4-Benzenediamine, N1-(1-methylethyl)-N4-phenyl-	SUPPORTING CHEMICAL 1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl-
	SPONSORED CHEMICAL 1,4-Benzenediamine, N1,N4-bis(1-methylpropyl)-	SPONSORED CHEMICAL 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)-	SPONSORED CHEMICAL 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs.	SPONSORED CHEMICAL 1,4-Benzenediamine, N1-(1,4-dimethylpentyl)-N4-phenyl-	SPONSORED CHEMICAL 1,4-Benzenediamine, N1-(1-methylheptyl)-N4-phenyl-		
CASRN	101-96-2	3081-14-9	68953-84-4	3081-01-4	15233-47-3	101-72-4	793-24-8
Photodegradation Half-life	1.1 hours (estimated) ²	1.0 hours (estimated) ²	0.64 hours (estimated) ²	0.56 hours (estimated) ²	0.56 hours (estimated) ²	0.59 hours (estimated) ²	0.57 hours (estimated) ²
Hydrolysis Half-life	No data	97% hydrolysis after 24 hours at pH 7.0 at 25°C	No data	96% hydrolysis in 24 hours at pH 7.0 at 25°C	No data	99% hydrolysis in 24 hours at pH 7.0 at 25°C; 50% loss in Mississippi River water in 2.5 hours; Half-life = 11, 5, and 2 hours in purified water, membrane-filtered river water, and unfiltered river water, respectively ³	93% hydrolysis in 24 hours at pH 7.0 at 25°C
Biodegradation	No data	50% in 35 days (inherently biodegradable)	0–0.64% in 28 days (not readily biodegradable)	0% in 35 days (not readily biodegradable)	4% in 28 days (not readily biodegradable) ⁴	18.9% after 32 days (not readily biodegradable)	2% after 28 days (not readily biodegradable) ⁴ 7.2% after 32 days (not readily biodegradable)

Table 2. Environmental Fate Characteristics of p-Phenylenediamines¹

Property	Subcategory I: N-Alkylated <i>p</i> -Phenylenediamines		Subcategory II: 4-Aminodiphenylamine Derivatives			SUPPORTING CHEMICAL 1,4-Benzenediamine, N1-(1-methylethyl)- N4-phenyl-	SUPPORTING CHEMICAL 1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl-
	SPONSORED CHEMICAL 1,4-Benzenediamine, N1,N4-bis(1-methylpropyl)-	SPONSORED CHEMICAL 1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)-	SPONSORED CHEMICAL 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs.	SPONSORED CHEMICAL 1,4-Benzenediamine, N1-(1,4-dimethylpentyl)- N4-phenyl-	SPONSORED CHEMICAL 1,4-Benzenediamine, N1-(1-methylheptyl)-N4-phenyl-		
Bioconcentration	BAF = 126 (estimated) ²	BAF = 1,620 (estimated) ²	BAF = 179–2,682 (estimated) ² BCF <5,000–7,000 (measured) ^{1,5}	BAF = 493 (estimated) ²	BAF = 775 (estimated) ²	BAF = 179 (estimated) ²	BAF = 375 (estimated) ²
Log K _{oc}	3.12 (estimated) ²	4.53 (estimated) ²	4.72–5.13 (estimated) ²	4.62 (estimated) ²	4.96 (estimated) ²	3.63 (estimated) ²	4.36 (estimated) ²
Fugacity (Level III Model) ²							
Air (%)	0.1	0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Water (%)	15.3	12.3	4.0–7.7	9.6	7.8	12.0	10.8
Soil (%)	83.5	66.0	60.1–70.2	67.9	56.0	84.1	75.0
Sediment (%)	1.1	21.7	22.1–35.8	22.5	36.2	3.0	14.2
Persistence ⁶	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation ⁶	B1 (low)	B2 (moderate)	B1 (low) to B2 (moderate)	B1 (low)	B1 (low)	B1 (low)	B1 (low)

¹ The American Chemistry Council. 2003. Revised Test Plan and Robust Summary for p-Phenylenediamines. The Rubber and Plastic Additives Panel, American Chemistry Council. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/sbphnyld/c13383tc.htm> as of February 28, 2011.

² U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episutedl.htm> as of February 28, 2011.

³ OECD SIDS. 2000. SIDS Initial Assessment Report for N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD). Available online at <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/101-72-4.pdf> as of February 28, 2011.

⁴ National Institute of Technology and Evaluation. 2002. Biodegradation and bioaccumulation of the existing chemical substances under the Chemical Substances Control Law. Available online at http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of March 7, 2011.

⁵ This study was conducted using a co-solvent, and since the test product was a mixture, bioconcentration factors (BCFs) were calculated by using individual data points, including those prior to reaching steady-state.

⁶ Federal Register. 1999. Category for persistent, bioaccumulative, and toxic new chemical substances. Federal Register 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: The p-Phenylenediamines Category comprises five substituted p-phenylenediamines that are used as antioxidants/antiozonants in rubber, fuel additives, or in monomer distillation. The first subcategory contains two dialkyl substituted p-phenylenediamines; the second subcategory contains one diaryl substituted p-phenylenediamine and two mixed alkyl/aryl substituted p-phenylenediamines. The two supporting chemicals are mixed alkyl/aryl substituted phenylenediamines. The members of this category are solids or liquids possessing low to moderate vapor pressure and low to moderate water solubility. Category members are expected to possess low to moderate mobility in soil. Volatilization is expected to be moderate to low. Due to their antioxidant properties, members of this category react rapidly with oxygen. Abiotic transformation in water, sometimes characterized as hydrolysis, is likely to be a chemical oxidation process and occurs at a moderate-to-rapid rate. The rate of atmospheric photooxidation is rapid. The members of the p-phenylenediamines category are expected to possess low persistence (P1) and low to moderate bioaccumulation potential (B1–B2).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

In two studies, Sprague-Dawley rats (5/sex/dose) were administered CASRN 101-96-2 (96.09% pure) via gavage at 200, 263, 346, 456 or 600 mg/kg-bw and at 200, 313, 490, 767 or 1200 mg/kg-bw and observed for 14 days following dosing. Mortality was observed at every dose tested.

LD₅₀ = 148 – 271 mg/kg

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

Sprague-Dawley rats (5/sex/dose) were administered p-phenylenediamine, CASRN 3081-14-9 (94% pure) via gavage at 501, 631, 794 or 1000 mg/kg-bw. Mortality occurred within 4 days.

LD₅₀ = 730 mg/kg

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

Sprague-Dawley rats (5/sex/dose) were administered CASRN 68953-84-4 via gavage at 5000 mg/kg-bw and observed for 14 days. One mortality was observed.

LD₅₀ > 5000 mg/kg-bw

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

Male and female Albino Sprague-Dawley rats (5/dose) were administered a single dose of CASRN 3081-01-4 (> 96% pure) via gavage at 1260, 1580, 2000, 2510 and 3160 mg/kg-bw and observed for an unknown number of days following dosing. At least one mortality was observed at each dose level tested.

LD₅₀ = 2100 mg/kg

p-phenylenediamine, N-(1-methylheptyl)-N'-phenyl- (CASRN 15233-47-3)

Male Holtzman rats (5/dose) were administered CASRN 15233-47-3 (> 95% pure) via an unspecified oral route at 0.046, 0.10, 2.15, 4.46, 10.0 or 21.5 mg/kg-bw and observed for 14 days following dosing. Mortalities were observed at the three highest doses.

LD₅₀ = 4.3 mg/kg

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

Sprague-Dawley Albino rats (5/sex/dose) were administered a single oral dose of CASRN 101-72-4 (97% pure) via gavage as a 20% suspension in corn oil at 631, 749, 1000 or 1260 mg/kg-bw and observed for 14 days following dosing. Mortality was observed in the three highest dose levels and the majority of deaths occurred within 2 days of dosing. Survivors were sacrificed following the 14-day observation period.

LD₅₀ = 900 mg/kg

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

(1) Sprague-Dawley albino rats (5/sex/dose) were administered a single oral dose of CASRN 793-24-8 (97.6% pure) at a concentration of 5000 mg/kg-bw and observed for 15 days. Three mortalities were observed.

LD₅₀ > 5000 mg/kg

(2) Sprague-Dawley albino rats (5/dose, males and females were used, number per dose not specified) were administered a single oral dose of CASRN 793-24-8 (> 96% pure) via gavage at concentrations of 2510, 3160, 3980, 5010 or 6310 mg/kg-bw and observed for 12 days. Mortality was observed at every dose level and with increasing frequency with dose.

LD₅₀ = 3580 mg/kg

Acute Inhalation Toxicity

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

Six male Albino Sprague-Dawley rats were exposed to CASRN 101-96-2 (> 96% pure) via inhalation at 0.2 mg/L for 6 hours and observed for 14 days following dosing. No mortalities were observed.

LC₅₀ > 0.2 mg/L

Subcategory II: 4-Aminodiphenylamine Derivatives

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

Six male albino Sprague-Dawley rats were exposed CASRN 3081-01-4 (> 95% pure) via inhalation at 0.14 mg/L for 6 hours and observed for 10 days following dosing. No mortalities were observed.

LC₅₀ > 0.14 mg/kg

Acute Dermal Toxicity

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

Albino New Zealand rabbits were administered CASRN 101-96-2 (96.09% pure) via the dermal route at 2500, 3536 or 5000 mg/kg-bw. Skin was shaved on all animals. Two animals from each group had their skin abraded in the treatment area and remaining animals' skin was left intact. Mortality was observed at all dose levels, regardless of skin treatment.

