

SCREENING-LEVEL HAZARD CHARACTERIZATION Monocyclic Aromatic Amines Category

Sponsored Chemicals

<i>N,N</i> -Diethylaniline	CASRN 91-66-7
<i>N,N</i> -Dimethyl- <i>p</i> -toluidine	CASRN 99-97-8
<i>N</i> -Ethyl- <i>m</i> -toluidine	CASRN 102-27-2
<i>N</i> -Ethylaniline	CASRN 103-69-5

Supporting Chemicals

Aniline	CASRN 62-53-3
<i>N,N</i> -Dimethylaniline	CASRN 121-69-7
<i>o</i> -Toluidine	CASRN 95-53-4
<i>m</i> -Toluidine	CASRN 108-44-1
<i>p</i> -Toluidine	CASRN 106-49-0

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^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

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

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

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

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.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p><u>Sponsored Chemicals</u></p> <p>CASRN 91-66-7 CASRN 99-97-8 CASRN 102-27-2 CASRN 103-69-5</p> <p><u>Supporting Chemicals</u></p> <p>CASRN 62-53-3 CASRN 121-69-7 CASRN 95-53-4 CASRN 108-44-1 CASRN 106-49-0</p>
<p>Chemical Abstract Index Name</p>	<p><u>Sponsored Chemicals</u></p> <p>Benzenamine, <i>N,N</i>-diethyl-</p> <p>Benzenamine, <i>N,N</i>, 4-trimethyl-</p> <p>Benezenamine, <i>N</i>-ethyl-3-methyl-</p>

	<p>Benzenamine, <i>N</i>-ethyl-</p> <p><u>Supporting Chemicals</u></p> <p>Benzenamine</p> <p>Benzenamine, <i>N,N</i>-dimethyl-</p> <p>Benzenamine, 2-methyl-</p> <p>Benzenamine, 3-methyl-</p> <p>Benzenamine, 4-methyl-</p>
<p>Structural Formula</p>	<p>See Section 1</p>
<p style="text-align: center;">Summary</p> <p>The monocyclic aromatic amines are liquids with moderate to high water solubility and moderate vapor pressure. They are expected to have moderate to high mobility in soil. Volatilization of the monocyclic aromatic amines from water and moist soils is considered moderate based upon their Henry's Law constants; however, the pK_a values for the category members indicates that these substances will partially exist in the conjugate acid form (cations) and cations will not volatilize. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate to rapid. Based on the measured data and professional judgments, the monocyclic aromatic amines are expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute toxicity by the oral and dermal routes is low for three sponsored category members and moderate for one sponsored category member (CASRN 103-69-5). The acute toxicity by the inhalation route is high for all four sponsored category members. Repeated-dose subchronic toxicity studies in rats with the sponsored category chemicals CASRNs 91-66-7 via the oral route and 102-27-2 via the inhalation route showed hematological and histopathological changes in the spleen and liver consistent with hemolytic anemia at 10 mg/kg-bw/day (lowest dose) and 0.18 mg/L, respectively; the NOAEL for systemic toxicity was not established by the oral route and was 0.03 mg/L by the inhalation route. Repeated-dose subchronic toxicity studies in rats and/or mice by the oral route with the supporting chemicals CASRNs 62-53-3, 121-69-7, 95-53-4, and 108-44-1 showed changes in the bone marrow and spleen between 31.25 and 225 mg/kg-bw/day; with mortality observed at 110 and 225 mg/kg-bw/day for CASRNs 62-53-3 and 95-53-4, respectively. Among the supporting chemicals, the only study reporting a NOAEL for systemic toxicity (30 mg/kg-bw/day) was CASRN 108-44-1. Reproductive toxicity studies were not available for any sponsored chemical; however, chronic toxicity studies in rats and mice by the oral route with the supporting chemical CASRN 62-53-3, showed no treatment-related effects to reproductive organs; the NOAEL for reproductive toxicity was 72 mg/kg-bw/day. A combined repeated-dose/reproductive/developmental toxicity screening study with limited postnatal evaluations by the oral route in rats with the supporting chemical, CASRN 108-44-1, showed adult systemic toxicity as demonstrated by hematological and histopathological changes in the liver and spleen consistent with hemolytic anemia, and reproductive toxicity as demonstrated by implantation losses, all at 100 mg/kg-bw/day; the NOAEL for adult systemic and reproductive</p>	

toxicity was 30 mg/kg-bw/day. There was no evidence of developmental toxicity in this study (NOAEL 100 mg/kg-bw/day). A prenatal developmental toxicity study in rats by the oral route with the sponsored chemical CASRN 91-66-7 showed mortality in the dams at 500 mg/kg-bw/day; the NOAEL for maternal and developmental toxicity was 250 mg/kg-bw/day. An oral prenatal developmental toxicity study in rats with the supporting chemical, CASRN 62-53-3, which included extensive postnatal evaluations, showed increases in relative spleen weights in the dams at 10 mg/kg-bw/day, the lowest dose; the NOAEL for maternal toxicity was not established. In the same study, there was developmental toxicity at 100 mg/kg-bw/day as demonstrated by increased relative liver weight and enhanced hematopoietic activity in fetuses sacrificed on gestation day 20; and transient decreases in postnatal pup body weight; the NOAEL for developmental toxicity was 30 mg/kg-bw/day. A Chernoff/Kavlock assay by the oral route in mice with the supporting chemical CASRN 121-69-7 showed mortality in the dams at doses \leq 365 mg/kg-bw/day, the only dose tested; the NOAEL for maternal toxicity was not established. There was no evidence of developmental toxicity in this study and the NOAEL was \geq 365 mg/kg-bw/day. Sponsored category members, CASRNs 103-69-5, 91-66-7 and 99-97-8, were not mutagenic when tested *in vitro*; whereas CASRN 102-27-2 was mutagenic *in vitro*. Supporting chemicals CASRNs 62-53-30, 121-69-7, 121-69-7, 106-49-0, and the sponsored chemical CASRN 99-97-8 induced chromosomal aberrations when tested *in vitro*; whereas the supporting chemical CASRN 108-44-1 did not. Supporting chemical CASRN 62-53-3 did induce chromosomal aberrations when tested *in vivo*, while sponsored chemical CASRN 91-66-7 and supporting chemical CASRN 106-49-0 did not. The sponsored category members were not irritating to rabbit eyes; were slightly-to-severely irritating to rabbit, but not rat skin; and are not sensitizing. Chronic/carcinogenicity studies with the supporting chemical CASRN 121-69-7, with aniline hydrochloride (CASRN 142-04-1), *o*-toluidine hydrochloride (CASRN 636-21-5), *m*-toluidine hydrochloride (CASRN 638-03-9), and *p*-toluidine hydrochloride (CASRN 540-23-8) showed evidence of carcinogenicity in rats and/or mice. (Based on these cancer data – and the concern for cancer for this class of chemicals - the sponsor proposed to conduct low pH Syrian Hamster Embryo (SHE) cell transformation assays with two of the sponsored chemicals (CASRNs 102-27-2 and 103-69-5).

The measured 96-hour LC₅₀ for the monocyclic aromatic amines category members for fish ranges from 16.4 to 49.5 mg/L. The measured 48-hour EC₅₀ for aquatic invertebrates is 1.3 mg/L, and the measured 72-hour/96-hour EC₅₀ for aquatic plants is 5.6 to 22 mg/L.

No data gaps were identified under the HPV Challenge Program.

The sponsor, American Chemistry Council, Monocyclic Aromatic Amines and Nitroaromatics Panel, submitted a Test Plan and Robust Summaries to EPA for the Monocyclic Aromatic Amines Category on November 21, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 11, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/aroamin/c13310tc.htm>). EPA comments on the original submission were posted to the website on April 4, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 3, 2002 which were posted to the ChemRTK website on July 24, 2002.

Category Justification

The four members of the monocyclic aromatic amines category are *N*-alkyl substituted aromatic amines having a single amino group with methyl or ethyl substituents on the nitrogen atom. Two of the category members also have a methyl substituent on the aromatic ring, i.e., the toluidines. The category members are typically manufactured by reaction of an aniline or a toluidine isomer with either methanol or formaldehyde for the *N*-methyl derivatives or ethanol or acetaldehyde for *N*-ethyl derivatives. The category members are used as chemical intermediates in the synthesis of a variety of organic chemicals. The sponsor grouped the chemicals based on the similarities in structure and available supporting data. Based on similarities in structure, physical-chemical properties and toxicological properties, EPA considers the grouping of the four substances into one category appropriate.

Supporting Chemicals Justification

The sponsor submitted data for supporting chemicals to address data gaps for the repeated-dose, reproductive and developmental toxicity and chromosomal aberrations endpoints. The supporting chemicals are similar in structure and exhibit toxicity similar to the sponsored substances. The carcinogenicity of the supporting chemicals was evaluated using the hydrochloride forms of aniline and *o*-toluidine (CASRNs 142-04-1 and 636-21-5, respectively) EPA considered them appropriate to use as supporting chemicals. Furthermore, the supporting chemicals, aniline, *o*-toluidine, *m*-toluidine and *p*-toluidine have been evaluated in the OECD HPV chemicals program and the data are available from the OECD website at <http://cs3-hq.oecd.org/scripts/hpv/>. These data have been used, where appropriate, to characterize the toxicity of the sponsored substances.

1 Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2001 Test Plan and Robust Summaries:

The aromatic amines all have a single amino group and are secondary or tertiary amines with methyl or ethyl substituents on the nitrogen atom. Some of these aromatic amines also have a methyl substituent on the aromatic ring. Test substance purity, when noted in the Robust Summaries, ranged between 98% - 99%. The chemical structures of the monocyclic aromatic amines category sponsored and supporting chemicals are depicted in Table 1.