LD₅₀ = 2806 mg/kg

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

Male and female New Zealand rabbits (1/dose) were administered CASRN 3081-14-9 (> 94% pure) via the dermal route at 1260, 2000, 3160, 5010 and 7940 mg/kg-bw to shaved skin, under occluded conditions for 24 hours and observed for 14 days following dosing. Mortality occurred at the two highest dose levels.

LD₅₀ > 3160 mg/kg

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

Albino rabbits (5/sex/dose) were administered CASRN 68953-84-4 via the dermal route at 2000 mg/kg-bw under occluded conditions to shaved skin for 24 hours and observed for 14 days following dosing. No mortalities were observed.

LD₅₀ > 2000 mg/kg

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

Male and female Albino New Zealand rabbits were administered CASRN 3081-01-4 (> 95% pure) via the dermal route under occluded conditions to shaved skin for 24 hours and were observed for 14 days. One male was exposed to 5010 mg/kg-bw and one male and one female were exposed to 7940 mg/kg-bw. The high-dose male did not survive to test termination.

LD₅₀ > 5010 mg/kg

p-Phenylenediamine, N,-1-methylheptyl)-N'-phenyl- (CASRN 15233-47-3)

New Zealand White rabbits (5/sex/dose) were administered CASRN 15233-47-3 (> 95% pure) via the dermal route at 2 g/kg-bw under unspecified conditions for 24 hours to shaved and abraded skin and observed for 14 days following dosing. One animal died.

LD₅₀ > 2000 mg/kg

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

New Zealand Albino rabbits (two males and one female) were administered CASRN 101-72-4 (97% pure) via the dermal route at 5010 or 7940 mg/kg-bw as a 40% suspension in corn oil under occluded conditions for 24-hours and observed for 14 days following dosing. No mortalities were observed.

LD₅₀ > 7940 mg/kg

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

New Zealand Albino rabbits (one female/low dose, one male/mid dose and one/sex/high dose) were exposed to a single dermal dose of CASRN 793-24-8 (> 96% pure) at concentrations of 3160, 5010 or 7940 mg/kg-bw for 24 hours under occlusive conditions and observed for 14 days following removal of occlusive wrap. No mortalities were observed.

LD₅₀ > 7940 mg/kg

Repeated-Dose Toxicity

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

(1) In a 28-day study, Sprague-Dawley rats (10/sex/dose) were administered CASRN 101-96-2 (96.0% pure) at 0, 10, 25, 50 or 100 mg/kg-day in corn oil via gavage. Body weight and food consumption were recorded, and hematology and clinical chemistry were evaluated. Gross necropsies were performed on all sacrificed animals. There were no apparent treatment-related mortalities. Gross necropsy observations included slightly pale liver in two high-dose females and dilation of the right renal pelvis in males at all dose levels (including control). Adverse effects included increased liver weights, elevation of serum enzymes indicative of hepatocellular damage and dose-dependent increase in the incidence of hepatocellular lesions.

LOAEL = 10 mg/kg-day (based on hepatic effects)

NOAEL = Not established

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

(1) Sprague-Dawley CD rats (5/sex/dose) were administered CASRN 3081-14-9 (99+% active pure) in the diet at 0, 100, 300, 500, 1000 or 2000 ppm (~ 0, 9.13, 27.39, 45.65, 91.30 or 182.6 mg/kg-bw/day) for 30 days. Body weight, food consumption and physical observations were conducted on all animals during the study. Hematology and chemistry parameters were evaluated at the end of the study. No mortalities were observed during the study. Treatment-related effects included variation from the control in mean body weight/body weight gain

at ≥ 300 ppm in males and ≥ 1000 ppm in females. Changes in mean body weight were observed at 500 and 1000 ppm in males and at 2000 ppm in males and females. Reduced food consumption was observed during week 1 in males at ≥ 500 ppm and in females at ≥ 300 ppm. At the two highest dose levels, an increased mean platelet count was observed in both sexes and an increased mean erythrocyte count was observed in males only. Mean terminal body weights were reduced at the two highest dose levels in females and at the three highest dose levels in males. No treatment-related effects were observed during gross pathological examination.

NOAEL (males) ~ 45.65 mg/kg-bw/day

LOAEL (males) \geq ~ 91.30 mg/kg-bw/day (based on difference from control in mean body weight/body weight gain and increased mean platelet counts)

NOAEL (females) ~ 45.65 mg/kg-bw/day

LOAEL (females) \geq ~ 91.30 mg/kg-bw/day (based on difference from control in mean body weight/body weight gain, increased mean platelet counts and reduced mean terminal body weight)

(2) In a 90-day study, Sprague-Dawley CD rats (10/sex/dose) were administered CASRN 3081-14-9 (99+% active pure) in the diet at 0, 100, 250 and 500 ppm and 0, 250, 500 and 750 ppm, to males and females, respectively (~ 0, 9.13, 22.82 and 45.65 mg/kg-bw/day (males), 0, 22.82, 45.65 and 68.47 mg/kg-bw/day (females). Body weight, food consumption and physical observations were conducted on all animals during the study. Hematology and chemistry parameters were evaluated in all animals at 1.5 and 3 months. Organ weights were recorded and organ-to-body and organ-to-brain weight ratios were calculated. Histopathological examinations were conducted on lungs, spleen, liver and kidneys for all animals postmortem. Observed effects included reduced mean body weight and body weight gain at 250 and 500 ppm in males and at all dose levels in females. Mean alkaline phosphatase levels were elevated at 45.65 mg/kg-bw/day in males and 68.47 mg/kg-bw/day in females. Mean serum glutamic oxaloacetic transaminase levels were decreased in males at all dose levels in the middle of the first month, but were normal by month 3. Mean serum glutamic pyruvic transaminase levels were reduced in the highest two dose levels in females in the third month. However, there were not accompanying abnormal histopathology.

LOAEL (males) ~ 22.83 mg/kg-bw/day (based on decreased body weight and body weight gain)

NOAEL (males) ~ 9.13 mg/kg-bw/day

LOAEL (females) ~ 22.82 mg/kg-bw/day (based on decreased mean body weight and body weight gain)

NOAEL (females) ~ not established

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

In a 28-day study, Fischer 344 rats (14/sex/dose, 12 weeks old) were exposed to 1,4-benzenediamine, CASRN 68953-84-4 at concentrations of 0, 7.5, 30 and 120 mg/kg-bw/day in the diet. A recovery group (6/sex/dose) was monitored for 2 weeks post-exposure. No treatment-related mortality was observed. During weeks 2 – 4 reduced body weight and food consumption was observed in high-dose females and reduced food consumption was observed in high-dose males and also mid-dose females. Hematological changes, including increased mean

corpuseular volumes and decreased mean corpuseular hemoglobin concentrations, were observed in high-dose males and females, but appeared to recover by the end of week 2. Liver and kidney weights were increased in high-dose males and high- and mid-dose females. Heart and spleen weights were increased in high-dose females. The primary treatment-related effect observed was macrocytic anemia, which was reversible within 2 weeks.

LOAEL = 30 mg/kg-bw/day (based on macrocytic anemia)

NOAEL = 7.5 mg/kg-bw/day

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

In a 28-day study, Sprague-Dawley rats (5/sex/dose) were exposed to CASRN 3081-01-4 (96.2% pure) at 0, 500, 750, 1500 and 3000 ppm (~ 0, 45.65, 68.47, 136.94 and 273.89 mg/kg-bw/day) in the diet. No mortalities were observed during the study. The only effects observed were reduced body weight and food consumption at all dose levels. There were no clinical signs of toxicity or gross pathology changes observed.

NOAEL ~ 273.89 mg/kg-bw/day (highest dose tested)

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

(1) Sprague-Dawley Albino rats (5/sex/dose) were administered CASRN 101-72-4 (97.2% pure) as a dietary mixture at 0, 500, 1000, 1750 or 2500 ppm (~ 0, 46, 91, 160 or 228 mg/kg-bw/day, average of male and female combined) daily for 30 days. Clinical signs of toxicity, body weight and food consumption were measured before study initiation and then at varying intervals during the study. No mortalities occurred during the study. At study termination, clinical chemistry and hematological parameters were measured and all animals were sacrificed and necropsied. At doses > 1000 ppm (~ 91 mg/kg-bw/day), there were differences in body weight gain compared to control animals, hematology and elevations in total serum protein, and increased liver and spleen weights. There were no significant findings in animals dosed at 500 ppm (~ 46 mg/kg-bw/day) when compared with controls.

LOAEL ~ 91 mg/kg-bw/day (based on differences in body weight gain, elevations in total serum protein, increased liver and spleen weights)

NOAEL ~ 46 mg/kg-bw/day

(2) In a 90-day study, Sprague-Dawley albino rats (10/sex/dose) were administered CASRN 101-72-4 (97.2% pure) daily as a dietary mixture at 0, 180, 360 or 720 ppm (~ 0, 16, 31 or 62 mg/kg-bw/day for males, respectively; ~ 0, 16, 32 or 71 mg/kg-bw/day for females, respectively). Clinical signs of toxicity body weight and food consumption were measured before study initiation and then at varying intervals during the study. Clinical chemistry and hematology determinations were made at 1.5 and 3 months. Two females died (one in the mid-dose group and one in the high-dose group) during the study; however, the cause of death could not be attributed to treatment. No other mortalities were observed during the study and all animals were sacrificed at study termination. At 720 ppm (~ 62 mg/kg-bw/day), mean body weight and mean body weight gains were slightly reduced in males (2 – 4%). A reduction in hemoglobin concentrations and hematocrit values and reduced mean erythrocyte counts were observed in males and females at 360 and 720 ppm (~ 31 and 62 mg/kg-bw/day in males; ~ 32 and 71 mg/kg-bw/day in females). There were differences in clinical chemistry parameters (not specified) in males and females in the mid- and high-dose groups. Mean liver weight, liver-to-

body-weight and liver-to-brain weight ratios were increased in mid- and high-dose males and in all treated females.