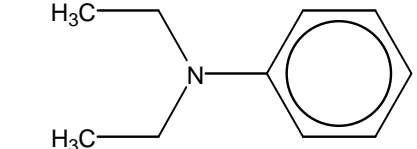
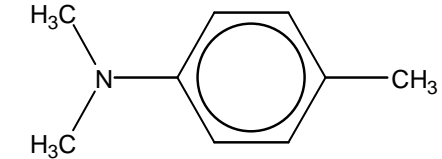
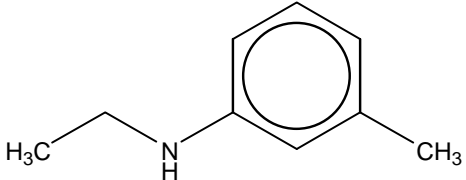
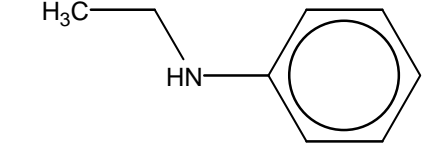
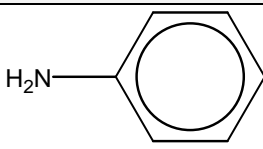
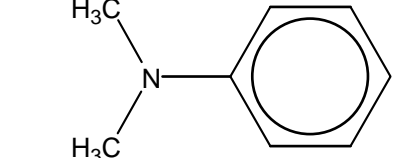
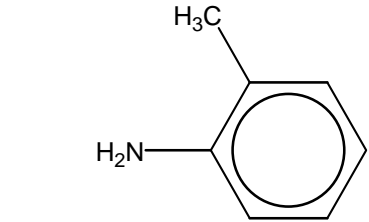
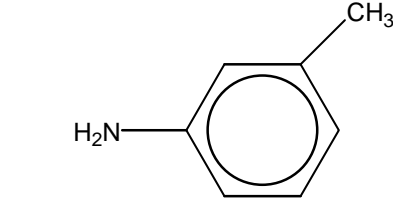
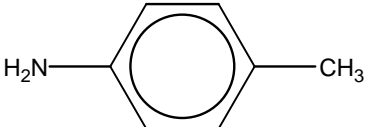
Table 1: Monocyclic Aromatic Amines Category Sponsored and Supporting Chemical Structures		
CASRN	Chemical Name	Structure
Sponsored Chemicals		
91-66-7	<i>N,N</i> -Diethylaniline	
99-97-8	<i>N,N</i> -Dimethyl- <i>p</i> -toluidine	
102-27-2	<i>N</i> -Ethyl- <i>m</i> -toluidine	
103-69-5	<i>N</i> -Ethylaniline	
Supporting Chemicals		
62-53-3	Aniline	
121-69-7	<i>N,N</i> -Dimethylaniline	
95-53-4	<i>o</i> -Toluidine	
108-44-1	<i>m</i> -Toluidine	

Table 1: Monocyclic Aromatic Amines Category Sponsored and Supporting Chemical Structures		
CASRN	Chemical Name	Structure
106-49-0	<i>p</i> -Toluidine	

1.2 Physical-Chemical Properties

The monocyclic aromatic amines are liquids with moderate to high water solubility and moderate vapor pressure. The physical-chemical properties of the monocyclic aromatic amines are summarized in Table 2.

Table 2. Physical-Chemical Properties of Monocyclic Aromatic Amines Category¹

Property	Sponsored Chemicals				Supporting Chemicals				
	N,N-Di-ethyl-aniline	N,N-Di-methyl- <i>p</i> -toluidine	N-Ethyl- <i>m</i> -toluidine	N-Ethyl-aniline	Aniline	<i>o</i> -Toluidine	<i>p</i> -Toluidine	<i>m</i> -Toluidine	N,N-Di-methyl-aniline
CASRN	91-66-7	99-97-8	102-27-2	103-69-5	62-53-3	95-53-4	106-49-0	108-44-1	121-69-7
Molecular Weight	149.2	135.2	135.2	121.2	93.1	107.2	107.2	107.2	121.2
Physical State	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Solid	Liquid	Liquid
Melting Point	-38.8°C (measured)	-6.6°C (estimated)	8.7°C (estimated)	-64°C (measured)	-6.2°C (measured)	-16.3°C (measured)	43.7°C (measured)	-31.2°C (measured)	2.4°C (measured)
Boiling Point	215.5–217.1°C (measured)	211°C (measured)	221°C (measured)	203–207°C (measured)	184.0°C (measured)	200.3°C (measured)	200.4°C (measured)	203.3°C (measured)	194.1°C (measured)
Vapor Pressure (mm Hg)	0.136 at 25°C (measured)	0.178 at 25°C (measured); 1.0 at 50°C (measured)	0.125 at 25°C (estimated); 1.0 at 54°C (measured)	0.30 at 20°C; 0.75 at 38°C; 1.4 at 50°C (measured)	0.49 at 25°C (measured)	0.26 at 25°C (measured)	0.286 at 25°C (measured)	0.303 at 25°C (measured)	0.70 at 25°C (measured)
Water Solubility (mg/L)	130 at 20°C pH 7 (measured)	455 (measured at unreported temperature); 650 at 37°C (measured)	1,131 at 20°C (measured)	2,700 at 20°C (measured)	36,000 at 20°C pH 8.8 (measured)	8,000 at 20°C pH 7.5 (measured); 16,600 at 20°C (measured)	11,000 at 20°C (measured)	12,000 at 20°C (measured); 17,000 at 25°C (measured)	1,200 at 20°C pH 7.4 (measured)
Log K _{ow}	3.17–4.00 (measured)	2.61 - 2.81 at 25°C (measured)	2.66 (estimated)	1.92–2.26 at 25°C (measured)	0.91 (measured)	1.4 at 24.5°C (measured)	1.39 (measured)	1.40 (measured)	2.28 (estimated)
Dissociation Constant (pK _a)	6.57 (measured)²	5.63 (measured)²	5.25 (measured) ²	5.12 (measured)²	4.60 (measured)²	4.44 (measured)²	5.10 (measured)²	4.70 (measured)	5.15 (measured) ²
Henry's Law Constant (atm-m ³ /mole)	1.9×10 ⁻⁴ (estimated) ³	9.45×10 ⁻⁵ (estimated) ³	6.12×10 ⁻⁶ (estimated) ³	9.78×10⁻⁶ (measured)²	2.02×10⁻⁶ (measured)²	1.98×10⁻⁶ (measured)²	2.02×10⁻⁶ (measured)²	1.66×10⁻⁶ (measured)	7.7×10 ⁻⁵ (estimated) ³

¹Bayer Corporation. July 8, 2002. Robust Summary for Monocyclic Aromatic Amines.

<http://www.epa.gov/chemrtk/pubs/summaries/aroamin/c13310tc.htm>.

²SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from <http://www.syrres.com/esc/physprop.htm> as of September 15, 2008.

³U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

The monocyclic aromatic amines category chemicals had the following aggregated production and/or import volumes in the United States in 2005:

- CASRNs 91-66-7 and 102-27-2: between 500,000 and one million pounds each
- CASRN 99-97-8: between one million and ten million pounds
- CASRN 103-69-5: between 10,000 and 500,000 pounds

Non-confidential information in the IUR submissions indicated that the industrial processing and uses of these chemicals include: processing as an intermediate in petrochemical manufacturing; as a process regulator used in vulcanization or polymerization processes; and as an intermediate in synthetic dye and pigment manufacturing. Non-confidential information in the IUR indicated that the commercial and consumer products containing these chemicals include the inherently nonspecific “other” category (C20). The HPV submission for this category states that the chemicals in the monocyclic aromatic amines category are used as chemical intermediates. CASRN 91-66-7 is used as a chemical intermediate to make dyes, pesticides, polyester resins, and pharmaceuticals. CASRN 102-27-2 is an intermediate in the production of dyes and color developers for photographic films, while CASRN 103-69-5 is an intermediate in the production of dyes and pharmaceuticals and is also used as a promoter in the production of polyester resins. The HSDB information for these chemicals states that they are used as chemical intermediates for dyes and other organic syntheses, and as an explosive stabilizer.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of the chemicals in this category to the environment.

The environmental fate properties are provided in Table 3. The monocyclic aromatic amines are expected to have moderate to high mobility in soil. Biodegradation data was available for three of the four sponsored monocyclic aromatic amines. *N,N*-Diethylaniline and *N*-ethylaniline were found to degrade rapidly in ready tests at low environmentally relevant concentrations, but showed no degradation at higher concentrations. *N*-Ethyl-*m*-toluidine was not readily biodegradable. The supporting chemicals, aniline, *N,N*-dimethylaniline, *m*-toluidine, *p*-toluidine, and *o*-toluidine have all been found to be readily biodegradable, although *N,N*-dimethyl aniline and *m*-toluidine had mixed results. The sponsored chemical *N,N*-dimethyl-*p*-toluidine, has not been tested for biodegradation, but is expected to biodegrade after acclimation based on results from the other chemicals in this group. Volatilization of the monocyclic aromatic amines from water and moist soils is considered moderate based upon their Henry's Law constants; however, the pK_a values for the category members indicates that these substances will partially exist in the conjugate acid form (cations) and cations will not volatilize. The rate of hydrolysis is expected to be negligible. The rate of atmospheric photooxidation is considered rapid except for *N*-ethylaniline which is considered moderate. Based on the measured data and professional

judgments, the monocyclic aromatic amines are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 3. Environmental Fate Characteristics of Monocyclic Amines Category¹