LOAEL (males) ~ 31 mg/kg-bw/day (based on reduction in hemoglobin concentrations and hematocrit values and reduced mean erythrocyte counts)

LOAEL (females) ~ 16 mg/kg-bw/day (based on increased mean liver weights, liver-to-body-weight and liver-to-brain-weight ratios)

NOAEL (males) ~ 16 mg/kg-bw/day

NOAEL (females) = Not established

***p*-Phenylenediamine, *N*-(1,3-dimethylbutyl) *N'*-phenyl (CASRN 793-24-8, supporting chemical)**

(1) In a 90day study, Sprague-Dawley rats (25/sex/dose) were administered CASRN 793-24-8 (97.1% pure) in feed at concentrations of 0, 250, 1000 or 2500 ppm (~ 0, 19, 75 or 188 mg/kg-bw/day). No mortalities were observed. Treatment-related effects included reduced feed consumption and body weight gain in high-dose animals of both sexes and mid-dose males. Anemia, lymphocytopenia and thrombocytosis were observed in both sexes at the two highest doses.

LOAEL ~ 75 mg/kg-bw/day (based on anemia, lymphocytopenia and thrombocytosis observed in both sexes and reduced feed consumption and body weight gain observed in males)

NOAEL ~ 19 mg/kg-bw/day

(2) In a 4-week study, Sprague-Dawley rats (5/sex/dose) were exposed to CASRN 793-24-8 (97.1% pure) as a dust via inhalation at concentrations of 0, 50, 250 or 500 mg/m³ (~ 0, 0.05, 0.2, 0.5 mg/L) for 6 hours/day, 5 days/week for 4 weeks for a total of 20 exposures. Treatment-related effects included hypoactivity at all dose levels, swollen snouts and scratching at mid- and high-dose levels, increased liver and kidney weights at all dose levels, reduced lung weights in high-dose males and mid-dose females and increased spleen weights in mid-dose males. [IBT study]

LOAEC = ~ 0.05 mg/L (50 mg/m³) (based on hypoactivity, increased liver and kidney weights)

NOAEC = Not established

Reproductive Toxicity

Subcategory I: N-Alkylated p-Phenylenediamines

***p*-Phenylenediamine, *N,N*-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)**

In a three-generation reproductive toxicity study, Charles River Albino rats were exposed to CASRN 3081-14-9 (99+% active pure) at 0, 30, 100 or 300 ppm (~ 0, 3.16, 10.53 and 31.59 mg/kg-bw/day) in the diet. F0 and F1 parents were exposed for 14 weeks prior to mating and through mating, gestation and lactation. The F2 generation was exposed for 18 weeks prior to mating and through mating, gestation and lactation. Parental toxicity manifested as reduced

body weight and mean body weight gain at 100 and 300 ppm. The survival rate of pups was reduced in the 100 and 300 ppm groups. [IBT study]

LOAEL (systemic toxicity) ~ 10.53 mg/kg-bw/day (based on reduced body weight and mean body weight gain)

LOAEL (reproductive toxicity) ~ 10.53 mg/kg-bw/day (based on reduced survival rate of pups)

NOAEL (systemic and reproductive toxicity) ~ 3.16 mg/kg-bw/day

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

In a two-generation reproductive toxicity study, Sprague Dawley rats (30/sex/dose) were exposed in the diet to CASRN 68953-84-4 at 0, 120, 400 or 1500 ppm (~ 0, 8.78, 29.27 or 109.76 mg/kg-bw/day). The F0 generation rats were exposed for 10 weeks prior to mating, 2 weeks during mating, 3 weeks during gestation and through weaning. The F1 generation rats were exposed for 10 weeks prior to mating. On postnatal day (PND) 4, litters were culled to 10 each and 30 F1 generation males and females/dose group were chosen for pairing and further exposure for 10 weeks. Dystocia was observed in pregnant rats, which was likely responsible for prolonged gestation, increased perinatal deaths and decreased live births and increased pup weights. Polycystic lesions were observed at all levels. High-dose females experienced reduced body weights for the majority of the study period. Treatment-related kidney lesions were also observed grossly and microscopically.

LOAEL (systemic toxicity) ~ 8.78 mg/kg-bw/day (based on effects to the kidneys)

LOAEL (reproductive toxicity) ~ 8.78 mg/kg-bw/day (based on dystocia, increased perinatal deaths, decreased live births and increased pup weights)

NOAEL (systemic and reproductive toxicity) = Not established

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

In a three-generation study, male and female Charles River Albino rats (unspecified number/dose) were administered CASRN 793-24-8 in the diet during pre-mating, through gestation and into lactation at concentrations of 0, 100, 300 or 1000 ppm (~ 0, 8, 23 or 75 mg/kg-bw/day). Treatment-related parental effects included reduced body weights and mean body weight gains at the highest doses (300 and 1000 ppm). There was no effect on mating, fertility or survival in fetuses, pups or adults. [IBT study]

NOAEL (parental) ~ 8 mg/kg-bw/day

LOAEL (parental) ~ 23 mg/kg-bw/day (based on reduced body weight gain)

NOAEL (F1 and F2 offspring) ~ 75 mg/kg-bw/day (highest dose tested)

Developmental Toxicity

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

(1) In a pre-natal developmental toxicity study, pregnant Charles River CD Albino rats (25/dose) were administered CASRN 3081-14-9 (99+% active pure) at 0, 25, 75 or 150 mg/kg-day via gavage during gestation days 6 – 15. On gestation day 20, Cesarean sections were performed on all surviving females and fetuses were removed for teratologic evaluation. Four mortalities were observed in the high-dose females and one mortality was observed in the 75 mg/kg-bw/day dose females. Adversely affected parameters in maternal rats at the two highest dose levels were survival, appearance, behavior and body weight gain. Malformations observed in fetuses were low in incidence and were not considered treatment related.

LOAEL (maternal toxicity) = 75 mg/kg-day (based on survival, appearance, behavior and body weight gain)

NOAEL (maternal toxicity) = 25 mg/kg-day

NOAEL (developmental toxicity) = 150 mg/kg-day (highest dose tested)

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

In a pre-natal developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) were exposed to CASRN 68953-84-4 via gavage at 0, 20, 70 and 200 mg/kg-day during gestation days 6 – 15. Maternal body weight, food consumption, liver weight, clinical changes, pregnancy rates and corpora lutea counts were monitored. No mortalities were observed. Fetal weight, sex and external and visceral abnormalities were assessed. In addition, half of the offspring was examined for skeletal abnormalities, while the other half was examined for cranial bone abnormalities. Only decreased body weight and food consumption was observed at the highest dose level in maternal rats. There were no treatment-related effects on pregnancy rates, litter sizes, number of live fetuses, uterine implantation or any gestational parameters. A dose-related trend for decreased fetal body weight was observed with an approximate 5% decrease at the highest dose. No visceral, external or skeletal abnormalities were observed in the fetuses.

LOAEL (maternal toxicity) = 200 mg/kg-day (based on reduced body weight and food consumption)

NOAEL (maternal toxicity) = 70 mg/kg-day

LOAEL (developmental toxicity) = 20 mg/kg-day (based on reduced body weight)

NOAEL (developmental toxicity) = Not established

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

(1) In a pre-natal developmental toxicity study, pregnant female Sprague-Dawley rats (24/dose) were administered CASRN 101-72-4 via gavage in polyethylene glycol 400 at 0, 12.5, 62.5 and 125 mg/kg-day on gestation days 6 – 15. Slight maternal toxicity was observed in high-dose rats, as evident by reduced food intake, pre-dosing salivation and soft, dark feces. Body weight was not affected and all animals survived until terminal sacrifice. There were no treatment-related effects on pregnancy. Effects were observed at 125 mg/kg-bw/day in fetuses, including

increased incidence of irregularly and incompletely ossified cranial and facial bones, increased incidence of no ossification of hyoid, unilateral/bilateral wavy ribs and semi-bipartite vertebrate centra. An increase in incomplete ossification of more than one cranial bone was observed at 62.5 mg/kg-bw/day. In addition, incomplete ossification of more than one facial bone was noted at 12.5 mg/kg-bw/day, but was not considered to be treatment-related.

LOAEL (maternal toxicity) = 125 mg/kg-day (based on reduced food intake, pre-dosing salivation and soft, dark feces)

NOAEL (maternal toxicity) = 62.5 mg/kg-day

LOAEL (developmental toxicity) = 62.5 mg/kg-day (based on incomplete ossification of more than one cranial bone)

NOAEL (developmental toxicity) = 12.5 mg/kg-day

(2) In a pre-natal developmental toxicity study, pregnant female Sprague-Dawley rats (24/dose) were administered CASRN 101-72-4 via gavage in polyethylene glycol 400 at concentrations of 0, 10, 50 or 100 mg/kg-day on gestation days 6 – 15. There were signs of post-dosing salivation and lethargy at the highest dose (100 mg/kg-bw) and there was a slight reduction in mean food consumption between days 6 and 9 of gestation. All animals survived until terminal sacrifice; there were no treatment-related effects on pregnancy or fetal parameters.