Property	Sponsored Chemicals				Supporting Chemicals				
	N,N-Diethyl-aniline	N,N-Dimethyl- <i>p</i> -toluidine	N-Ethyl- <i>m</i> -toluidine	N-Ethyl-aniline	Aniline	<i>o</i> -Toluidine	<i>p</i> -Toluidine	<i>m</i> -Toluidine	N,N-Dimethyl-aniline
CASRN	91-66-7	99-97-8	102-27-2	103-69-5	62-53-3	95-53-4	106-49-0	108-44-1	121-69-7
Photodegradation Half-life	0.8 hours (estimated)	0.6 hours (estimated)	1.1 hours (estimated)	2.5 hours (estimated)	3.26–3.5 hours (measured)	9.7 hours (estimated) ⁴	1.0 hours (estimated)	1.8 hours (estimated)	2.6 hours (measured)
Biodegradation Half-life	0% in 28 days (OECD 301C); >90% in 20 days (OECD 301D); 0% after 14 days (OECD 301C)	No data	0% in 20 days (OECD 301D)	0% in 28 days (OECD 301D); 0% in 28 days (OECD 301C) ² ; 97% in 14 days (OECD 301A); 100% in 12 days (OECD 302B) ³	97% in 5 days (OECD 301A); 92% in 6 days (OECD 301A)	88–90% after 28 days (OECD 301A); >90% in 28 days (OECD 301E)	94% in 8 days (OECD 302B); 97.7% in 5 days	64–84% in 28 days (OECD 301E); 97.7% in 5 days	65–95% in 28 days (OECD 301C, adapted sludge); <10% in 28 days (OECD 301C, non-adapted sludge); 22% in 5 days
Hydrolysis	No data	No data	No data	No data	11.3% loss at pH 6.0 at 30°C in 48 hours (measured)	4% loss at pH 6.4 in 48 hours (measured)	8.8% loss at pH 6.4 at 30°C in 48 hours (measured)	8% loss at pH 6.4 at 30°C in 48 hours (measured)	No data
Log K _{oc}	2.46 (estimated) ⁴	2.10 (estimated) ⁴	2.29 (estimated) ⁴	2.08 (estimated) ⁴	2.07 (measured) 2.14 (measured)	1.90 (estimated) ⁴	1.86 (estimated) ⁴	1.86 (estimated) ³⁴	1.99 (estimated) ⁴ 2.06 (estimated) 2.58 (estimated)
Bioconcentration	BCF = 44–161 (measured in carp at 0.2 ppm); BCF = 17–125; (measured in carp at 0.02 ppm)	BCF = 29.09 (estimated)	BCF = 22.36 (estimated)	BCF = 6–13 (measured in carp at 0.1 ppm); BCF = 3–11 (measured in carp at 1 ppm)²	BCF = 2.6 (measured in zebrafish)	BCF = 2.072 (estimated) ³	BCF = 2.35 (estimated)	BCF = 2.39 (estimated) ³	BCF = 4.7–13.6 (measured in carp)

Property	Sponsored Chemicals				Supporting Chemicals				
	N,N-Diethyl-aniline	N,N-Dimethyl- <i>p</i> -toluidine	N-Ethyl- <i>m</i> -toluidine	N-Ethyl-aniline	Aniline	<i>o</i> -Toluidine	<i>p</i> -Toluidine	<i>m</i> -Toluidine	N,N-Dimethyl-aniline
CASRN	91-66-7	99-97-8	102-27-2	103-69-5	62-53-3	95-53-4	106-49-0	108-44-1	121-69-7
Fugacity (Level III Model)									
Air (%)	0.2	0.156	0.176	0.88	0.49	0.355	0.352	0.26	0.223
Water (%)	22.3	26.8	32.5	42.2	44.9	50.4	49.8	40	24.3
Soil (%)	76.8	72.7	67	56.8	54.5	49.1	49.8	59.6	75.3
Sediment (%)	0.718	0.329	0.305	0.149	0.088 ⁴	0.099	0.1	0.091 ⁴	0.144 ⁴
Persistence ⁵	P1	P1	P1-P2	P1	P1	P1	P1	P1	P1
Bioaccumulation ⁵	B1	B1	B1	B1	B1	B1	B1	B1	B1

¹Bayer Corporation. July 8, 2002. Revised Robust Summary for Monocyclic Aromatic Amines.

<http://www.epa.gov/chemrtk/pubs/summaries/aroamin/c13310tc.htm>.

²National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

³Wellens, H. 1990. Zur Biologischen Abbaubarkeit Mono- und Disubstituierter Benzolderivate. Z. Wasser- Abwasser-Forsch. 23:85–98.

⁴U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

⁵Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3 Human Health Hazard

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

Acute Oral Toxicity

N-Ethylaniline (CASRN 103-69-5)

(1) Sprague-Dawley rats (5/sex/dose) were administered single doses of undiluted N-ethylaniline via gavage at 275, 307, 342, 381 and 425 mg/kg-bw. Mortality was observed at 307, 381, and 425 mg/kg-bw.

LD₅₀ = 362.7 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered N-ethylaniline in corn oil (dose levels not stated) via gavage. Exposure period unspecified.

LD₅₀ = 478 mg/kg-bw

N-Ethyl-*m*-toluidine (CASRN 102-27-2)

(1) Wistar rats (5/sex/dose) were administered N-ethyl-*m*-toluidine via gavage at doses of 0.5, 0.6, 0.7, 0.8, 1.0 and 1.2 mL/kg (~ 500, 600, 700, 800, 1000 and 1200 mg/kg-bw, respectively) and observed for 14 days. Mortality was 3/10, 7/10, 7/10, 9/10 and 10/10 in 600, 700, 800, 1000 and 1200 mg/kg-bw, respectively, and occurred within 4 days post-treatment.

LD₅₀ = 650 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered N-ethyl-*m*-toluidine in corn oil via gavage at doses of 100, 500, 750 and 1000 mg/kg-bw. Exposure period unspecified.

LD₅₀ = 787 mg/kg-bw

***N,N*-Dimethyl-*p*-toluidine (CASRN 99-97-8)**

Sprague-Dawley rats (10/sex/dose) were administered N,N-dimethyl-*p*-toluidine via gavage at unspecified doses. Exposure period unspecified.

LD₅₀ = 1650 mg/kg-bw

***N,N*-Diethylaniline (CASRN 91-66-7)**

Wistar rats (10 males/dose) were administered N,N-diethylaniline via gavage at doses of 0.1, 0.5, 0.6, 0.7 and 0.8 mL/kg (~ 100, 500, 600, 700 and 800 mg/kg-bw, respectively) and observed for 14 days. There were no mortalities at 100 mg/kg-bw, one at 500 mg/kg-bw, two at 600 mg/kg-bw and six at 700 mg/kg-bw; all animals died at 800 mg/kg-bw.

LD₅₀ = 606 mg/kg-bw

Acute Dermal Toxicity

***N*-Ethylaniline (CASRN 103-69-5)**

(1) New Zealand White rabbits (5/sex/dose) were exposed to undiluted N-ethylaniline via the dermal route. Exposure period unspecified.

LD₅₀ > 2000 mg/kg-bw

(2) Rats (6/sex/dose) were exposed to undiluted N-ethylaniline via the dermal route at 1200, 1483, 1833, 2265 and 2800 mg/kg-bw. Exposure period unspecified.

LD₅₀ = 1347 – 1915 mg/kg-bw

***N*-Ethyl-*m*-toluidine (CASRN 102-27-2)**

New Zealand White rabbits (5/sex/dose) were exposed to N-ethyl-*m*-toluidine via the dermal route at 2000 mg/kg-bw/day. Exposure period unspecified.

LD₅₀ > 2000 mg/kg-bw

***N,N*-Dimethyl-*p*-toluidine (CASRN 99-97-8)**

New Zealand White rabbits (5/sex/dose) were exposed to N,N-dimethyl-*p*-toluidine via the dermal route at 2000 mg/kg-bw/day. Exposure period unspecified.

LD₅₀ > 2000 mg/kg-bw

***N,N*-Diethylaniline (CASRN 91-66-7)**

(1) Rats (strain/number/sex unspecified) were exposed to N,N-diethylaniline via the dermal route at 5000 mg/kg-bw/day and observed for 14 days.

LD₅₀ > 5000 mg/kg-bw

(2) Rabbits (4/dose; sex unspecified) were exposed to N,N-diethylaniline via the dermal route at 468 and 935 mg/kg-bw. Exposure period unspecified. No mortalities occurred at 468 mg/kg-bw and all animals died at 935 mg/kg-bw.

LD₅₀ < 935 mg/kg-bw

Acute Inhalation Toxicity

N-Ethylaniline (CASRN 103-69-5)

Sprague-Dawley rats (5/sex/dose) were exposed to N-ethylaniline via inhalation at chamber concentrations of 0.01, 0.026, 0.3, 1.13, 1.38, 1.42 and 1.48 mg/L for a single 4-hour period.

LC₅₀ = 1.13 – 1.48 mg/L

N-Ethyl-m-toluidine (CASRN 102-27-2)

Rats (strain/number/sex unspecified) were exposed to N-ethyl-m-toluidine via inhalation for 4 hours. The concentrations tested were not reported.

LC₅₀ = 2.4 mg/L

N,N-Dimethyl-p-toluidine (CASRN 99-97-8)

Sprague-Dawley rats (5/sex/dose) were exposed to N, N-dimethyl-p-toluidine via inhalation for 4 hours. The concentrations tested were not reported.

LC₅₀ = 1.4 mg/L

N,N-Diethylaniline (CASRN 91-66-7)

Rats (number/sex not stated) were exposed to N,N-diethylaniline via inhalation at measured concentrations (concentrations not stated) for 4 hours.

LC₅₀ = 1.92 mg/L

Repeated-Dose Toxicity

N,N-Diethylaniline (CASRN 91-66-7)

In a repeated-dose toxicity study, Wistar rats (male and female; number unspecified) were administered N,N-diethylaniline via gavage at 0, 10, 50 or 250 mg/kg-bw/day, 7 days/week for 28 days. No mortalities were observed. No changes in body weight, food, and water consumption were reported. Clinical signs of toxicity consisted of increased frequency of respiratory sounds in males at 50 mg/kg-bw/day, and increased frequency of respiratory sounds and salivation in females at 250 mg/kg-bw/day. Hematological effects (decreased red cell counts, decreased hemoglobin concentrations, decreased packed cell volume (PCV) in both sexes and increased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) in females) were reported at all doses (dose-response not specified). Histological effects were reported for the liver and spleen. In the liver, hemosiderosis of the Kupffer cells at 10 mg/kg-bw/day and extra medullary hematopoiesis at 50 and 250 mg/kg-bw/day were observed. In the

spleen, hemosiderosis, extramedullary hematopoiesis and splenic hyperemia were reported at 10 mg/kg-bw/day. Swollen spleens were observed at 50 and 250 mg/kg-bw/day. Increased absolute and relative weights and black pigmentation of the spleen were also reported at 10mg/kg-bw/day. At 50 and 250 mg/kg-bw/day, hyperbilirubinemia, polychromasia were reported, and at 250 mg/kg-bw/day, decreased potassium levels, histopathological findings in the kidneys of both sexes, black pigmentation in the kidneys of females, and increased albumin levels in males were reported. Dose-response and statistical significance were not indicated for any of these observed effects.