LOAEL (maternal toxicity) = 100 mg/kg-day (based on signs of post-dosing salivation and lethargy)

NOAEL (maternal toxicity) = 50 mg/kg-day

NOAEL (developmental toxicity) = 100 mg/kg-day (highest dose tested)

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

(1) In a pre-natal developmental toxicity study, pregnant female Sprague-Dawley rats (25/dose) were administered CASRN 793-24-8 (> 97% pure) in corn oil via gavage at concentrations of 0, 50, 100 or 250 mg/kg-day on gestation days 6 – 15. Animals were observed for behavior, appearance, body weight and food consumption. All animals were sacrificed on day 20 and fetuses were removed via cesarean section, weighed, sexed and examined for external, skeletal and soft tissue abnormalities and developmental variations. Treatment-related signs of maternal toxicity included salivation prior to dosing, soft stool, diarrhea and green fecal discoloration in the high-dose groups. There was a small increase in the incidence and number of skeletal variations in the fetuses; however, these were judged to be common developmental variations of this species.

LOAEL (maternal toxicity) = 100 mg/kg-day (based on salivation prior to dosing, soft stool, diarrhea and green fecal discoloration)

NOAEL (maternal toxicity) = 50 mg/kg-day

NOAEL (developmental toxicity) > 250 mg/kg-day (highest dose tested)

(2) In a pre-natal developmental toxicity study pregnant female New Zealand Albino rabbits (number per dose not specified) were administered CASRN 793-24-8 (> 96% pure) orally in gelatin capsules at concentrations of 0, 10 or 30 mg/kg-day on gestation days 6–18 and observed until terminal sacrifice on gestation day 29. There was a slight increase in the number of resorption sites in the high-dose group and a decrease in the number of live young per

implantation site in the mid- and high-dose groups. There were no fetal treatment-related effects. [IBT study]

NOAEL (maternal and developmental toxicity) = 30 mg/kg-day (highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to CASRN 3081-14-9 (99+% active pure) at 0.01, 0.04, 0.2, 1, 3, 10, 40 and 200 µg/plate with and without metabolic activation. Positive controls were tested and responded appropriately. Cytotoxicity was observed at 200 µg/plate with metabolic activation and at 10 µg/plate without metabolic activation. Precipitation was observed at 1 µg/plate.

CASRN 3081-14-9 was not mutagenic in this assay.

(2) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 3081-14-9 (96% pure) at 0.001, 0.01, 0.10, 1.00 or 5.00 µL/plate with and without metabolic activation. Positive controls were tested and responded appropriately. Cytotoxicity was observed at 1.00 µL/plate with metabolic activation and at 5.00 µL/plate without metabolic activation.

CASRN 3081-14-9 was not mutagenic in this assay.

(3) L5178Y mouse lymphoma cells were exposed to CASRN 3081-14-9 in triplicate at 0.002, 0.004, 0.008 and 0.0016 µg/mL with and without activation in a forward mutation assay. An additional dose of 0.032 was tested, but only with metabolic activation. Positive and negative controls were used. Cytotoxicity was observed at 0.032 µg/mL with metabolic activation and 0.016 µg/mL without metabolic activation. Forward mutations were not observed at the TK locus of exposed cells.

CASRN 3081-14-9 did not induce forward mutations in this assay.

(4) Chinese hamster ovary (CHO) cells were exposed to CASRN 3081-14-9 (99% pure) with and without metabolic activation in a forward gene mutation assay. Positive controls were tested and responded appropriately.

CASRN 3081-14-9 was not mutagenic in this assay.

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

(1) *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 were exposed to CASRN 68953-84-4 with S9 metabolic activation at concentrations of 1.67, 5, 16.7, 50, 167 and 500 µg/plate and strains TA1535, TA1538, TA98 and TA100 were exposed to 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives without metabolic activation at concentrations of 0.167, 0.5, 1.67, 5, 16.7 and 50 µg/plate. *Escherichia coli* strain WP2 uvrA were exposed to 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives with and without S9 metabolic activation at concentrations of 1.67, 5, 16.7, 50, 167 and 500 µg/plate. Positive and negative controls were tested concurrently and responded appropriately. Treatment-related increases in frequencies were observed in strains TA1538, TA1537 and TA98 with metabolic activation and increases in frequencies were seen in TA1537 and TA98 without activation. **CASRN 68953-84-4 was mutagenic in these assays.**

(2) *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to 1.67, 5, 16.7, 50, 167 and 500 µg/plate of CASRN 68953-84-4 with metabolic activation. *Escherichia coli* strain WP2 uvrA were exposed to the concentrations listed above with and without metabolic activation. The *Salmonella* strains were also exposed without metabolic activation at 0.167, 0.5, 1.67, 5, 16.7 and 50 µg/plate. Positive and negative controls were tested concurrently and responded appropriately. 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives caused mutations in strains TA1537 and TA1538 with metabolic activation and in strain TA98 with and without metabolic activation. **CASRN 68953-84-4 was mutagenic in these assays.**

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

(1) *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to CASRN 3081-01-4 (96.2% pure) at 0.001, 0.01, 0.1, 1.0 and 5.0 µL/plate with and without metabolic activation. A positive control was tested. Cytotoxicity was observed with and without metabolic activation at 5.0 µL/plate in strain TA98 only. **CASRN 3081-01-4 was not mutagenic in this assay.**

(2) L5178Y mouse lymphoma cells were exposed to CASRN 3081-01-4 (> 96% pure) at 0.625 – 10.0 nL/mL without metabolic activation and 1.25 – 50.0 nL/mL with metabolic activation in a forward mutation mouse lymphoma assay. A negative control was tested concurrently. Cytotoxicity was observed at 60 nL/mL with metabolic activation and 20 nL/mL without metabolic activation. **CASRN 3081-01-4 was not mutagenic in this assay.**

(3) CHO/HGPRT cells were exposed in triplicate to CASRN 3081-01-4 (96.2% pure) at 0, 1, 3, 5, 7 and 10 µg/mL without activation and 1, 10, 15, 20, 25 and 30 µg/mL with activation. A positive control was tested concurrently. Cytotoxicity was observed at 7 µg/mL with metabolic activation and 5 µg/mL without metabolic activation. **CASRN 3081-01-4 was not mutagenic in this assay.**

***p*-Phenylenediamine, *N*-(1-methylheptyl)-*N'*-phenyl- (CASRN 15233-47-3)**

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to CASRN 15233-47-3 (> 95% pure) at 0.0005, 0.001, 0.0025, 0.005, 0.01, 0.05, 0.1 and 0.5 µg/plate in the presence and absence of liver microsomal preparations. Positive controls were tested concurrently. Cytotoxicity was observed without activation at > 0.7 µg/plate. Precipitation was observed at 0.59 µg/plate.

CASRN 15233-47-3 was not mutagenic in this assay.

***p*-Phenylenediamine, *N*-isopropyl-*N'*-phenyl- (CASRN 101-72-4, supporting chemical)**

(1) In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 101-72-4 (> 97% pure) at concentrations of 0.1, 1, 10, 100 and 500 µg/plate with and without metabolic activation. Positive controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 500 µg/plate with and without metabolic activation.

CASRN 101-72-4 was not mutagenic in this assay.

(2) In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to CASRN 101-72-4 (92 – 99% pure) at concentrations of 0.2, 0.8, 4, 20, 60 and 200 µg/plate with and without metabolic activation. Positive and negative controls were tested concurrently. Cytotoxicity was observed at 200 µg/plate with and without metabolic activation.

CASRN 101-72-4 was not mutagenic in this assay.

(3) In a mammalian cell gene forward mutation assay, mouse lymphoma cells (L5178Y) were exposed to CASRN 101-72-4 (97% pure) at concentrations of 0.156, 0.313, 0.625, 1.250 and 2.500 µg/mL without metabolic activation and 0.625, 1.250, 2.500, 5.000 and 10.000 µg/mL with metabolic activation. Positive and negative controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 10.0 µg/mL with metabolic activation and 2.5 µg/mL without metabolic activation.

CASRN 101-72-4 was not mutagenic in this assay.

(4) In a forward gene mutation assay, CHO/HGPRT cells were exposed to CASRN 101-72-4 (92 – 99% pure) at concentrations of 2, 5, 10, 15 and 30 µg/plate with and without metabolic activation. Positive controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 30 µg/plate with metabolic activation and 10 µg/plate without metabolic activation.

CASRN 101-72-4 was not mutagenic in this assay.

(5) In a mitotic recombination assay, *Saccharomyces cerevisiae* (D4) were exposed to CASRN 101-72-4 (97% pure) at concentrations of 0.1, 1, 10, 100 and 500 µg/plate with and without metabolic activation. A positive control was tested concurrently.

CASRN 101-72-4 was not mutagenic in this assay.

***p*-Phenylenediamine, *N*-(1,3-dimethylbutyl) *N*'-phenyl (CASRN 793-24-8, supporting chemical)**

(1) In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 793-24-8 (> 96% pure) at concentrations of 0.1, 1.0, 10.0, 100.0 and 500.0 µg/plate with and without metabolic activation. Positive controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 500 µg/plate with and without metabolic activation.

CASRN 793-24-8 was not mutagenic in this assay.

(2) In two bacterial reverse mutation assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 793-24-8 (> 96% pure) at concentrations of 0.001, 0.01, 0.1, 1.0 and 5.0 µL/plate with and without metabolic activation. Positive controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 5 µL/plate with metabolic activation and 1.0 µL/plate without metabolic activation in one study and at 5 µL/plate with and without metabolic activation in the other.