LOAEL = 10 mg/kg-bw/day (based on hematological and histopathological changes in the spleen and liver consistent with hemolytic anemia)

NOAEL = Not Established

N-Ethyl-m-toluidine (CASRN 102-27-2)

In a repeated-dose toxicity study, Sprague-Dawley rats (male and female; number unspecified) were exposed to N-ethyl-m-toluidine via inhalation at 0, 5.6, 32.8 or 67.6 ppm (~0.03, 0.18, 0.37 mg/L, respectively), 6 hours/day, 5 days/week for 14 days. No deaths or changes in body weight, food consumption, clinical observations or clinical chemistry parameters were reported for any exposure level, with the exception of significant increases in methemoglobinemia at both terminal and recovery necropsies in both sexes across all concentrations; dose-response was not indicated. However, because the increase in methemoglobinemia was not accompanied by adverse histopathology or clinical signs, this effect was not considered in the robust summary of this study to be treatment-related. Enlarged spleens, increased red blood cells in the spleen, bone marrow and liver, and other hematological changes were consistent with the induction of hemolytic anemia at concentrations > 5.6 ppm (0.03 mg/L); dose-response and statistical significance was not indicated. Observed kidney effects were considered secondary to hemolytic anemia.

LOAEL = 0.18 mg/L (based on hematological changes consistent with hemolytic anemia)

NOAEL = 0.03 mg/L

Aniline (CASRN 62-53-3, supporting chemical)

(1) In a repeated-dose toxicity study, rats (gender, number, and strain unspecified) were exposed to aniline via inhalation at 0, 10, 30 or 90 ppm (0.038, 0.114 or 0.34 mg/L, respectively) daily (3, 6 or 12 hours/day), 5 days/week for 2 weeks and observed for 14 days post-treatment. At 30 and 90 ppm, splenic congestion, hemolysis, increased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) and changes in methemoglobin levels were observed. After 14 days, the methemoglobin values returned to normal levels. The robust summary was lacking in sufficient details to draw definitive conclusions.

LOAEL/NOAEL= Could not be established

(2) In a Chernoff/Kavlock assay, male Fisher 344 rats (30/dose) were administered aniline by gavage at 0 and 110 mg/kg-bw/day for either 5, 10, or 20 days. After each exposure period, 10 rats were sacrificed and underwent a histopathological examination of specific target organs. Aniline was included in this study as a positive control for splenic and bone marrow effects. Transient cyanosis was observed after dosing. Body weight was significantly reduced at 5 days following treatment. Significant mortality (8/30) was observed; 4 animals died within the first 4 days, and 2 between 5-10 days and 2 more between 10-20 days of treatment. Lesions

characteristic of erythrocytic damage such as, increased weight, engorgement, and congestion of the spleen; extramedullary splenic hematopoiesis, hemosiderin accumulation, and bone marrow hypercellularity were observed.

LOAEL \leq 110 mg/kg-bw/day (based on mortality and changes in the bone marrow and spleen)
NOAEL = Not Established

N,N-Dimethylaniline (CASRN 121-69-7, supporting chemical)

In a repeated-dose toxicity study, 10/sex/dose Fisher 344 rats and B6C3F1 mice were administered N,N-dimethylaniline via gavage at 0, 31.25, 62.5, 125, 250, and 500 mg/kg-bw/day 5 days/week for 90 days. In both rats and mice, no mortality was observed. In rats, decreased body weight gain was observed in males at 250 and 500 mg/kg-bw/day. Hyperplasia of the bone marrow and hematopoiesis in the spleen were observed in all rats in a dose-related manner. In mice, dose-related clinical signs of toxicity consisted of lethargy and salivation. Dose-related increases in splenomegaly, and extramedullary hematopoiesis and hemosiderosis of the spleen were observed in mice; at the lowest dose, splenomegaly was reported as minimal in 4/10 mice, and extramedullary hematopoiesis and hemosiderosis were reported as mild in 1/10 mice.

LOAEL = 31.25 mg/kg-bw/day(based on changes in the bone marrow and the spleen)
NOAEL = Not Established

o-Toluidine (CASRN 95-53-4, supporting chemical)

In a Chernoff/Kavlock assay, male Fisher 344 rats (30/dose) were administered *o*-toluidine by gavage at 0 and 225 mg/kg-bw/day for either 5, 10, or 20 days. After each exposure period, 10 rats were sacrificed and underwent a histopathological examination of specific target organs. *o*-Toluidine was included in this study as a positive control for splenic and bone marrow effects. Transient cyanosis was observed after dosing. Body weight was significantly reduced at 5 and 10 days following treatment. Significant mortality (10/30) was observed; 4 animals died within the first 4 days, and 4 between 5-10 days and 2 more between 10-20 days of treatment. Lesions characteristic of erythrocytic damage such as, increased weight, engorgement, and congestion of the spleen; extramedullary splenic hematopoiesis, hemosiderin accumulation, and bone marrow hypercellularity were observed.