CASRN 793-24-8 was not mutagenic in these assays.

(3) In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 793-24-8 (> 96% pure) in triplicate at concentrations of 0.167, 0.500, 1.67, 5.0, 16.7 and 50.0 µg/plate with and without metabolic activation. Positive and negative controls were tested concurrently and responded appropriately. Precipitation was observed at doses \geq 500 µg/plate.

CASRN 793-24-8 was not mutagenic in this assay.

(4) In a mammalian cell gene forward mutation assay, mouse lymphoma cells (L5178Y) were exposed to CASRN 793-24-8 (> 96% pure) at concentrations of 0.25, 0.5, 1.0, 2.0, 4.0 or 8.0 µg/mL with and without metabolic activation. Positive controls were tested concurrently. Cytotoxicity was observed with metabolic activation at 33 µg/mL and without metabolic activation at > 4 µg/mL.

CASRN 793-24-8 was not mutagenic in this assay.

(5) In a cytogenetics assay, CHO/HGPRT cells were exposed to CASRN 793-24-8 (> 96% pure) at concentrations of 5, 10 and 12.5 µg/mL without activation and 5, 10, 12.5 and 15 µg/mL with activation. Positive controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 20 µg/mL with and without metabolic activation.

CASRN 793-24-8 was mutagenic in this assay.

(6) In a forward gene mutation assay, CHO/HGPRT cells were exposed to CASRN 793-24-8 (96% pure) at concentrations of 3 – 15 µg/mL with activation and 1 – 5 µg/mL without activation. Precipitation was observed at the solubility limit of 333 µg/mL. Cytotoxicity was observed at 9 µg/mL with metabolic activation and 4 µg/mL without metabolic activation. Positive controls were tested concurrently and responded appropriately.

CASRN 793-24-8 was not mutagenic in this assay.

In vivo

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

In two studies, *Drosophila melanogaster* were exposed to CASRN 68953-84-4 in the diet at concentrations of 10 and 50 µg/mL for 24 hours.

CASRN 68953-84-4 was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

In two studies, CHO cells were exposed to CASRN 68953-84-4 at concentrations of 0.4, 2, 4 and 25 µg/mL in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately.

CASRN 68953-84-4 did not induce chromosomal aberrations in these assays.

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

CHO cells were exposed in duplicate to CASRN 3081-01-4 (96.2% pure) at 0, 1.5, 5, 7.5, 10.0 and 15 µg/mL with and without S9 metabolic activation. A positive control was tested concurrently and responded appropriately. An increase in the number of cells with structural aberrations and number of aberrations per cell was observed at 10 µg/mL. An increased number of aberrations per cell was observed at 7.5 µg/mL. Aberrations were in the form of deletions, chromatid interchanges, interchanges and triradials.

CASRN 3081-01-4 was weakly clastogenic in this assay.

In vivo

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

CD-1 mice (5/sex/dose) were exposed to a single dose of CASRN 68953-84-4 via intraperitoneal injection at 0, 250, 1250 and 2500 mg/kg-bw in a micronucleus assay. Positive and negative controls were tested concurrently and responded appropriately.

CASRN 68953-84-4 did not induce chromosomal aberrations in this assay.

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

Sprague-Dawley rats (5/sex/dose) were exposed to CASRN 3081-01-4 (96.2% pure) at 1100 mg/kg-bw via gavage and were observed for pharmacotoxicity immediately and at 6, 18 and 30 hours after. A positive control was tested concurrently. Signs of pharmacotoxicity that were observed during the study indicated that the doses used were nearing the maximum

tolerated dose. No increases in the numbers of aberrations or aberrant metaphases were observed. No structural chromosomal aberrations were observed in the hemopoietic cells of the rat bone marrow.

CASRN 3081-01-4 did not induce chromosome aberrations in this assay.

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

In a mammalian bone marrow cytogenetic assay, Sprague-Dawley rats (5/sex/group) were exposed to CASRN 793-24-8 (96% pure) in corn oil via gavage at a concentration of 1000 mg/kg-bw. Positive controls were tested concurrently and responded appropriately.

CASRN 793-24-8 did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

(1) Six New Zealand White rabbits were exposed to 0.5 mL CASRN 101-96-2 (96.09% pure) on intact and abraded shaved skin for 24 hours and observed for 17 days. Effects observed in all animals included scarring, hardening of the skin, scabbing and sloughing skin.

CASRN 101-96-2 was corrosive to rabbit skin in this study.

(2) Six New Zealand White rabbits were exposed to 0.5 mL CASRN 101-96-2 (purity not stated) on shaved skin under occluded conditions for 4 hours. Skin was scored for erythema, eschar formation and corrosion for 2 weeks.

CASRN 101-96-2 was irritating to rabbit skin in this study.

(3) Guinea pigs were exposed to 0.2, 50 and 100% of CASRN 101-96-2 (99% pure) to intact skin to determine primary irritation and then nine sensitizing exposures to abraded skin over a period of 3 weeks. Mild redness was observed at 0.2%, redness and swelling at 50% and necrosis at 100%. (TSCATS OTS0571469).

CASRN 101-96-2 was irritating to guinea pig skin in this study.

(4) Albino rabbits (one male and two females) were exposed to undiluted CASRN 101-96-2 to shaved skin under occlusive conditions for 48 hours. After 2 hours, slight erythema with moderate edema was noted; the inflammation increased overnight and slight eschar formation was present. (TSCATS OTS0570623).

CASRN 101-96-2 was severely irritating to rabbit skin in this study.

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

(1) Six Albino New Zealand rabbits were exposed to 0.5 mL CASRN 3081-14-9 (96% pure) to shaved skin under occluded conditions for 24 hours. Irritation was scored at intervals up to 168 hours after exposure. Effects observed included a slight defatting with skin flaking off in 7 – 10 days. The irritation score was 0.0/8.0.

CASRN 3081-14-9 was not irritating to rabbits in this study.

(2) Guinea pigs were exposed to 0.2, 50 and 100% of CASRN 3081-14-9 (97% pure) to intact skin to determine primary irritation and then nine sensitizing exposures to abraded skin over a period of 3 weeks. Mild redness was observed at 0.2%, redness at 50% and redness and swelling at 100%. (TSCATS OTS0571469).

CASRN 3081-14-9 was irritating to guinea pig skin in this study.

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

(1) Six albino female rabbits were exposed to 0.5 g CASRN 68953-84-4 under occluded conditions to shaved skin for four hours. Irritation was scored for 72 hours. No mortality was observed. Slight erythema was observed in five animals from 1 to 48 hours. 1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives was noncorrosive in this assay.

CASRN 68953-84-4 was slightly irritating to rabbits in this study.

(2) Shaved skin of six albino rabbits were exposed to a 20% suspension of CASRN 68953-84-4 (purity unknown) under unspecified conditions.

CASRN 68953-84-4 was not irritating to rabbits in this study.

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

Six male and female Albino New Zealand rabbits were exposed to 0.5 mL CASRN 3081-01-4 (> 96% pure) under occluded conditions to shaved skin for 24 hours. Irritation was scored intermittently for 168 hours following exposure. Observed effects included slight defatting with skin flaking off in 7 – 10 days.

CASRN 3081-01-4 was not irritating to rabbits in this study.

p-Phenylenediamine, N-(1-methylheptyl)-N'-phenyl- (CASRN 15233-47-3)

(1) Six New Zealand White rabbits were exposed to 0.5 mL CASRN 15233-47-3 (>95% pure) under semi-occluded conditions to two abraded areas and two intact areas on each rabbit for 24 hours. Irritation was scored after removing patches and at 72 hours. Very slight to well-defined erythema was observed at all sites of exposure of all animals. Very slight to slight edema was observed at all sites of exposure in five animals. Some loss of atonicity was also observed.

CASRN 15233-47-3 was slightly irritating to rabbits in this study.

(2) Rabbits (unspecified strain, 3/sex) were exposed to an unspecified dose of CASRN 15233-47-3 (> 95% pure) for 3 minutes, 1 hour or 4 hours under semi-occluded conditions. Corrosion was not observed for any duration that was tested.

CASRN 15233-47-3 was not corrosive to rabbits in this study.

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

Six New Zealand Albino rabbits (sex not specified) were exposed to CASRN 101-72-4 (97% pure) via the dermal route at a concentration of 0.5 mL under occlusive conditions for 24 hours and then observed for 7 days. Dermal irritation was scored by the Draize method and results were recorded 24, 48, 72 and 168 hours after application; all animals scored 0 at every observation time.

CASRN 101-72-4 was not irritating in this study.

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

Six New Zealand Albino rabbits (sex not specified) were exposed to CASRN 793-24-8 (> 96% pure) via the dermal route at a concentration of 0.5 mL under occlusive conditions for 24 hours and then observed for 7 days. Dermal irritation was scored by the Draize method and results were recorded 24, 48, 72 and 168 hours after application.

CASRN 793-24-8 was not irritating in this study.

Eye Irritation

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

(1) New Zealand rabbits (3/sex/dose) were exposed to a single dose of 0.1 mL CASRN 101-96-2 (96.09% pure) in one eye. Irritation was scored according to the Draize procedure at 24, 48 and 72 hours after exposure. Discomfort at application appeared slight and observations at 24 hours included severe erythema with necrosis, severe edema, copious discharge with a whitish exudate and severe swelling of conjunctivae. No permanent corneal damage was observed after 21 days.

CASRN 101-96-2 was corrosive to rabbit eyes in this study.

(2) Albino New Zealand rabbits (1/sex/dose) were exposed to a single dose of 0.1 mL CASRN 101-96-2 (96.09% pure) in one eye and observed for 17 days. Irritation was scored according to the Draize method. All corneal and iridal involvement in animals had subsided by the seventh day after exposure. Treatment-related effects included hardened skin around the eyes and blistered conjunctival tissue.

CASRN 101-96-2 was corrosive to rabbit eyes in this study.

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

Six albino New Zealand rabbits (both male and female) were exposed to a single dose of CASRN 3081-14-9 (96% pure) in one eye for 24 hours. Slight discomfort was observed immediately following application. Slight erythema, very slight edema and copious discharge

were observed during the first 24 hours following treatment. The severity of these symptoms lessened with time and were absent at 168 hours.

CASRN 3081-14-9 was slightly irritating to rabbit eyes in this study.

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

Nine albino rabbits were exposed to 0.1 mL (0.06 g) CASRN 68953-84-4 for 30 seconds in one eye. Three of the animals' eyes were then rinsed with water. All were assessed intermittently for 72 hours for gross corneal, iridal or conjunctival injury. Conjunctival and iridal changes were observed in unrinsed rabbits after 1 hour. Adverse effects were resolved by 72 hours in all but one rabbit with conjunctival redness, which resolved by 7 days.

CASRN 68953-84-4 was slightly irritating to rabbit eyes in this study.

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

Six albino New Zealand male and female rabbits were exposed to 0.1 mL CASRN 3081-01-4 (>96% pure) in one eye. The cornea, iris and conjunctiva were examined immediately after treatment and then intermittently for 168 hours. Observed effects included slight erythema, very slight edema and copious discharge. The severity of observed effects decreased with time and were absent by 72 hours.

CASRN 3081-01-4 was slightly irritating to rabbit eyes in this study.

p-Phenylenediamine, N-(1-methylheptyl)-N'-phenyl- (CASRN 15233-47-3)

Nine rabbits (unspecified strain and sex) were exposed to CASRN 15233-47-3 (> 95% pure) at 0.1 mL in one eye. The eyes of three rabbits were rinsed for 60 seconds with lukewarm water after 30 second of exposure. All other animals were left unrinsed. Rabbits were monitored for gross signs of irritation periodically for 19 days. Mild corneal opacity and mild erythema was observed in unrinsed animals. Mild corneal irritation that cleared after 4 days post-treatment was observed in rabbits with rinsed eyes. Mild to moderate conjunctival irritation was also observed in animals with rinsed eyes on days 13 and 19 in three rabbits.

CASRN 15233-47-3 was mildly irritating to rabbit eyes in this study.

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

Six male and female New Zealand Albino rabbits were exposed to CASRN 101-72-4 (97% pure) in the eye at a concentration of 100 mg and observed for 7 days. The Draize method was used for scoring eye irritation. Treatment-related effects only lasted for the first 24 hours and included slight erythema and discharge.

CASRN 101-72-4 was slightly irritating in this study.

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

Six New Zealand Albino rabbits (sex not specified) were exposed to CASRN 793-24-8 (> 96% pure) in the eye at a concentration of 0.1 mL and observed for 7 days. The Draize method was used for scoring eye irritation. Treatment-related effects only lasted for the first 48 hours and

included slight discomfort, slight erythema and discharge.
CASRN 793-24-8 was slightly irritating in this study.

Sensitization

Subcategory I: N-Alkylated p-Phenylenediamines

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

Guinea pigs were exposed to 0.2, 50 and 100% CASRN 101-96-2 (99% pure) to intact skin to determine primary irritation and then nine sensitizing exposures to abraded skin over a period of 3 weeks. Mild redness was observed at 0.2%, redness and swelling at 50% and necrosis at 100%. (TSCATS OTS0571469).

CASRN 101-96-2 was sensitizing to guinea pig skin in this study.

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

Guinea pigs were exposed to 0.2, 50 and 100% CASRN 3081-14-9 (97% pure) to intact skin to determine primary irritation and then nine sensitizing exposures to abraded skin over a period of 3 weeks. Mild redness was observed at 0.2%, redness at 50% and redness and swelling at 100%. (TSCATS OTS0571469).

CASRN 3081-14-9 was sensitizing to guinea pig skin in this study.

Subcategory II: 4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

Guinea pigs (20/dose) were administered pairs of intradermal injections (0.1 mL) of Freund's adjuvant, 5% CASRN 68953-84-4 in 0.5% acetone in propylene glycol and 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives plus Freund's adjuvant at opposite sites from the dorsal midline. Appropriate negative and positive controls were tested. Seven days following the initial injection, topical induction exposures under occluded conditions were performed after a 24-hour test site exposure to sodium lauryl sulfate. On day 21, challenge exposures were performed using 25 and 100% test substance. This was repeated on day 28. Erythema and edema were observed after the initial challenge exposure of 25%. The induction phase did not produce adverse clinical signs. After the rechallenge, both concentrations produced more severe dermal responses (erythema and edema).

CASRN 68953-84-4 was a contact sensitizer to guinea pigs in this study.

p-Phenylenediamine, N-isopropyl-N'-phenyl- (CASRN 101-72-4, supporting chemical)

(1) Volunteers (50, sex not specified) were exposed to 50% CASRN 101-72-4 (> 96% pure) in dimethylphthalate via the dermal route using a patch moistened with the test material for 24 hours and repeated for 15 applications, given every other day with a 48-hour rest period during the weekend. Volunteers were subjected to a challenge application after a 2-week resting period.
CASRN 101-72-4 was sensitizing to humans in this study.

(2) Volunteers (82, sex not specified) were exposed 3 times/week for 3 weeks to 1% CASRN 101-72-4 (> 96% pure) in petrolatum via the dermal route using a patch moistened with the test material. The patch was applied to the same site on one arm each time. After a rest period of unspecified duration, volunteers were administered a challenge application to a different area of the body.

CASRN 101-72-4 was sensitizing to humans in this study.

p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)

(1) Volunteers (94, sex not specified) were exposed to 1% CASRN 793-24-8 (purity unspecified) in petrolatum 3 times/week for 3 weeks, followed by a challenge phase. No further study details were provided.

CASRN 793-24-8 was not sensitizing to humans in this study.

(2) Volunteers (50, sex not specified) were exposed to CASRN 793-24-8 (purity unspecified) in dimethylphthalate at a concentration of 50% w/v in dimethylphthalate for 3 weeks. A challenge phase followed. No further study details were provided. Five out of the 50 subjects showed skin reactions in the induction phase and 5 out of 50 showed skin reactions in the challenge phase.

CASRN 793-24-8 was sensitizing to humans in this study.

Conclusion:

Subcategory I: N-Alkylated p-Phenylenediamines

The acute oral toxicity of CASRN 101-96-2 to rats is moderate while that for CASRN 3081-14-9 is low. The acute dermal toxicity of CASRN 101-96-2 and 3081-14-9 to rabbits is low. The acute inhalation toxicity of CASRN 101-96-2 to rats is low.

Repeated administration of CASRN 101-96-2 via oral gavage to rats for 28 days resulted in increased liver weights and elevation of serum enzymes with a dose-dependent increase in the incidence of hepatocellular lesions indicative of hepatocellular damage at 10 mg/kg bw/day; the NOAEL is not determined. Following 90 days of dietary exposure of CASRN 3081-14-9 to rats, adverse effects included reduced mean body weight and body weight gain at \geq ~22.82 mg/kg-bw/day in males and at all doses in females. Increased alkaline phosphatase levels at high doses in males and females and decreased serum glutamic pyruvic transaminase levels in females were seen at \geq ~45.65 mg/kg-bw/day; however, there were no accompanying histopathological changes. For females, the LOAEL is ~ 22.82 mg/kg-bw/day; NOAEL is not established. For males, the NOAEL is ~ 9.13 mg/kg-bw/day (lowest dose tested).

There was no adequate reproductive toxicity study; however, no effects were reported on reproductive organs in the 90-day repeated exposure study, mentioned above, and no developmental effects were reported in the pre-natal developmental toxicity study.

A prenatal developmental toxicity study in rats of CASRN 3081-14-9 resulted in no adverse fetus effects; the NOAEL is 150 mg/kg-bw/day (highest dose tested). In this study the maternal

toxicity NOAEL is 25 mg/kg-bw/day, based on effects seen at ≥ 75 mg/kg/day (survival, behavior and body weight gain).

CASRN 3081-14-9 did not induce gene mutations in bacteria and mammalian cells *in vitro*. No data are available on chromosomal aberrations. CASRN 101-96-2 is corrosive to the rabbit skin and eyes and sensitizing to guinea pigs, while CASRN 3081-14-9 is irritating to the rabbit skin and eyes and sensitizing to guinea pigs.

Subcategory II: 4-Aminodiphenylamine Derivatives

The acute oral toxicity of CASRNs 68953-84-4 and 3081-01-4 to rats is low, while the acute oral toxicity of CASRN 15233-47-3 to rats is high. The acute inhalation toxicity of CASRN 3081-01-4 to rats is high. The acute dermal toxicity of CASRNs 68953-84-4, 3081-01-4 and 15233-47-3 to rabbits is low.

Repeated administration of CASRN 68953-84-4 to rats via the diet for 28 days resulted in macrocytic anemia at ≥ 30 mg/kg-bw/day; the NOAEL is 7.5 mg/kg-bw/day. Repeated administration of CASRN 3081-01-4 to rats via the diet for 28 days resulted in no adverse effects; the NOAEL is ~ 273.89 mg/kg-bw/day (highest dose tested).

In a two generation reproductive toxicity study, dietary administration of CASRN 68953-84-4 to rats resulted in increased dystocia, perinatal deaths, decreased live births and increased pup weights at $\geq \sim 8.78$ mg/kg-bw/day; a NOAEL for reproductive toxicity is not established. In this study, exposure at $\geq \sim 8.78$ mg/kg-bw/day resulted in polycystic kidney lesions in parental animals; NOAEL for systemic toxicity is not established.

A prenatal developmental toxicity of CASRN 68953-84-4 in rats resulted in no treatment-related effects on pregnancy rates, litter sizes, number of live fetuses, uterine implantation or any gestational parameters. A linear dose-related trend for decreased fetal body weight was observed with an approximate 5% decrease at the highest dose, 200 mg/kg-bw/day; the NOAEL for developmental toxicity is not established. In maternal rats, exposure to 200 mg/kg-bw/day resulted in reduced body weight and food consumption; the maternal toxicity NOAEL is 70 mg/kg-bw/day.

CASRN 68953-84-4 induced gene mutation in bacteria *in vitro*, but CASRNs 3081-01-4 and 15233-47-3 did not. CASRN 3081-01-4 was weakly positive in mammalian cells *in vitro*. CASRNs 68953-84-4 and 3081-01-4 did not induce chromosomal aberrations in bone marrow erythrocytes mice or rats *in vivo*. CASRN 3081-01-4 is not irritating to rabbit skin. CASRN 68953-84-4 and CASRN 15233-47-3 are irritating to the rabbit skin. CASRNs 68953-84-4, 3081-01-4 and 15233-47-3 are irritating to rabbit eyes. CASRN 68953-84-4 is a contact sensitizer in guinea pigs.

**Table 3. Summary Table of the Screening Information Data Set
as Submitted under the U.S. HPV Challenge Program –
Human Health Data**

	Subcategory I: N-Alkylated <i>p</i> -Phenylenediamines		Subcategory II: 4-Aminodiphenylamine Derivatives			
Endpoints	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N,N-di- sec-butyl (101-96-2)	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N,N-bis(1,4-di- methylpentyl) (3081-14-9)	SPONSORED CHEMICAL 1,4-Benzene- diamine, N,N'-mixed Ph and tolyl derivatives (68953-84-4)	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N-(1,4-dimethyl- pentyl)-N'-phenyl- (3081-01-4)	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N-(1-methylheptyl)- N'-phenyl- (15233-47-3)	SUPPORTING CHEMICAL <i>p</i> -Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)
Acute Oral Toxicity LD ₅₀ (mg/kg)	148	730	> 5000	2100	4.3	3580
Acute Inhalation Toxicity LC ₅₀ (mg/L)	> 0.2	No Data > 0.2 (RA)	No Data > 0.14 (RA)	> 0.14	No Data > 0.14 (RA)	–
Acute Dermal Toxicity LD ₅₀ (mg/kg)	2806	> 3160	> 2000	> 5010	> 2000	> 7940
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg- bw/day)	NOAEL = NE LOAEL = 10	NOAEL = 9.1 LOAEL = 22.8 (males) NOAEL = NE LOAEL = 45.65 LOAEL = 22.8 (females)	NOAEL = 7.5 LOAEL = 30	NOAEL = 273.89 (highest dose tested)	No Data NOAEL = 7.5 LOAEL = 30 (RA)	NOAEL = 19 LOAEL = 75
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg- bw/day)			NOAEL = NE LOAEL = 8.8	NOAEL = NE LOAEL = 8.8	NOAEL = NE LOAEL = 8.8	NOAEL = 8 LOAEL = 23
Systemic Toxicity			NOAEL = NE LOAEL = 8.8	NOAEL = NE LOAEL = 8.8	NOAEL = NE LOAEL = 8.8	NOAEL = 8 LOAEL = 23
Reproductive Toxicity	No adequate data. No effects on reproductive organs in the 90- day study (RA)	No adequate data. No effects on reproductive organs in the 90- day study.	NOAEL = Not established LOAEL = 8.78	NOAEL = Not established LOAEL = 8.78 (RA)	NOAEL = Not established LOAEL = 8.78(RA)	NOAEL = 75 (highest dose tested)
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg- bw/day)	No Data	(Rat)		No Data	No Data	

**Table 3. Summary Table of the Screening Information Data Set
as Submitted under the U.S. HPV Challenge Program –
Human Health Data**

	Subcategory I: N-Alkylated <i>p</i> -Phenylenediamines		Subcategory II: 4-Aminodiphenylamine Derivatives			
Endpoints	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N,N-di- sec-butyl (101-96-2)	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N,N-bis(1,4-di- methylpentyl) (3081-14-9)	SPONSORED CHEMICAL 1,4-Benzene- diamine, N,N'-mixed Ph and tolyl derivatives (68953-84-4)	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N-(1,4-dimethyl- pentyl)-N'-phenyl- (3081-01-4)	SPONSORED CHEMICAL <i>p</i> -Phenylene- diamine, N-(1-methylheptyl)- N'-phenyl- (15233-47-3)	SUPPORTING CHEMICAL <i>p</i> -Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)
Maternal Toxicity	NOAEL = 25 LOAEL = 75	NOAEL = 25 LOAEL = 75	NOAEL = 70 LOAEL = 200	NOAEL = 70 LOAEL = 200	NOAEL = 70 LOAEL = 200	NOAEL = 50 LOAEL = 100
Developmental Toxicity	NOAEL = 150 (hdt) (RA)	NOAEL = 150 (hdt)	NOAEL=NE LOAEL=20	NOAEL=NE LOAEL=20 (RA)	NOAEL=NE LOAEL=20(RA)	NOAEL = 250 (hdt)
Maternal and Developmental Toxicity						
Genetic Toxicity – Gene Mutation <i>In vitro</i>	No Data Negative (RA)	Negative	Positive	Negative	Negative	Weakly positive
Genetic Toxicity – Gene Mutation <i>In vivo</i>	– ¹	– ¹	Negative	No Data Negative (RA)	No Data Negative (RA)	– ¹
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	No data	No data	Negative	Weakly positive	No Data Weakly positive (RA)	– ¹
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	– ¹	– ¹	Negative	Negative	No Data Negative (RA)	Negative
Additional Information						
Skin Irritation	Corrosive	Irritating	Irritating	Not irritating	Irritating	Not irritating
Eye Irritation	Corrosive	Irritating	Irritating	Irritating	Irritating	Irritating
Sensitization	Sensitizing	Sensitizing	Sensitizing			Sensitizing

Measured data in bold: (RA) = read-across; –¹ indicates endpoint not needed for this chemical; hdt = highest dose tested; NE= not established

4. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

p-Phenylenediamine, N,N-di-sec-butyl (CASRN 101-96-2)

(1) Rainbow trout (*Salmo gairdneri*) were exposed to *p*-phenylenediamine, N,N-di-sec-butyl (> 97% pure) at concentrations of 0, 0.018, 0.032, 0.056, 0.10 and 0.18 mg/L under static conditions for 96 hours in a closed system. Nanograde acetone was used as a solvent control.

96-h LC₅₀ = 0.13 mg/L

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to *p*-phenylenediamine, N,N-di-sec-butyl (> 97% pure) at concentrations of 0, 0.032, 0.056, 0.10, 0.18 and 0.32 mg/L under static conditions for 96 hours in a closed system. Nanograde acetone was used as a solvent control.

96-h LC₅₀ = 0.18 mg/L

(3) Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N,N-di-sec-butyl (> 97% pure) at concentrations of 0, 0.056, 0.10, 0.18, 0.32 and 0.56 mg/L under static conditions for 96 hours in a closed system. Nanograde acetone (1.0 mL) was used as a solvent control.

96-h LC₅₀ = 0.13 mg/L

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

(1) Rainbow trout (*Salmo gairdneri*) were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) (> 99% pure) at nominal concentrations of 0, 24, 32, 42, 56, 75 or 140 µg/L (0, 0.024, 0.032, 0.042, 0.056, 0.075 or 0.14 mg/L, respectively) under static conditions for 96 hours in a closed system. Acetone was used as a solvent control.

96-h LC₅₀ = 0.032 mg/L

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) (> 99% pure) at nominal concentrations of 0, 140, 180, 240, 320 or 560 µg/L (0, 0.14, 0.18, 0.24, 0.32 or 0.56 mg/L, respectively) under static conditions for 96 hours in a closed system.

96-h LC₅₀ = 0.182 mg/L

(3) Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) (> 99% pure) at concentrations of 0, 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2 or 5.6 mg/L for 96 hours under static conditions in a closed system. Nanograde acetone was used as a solvent control.

96-h LC₅₀ = 0.28 mg/L

p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)

(1) Rainbow trout (*Salmo gairdneri*) were exposed to *p*-phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (> 96% pure) at concentrations of 0, 0.10, 0.18, 0.32, 0.56 and 1.0

mg/L under static conditions for 96 hours in a closed system. Nanograde acetone (1.0 mL) was used as a solvent control.

96-h LC₅₀ = 0.42 mg/L

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to *p*-phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (97.9% pure) at concentrations of 0, 0.1, 0.18, 0.32, 0.56 and 1.0 mg/L under static conditions for 96 hours in a closed system. Nanograde acetone was used as a solvent control.

96-h LC₅₀ = 0.30 mg/L

(3) Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (97.9% pure) at concentrations of 0, 0.32, 0.56, 1.0, 1.8 and 3.2 mg/L under static conditions for 96 hours in a closed system. Nanograde acetone (1.0 mL) was used as a solvent control.

96-h LC₅₀ = 1.10 mg/L

(4) Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) at measured concentrations of 0, 0.03, 0.03, 0.05, 0.010 and 0.17 mg/L.

96-h LC₅₀ = 0.06 mg/L

Acute Toxicity to Aquatic Invertebrates

p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)

Daphnia magna were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) at nominal concentrations of 0.10, 0.18, 0.32, 0.56 and 1.0 mg/L under static conditions for 48 hours.

48-h LC₅₀ = 0.37 mg/L

4-Aminodiphenylamine Derivatives

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

Daphnia magna were exposed to 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives at nominal concentrations of 0, 1.3, 2.2, 3.6, 6.0 and 10 mg/L under unspecified conditions.

48-h LC₅₀ = 0.36 mg/L

Toxicity to Aquatic Plants

1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)

Green algae (*Pseudokirchneriella subcapitata*) were exposed to 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives for 72 hours under measured concentrations of 7.5, 13, 14, 28, 50 and 79 µg/L (0.0075, 0.013, 0.014, 0.028, 0.05 and 0.079 mg/L, respectively). Conditions were unspecified.

72-h EC₅₀ (biomass) = 0.018 mg/L

72-h EC₅₀ (growth) > 0.079 mg/L

***p*-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (CASRN 3081-01-4)**

Green algae (*Pseudokirchneriella subcapitata*) were exposed to *p*-phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (> 96% pure) at concentrations of 0, 0.3, 0.6, 1.2, 2.5 and 5.0 ppm (0, 0.3, 0.6, 1.2, 2.5 and 5.0 mg/L) under unspecified conditions for 96 hours in a closed system. Reagent-grade dimethylformamide (DMF) was used (maximum volume 0.05 mL) as the solvent control. pH was monitored during testing.

96-h EC₅₀ (biomass) = 0.7 mg/L

96-h EC₅₀ (growth) = 0.7 mg/L

Chronic Toxicity to Fish

***N*-Alkylated *p*-Phenylenediamines**

***p*-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (CASRN 3081-14-9)**

(1) Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) (99+% pure) under flow-through, dynamic acute conditions for 14 days in an open system. The mean measured concentrations were 0.018, 0.046, 0.11, 0.22 and 0.45 mg/L. Temperature, pH and ammonia levels were monitored during the study; analytical monitoring was conducted. The 14-day NOEC and LOEC values were 0.018 and 0.046 mg/L, respectively.

14-d LC₅₀ = 0.067 mg/L

(2) Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N,N-bis(1,4-dimethylpentyl) (99+% pure) under flow-through (time-independent bioassay) conditions for 14 days in an open system. Measured concentrations were 0, 0.03, 0.03, 0.05, 0.10 and 0.17 mg/L.

14-d LC₅₀ = 0.05 mg/L

***4*-Aminodiphenylamine Derivatives**

***1,4*-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (CASRN 68953-84-4)**

(1) Carp (*Cyprinus carpio*) were exposed to 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives at nominal concentrations of 0, 0.1, 0.23, 0.51, 1.1 and 2.5 mg/L under flow-through conditions for 14 days. Mortality occurred only at the highest test concentration. Other treatment-related effects included darkened pigmentation, lethargic swimming behavior and loss of equilibrium. The NOEC was 0.28 mg/L.

14-d LC₅₀ = 0.43 mg/L

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to 1,4-benzenediamine, N,N'-mixed Ph and tolyl derivatives under flow-through conditions for 14 days. The mean measured concentrations were 0.062, 0.093, 0.14, 0.35 and 0.66 mg/L. Mortality occurred at concentrations of 0.35 and 0.66 mg/L. Other treatment-related effects included darkened pigmentation, lethargic swimming behavior and loss of equilibrium. The NOEC was 0.14 mg/L.

14-d LC₅₀ = 0.26 mg/L

***p*-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CASRN 793-24-8, supporting chemical)**

Fathead minnows (*Pimephales promelas*) were exposed to *p*-phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl- (> 95% pure) in acetone at nominal concentrations of 0, 0.066, 0.12, 0.23, 0.45 or 1.0 mg/L under flow-through conditions for 28 days in an open system. Measured concentrations were 0, 0.033, 0.075, 0.16, 0.40 and 1.0 mg/L. Water quality parameters (dissolved oxygen, temperature, pH and ammonia) were monitored during testing. LC₅₀ values were provided at 2, 7, 14 and 28 days.

28-d LC₅₀ = 0.15 mg/L

Conclusion:

The 96-hour LC₅₀ of CASRN 101-96-2 for fish ranges from 0.13 to 0.18 mg/L. The 96-hour LC₅₀ of CASRN 3081-14-9 for fish ranges from 0.032 to 0.28 mg/L. The 96-hour LC₅₀ for CASRN 3081-01-4 for fish ranges from 0.06 to 1.10 mg/L.

The 48-hour EC₅₀ of CASRN 3081-14-9 for aquatic invertebrates is 0.37 mg/L. The 48-hour EC₅₀ of CASRN 68953-84-4 for aquatic invertebrates is 0.36 mg/L.

The 96-hour EC₅₀ of CASRN 68953-84-4 for aquatic plants is 0.018 mg/L (biomass) and 0.079 mg/L (growth rate). The 96-hour EC₅₀ for CASRN 3081-01-4 for aquatic plants is 0.7 mg/L (biomass and growth rate).

The 28-day LC₅₀ of CASRN 793-24-8 for fish ranges from 0.15 to 0.067 mg/L.

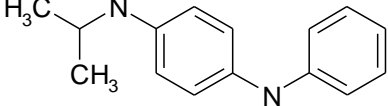
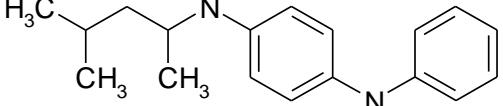
Table 4. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	<i>p</i> -Phenylenediamine, N,N-di-sec-butyl (101-96-2)	<i>p</i> -Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivatives (68953-84-4)	<i>p</i> -Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl- (3081-01-4)	<i>p</i> -Phenylenediamine, N-(1-methylheptyl)-N'-phenyl- (15233-47-3)	<i>p</i> -Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8), supporting chemical
Fish 96-h LC₅₀ (mg/L)	0.13 - 0.18 (m)	0.032 -0.28 (m)	No Data 0.06 – 1.10 (RA)	0.06 – 1.10 (m)	No Data 0.06 – 1.10 (RA)	0.14 (m)
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	No Data 0.37 (RA)	0.37 (m)	0.36 (m)	No Data 0.36 (RA)	No Data 0.36 (RA)	–
Aquatic Plants 96-h EC₅₀ (mg/L)	No Data	No Data			No Data	
Biomass Growth rate	0.018 – 0.7 (RA) 0.079 – 0.7(RA)	0.018 – 0.7 (RA) 0.079 – 0.7(RA)	0.018 (m) 0.079 (m)	0.7 (m) 0.7 (m)	0.018 – 0.7 (RA) 0.079 – 0.7(RA)	0.6 (m) 0.6 (m)
Chronic fish/ invertebrate toxicity 28-d Chv	No Data 0.15 (RA)	No Data 0.15 (RA)	No Data 0.15 (RA)	No Data 0.15 (RA)	No Data 0.15 (RA)	0.15 (28-d; m)

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read-Across; – indicates that endpoint was not evaluated for this substance

APPENDIX

Chemical Name	CASRN	Structure
Sponsored Chemicals		
Subcategory I: N-Alkylated <i>p</i>-Phenylenediamines		
1,4-Benzenediamine, N1,N4-bis(1-methylpropyl)-	101-96-2	<p>SMILES: <chem>N(c(ccc(NC(CC)C)c1)c1)C(CC)C</chem></p>
1,4-Benzenediamine, N1,N4-bis(1,4-dimethylpentyl)-	3081-14-9	<p>SMILES: <chem>N(c(ccc(NC(CCC(C)C)C)c1)c1)C(CCC(C)C)C</chem></p>
Subcategory II: 4-Aminodiphenylamine derivatives		
1,4-Benzenediamine, N,N'-mixed Ph and tolyl derivs.	68953-84-4	<p>Representative SMILES: <chem>C1=CC=CC=C1NC2=CC=C(NC3=CC=CC=C3)C=C2</chem>; <chem>C1=CC(C)=CC=C1NC2=CC=C(NC3=CC=CC=C3)C=C2</chem>; <chem>C1=CC(C)=CC=C1NC2=CC=C(NC3=CC=C(C)C=C3)C=C2</chem></p>
1,4-Benzenediamine, N1-(1,4-dimethylpentyl)-N4-phenyl-	3081-01-4	<p>SMILES: <chem>N(c(ccc(Nc1ccc2ccccc2c1)1)c1)c2)c2)C(CCC(C)C)C</chem></p>
1,4-Benzenediamine, N1-(1-methylheptyl)-N4-phenyl-	15233-47-3	

Chemical Name	CASRN	Structure
		SMILES: N(c(ccc(Nc(cccc1) c1) c2) c2) C(CCCCC) C
Supporting Chemicals		
1,4-Benzenediamine, N1-(1-methylethyl)-N4-phenyl-	101-72-4	 SMILES: N(c(ccc(Nc(cccc1) c1) c2) c2) C(C) C
1,4-Benzenediamine, N1-(1,3-dimethylbutyl)-N4-phenyl-	793-24-8	 SMILES: N(c(ccc(Nc(cccc1) c1) c2) c2) C(CC(C) C) C