LOAEL \leq 225 mg/kg-bw/day (based on mortality and changes in the bone marrow and spleen)
NOAEL = Not Established

m-Toluidine (CASRN 108-44-1, supporting chemical)

In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (13/sex/dose) were administered *m*-toluidine via gavage at 0, 30, 100 and 300 mg/kg-bw/day; males for 42 days, and females from 2 weeks prior to mating to day 3 of lactation (41-53 days). Clinical observations, organ weights/histopathology, and hematological/biochemical analyses (in males only) were conducted. No deaths were reported. Signs of systemic toxicity in the adults consisted of the following: Mean body weight gains during week 1 were significantly lower than controls in the 300 mg/kg-bw/day males and the 100 and 300 mg/kg-bw/day females. Signs of clinical toxicity, evidence suggestive of hemolytic anemia (decreased erythrocyte counts and hemoglobin concentration), and effects on various biochemical parameters were observed at 100 and 300 mg/kg-bw/day. A statistically significant increase in relative kidney weight in high-dose males was observed. No other changes in organ weights were reported. Histopathological signs in the liver, spleen, and kidney were reported at

varying degrees of severity in both males and females ranging from slight to marked and occurring in some instances in a dose-response manner beginning at 100 mg/kg-bw/day; signs of marked severity occurred only at 300 mg/kg-bw/day. The histological changes reported in the liver and spleen (pigment deposit and extramedullary hematopoiesis) were considered to be consistent with the reductions in erythrocyte counts and hemoglobin concentrations characteristic of hemolytic anemia. (<http://cs3-hq.oecd.org/scripts/hpv/>)

LOAEL = 100 mg/kg-bw/day (based on hematological and histopathological changes in the liver and spleen consistent with hemolytic anemia)

NOAEL = 30 mg/kg-bw/day

p-Toluidine (CASRN 106-49-0, supporting chemical)

In a repeated-dose toxicity study, rats (10 males/dose; strain unspecified) were administered *p*-toluidine orally at 0, 125, 825, 1650 ppm (0, 13.8, 66.8, 125.7 mg/kg-bw/day) for 4 weeks.

Decreased body weight gain at 1650 ppm and increased relative liver weight at 825 and 1650 ppm were reported. No other effects were noted and no further details provided. Based on the limited information, this study is not considered useful for the purposes of hazard assessment.

LOAEL/NOAEL= Not Established

Reproductive Toxicity

There were no reproductive toxicity studies performed on any of the four sponsored chemicals in this category.

Aniline (CASRN 62-53-3, supporting chemical)

(1) In a chronic toxicity study, Fischer 344 rats (50/sex/dose) were administered aniline hydrochloride in the diet at 0, 7, 22 and 72 mg/kg-bw/day for 104 weeks. At 26 weeks (10/sex/dose), 52 weeks (10/sex/dose) and 78 weeks (20/sex/dose), animals were sacrificed and necropsied. The remaining animals were sacrificed at the termination of the study at 104 weeks. Limited reproductive organs were evaluated for weight and histopathology. In males, no treatment-related effects were observed in the testes when compared to control animals. In high-dose females, a slight increase in (but not statistically significantly different from control) absolute and relative ovarian weight was observed at 26, 52 and 78 weeks; whereas at 104 weeks, a statistically significant decrease (p-value not stated) in absolute and relative ovarian weights was observed. Females sacrificed at 78 weeks showed an increased incidence of uterine endometrial polyps; however, since there was no dose-response and because these polyps are commonly observed in this strain of rat, the study authors considered this finding incidental and unrelated to treatment. No other histopathological observations in female reproductive organs were reported.

NOAEL (reproductive toxicity) = 72 mg/kg-bw/day (based on no treatment-related effects observed)

(2) In a National Toxicology Program chronic toxicity/carcinogenicity study, Fischer 344 rats (50/sex/dose) were administered aniline hydrochloride in the diet at 0.3 and 0.6% (~174.4 and 350.5 mg/kg-bw/day, respectively) for 103 weeks. Histopathological examination of the male reproductive organs indicated that no treatment-related effects were observed. In female rats, after 103 weeks, increased incidences of uterine endometrial polyps were observed when

compared to control groups. These polyps are considered a common finding in this strain of rat. No other treatment-related effects were observed. [http://ntp-apps.niehs.nih.gov/ntp_tox/]

NOAEL (reproductive toxicity) = 350.5 mg/kg-bw/day (based on no treatment-related effects observed)

(3) In a National Toxicology Program carcinogenicity study, B6C3F1 mice (50/dose) were administered aniline hydrochloride at 0.6 and 1.2% (~ 737 and 1510 mg/kg-bw/day, respectively) for 103 weeks. Histopathological examination of the male and female reproductive organs indicated that no treatment-related effects were observed at the highest dose tested.

[http://ntp-apps.niehs.nih.gov/ntp_tox/]

NOAEL (reproductive toxicity) = 1510 mg/kg-bw/day (based on no treatment-related effects observed)

o-Toluidine (CASRN 95-53-4, supporting chemical)

In a repeated-dose toxicity study, male and female rats (15/sex/group; strain unspecified) were exposed to 0, 8, and 80 mg/kg-bw/day *o*-toluidine dermally (to 2/3 of the tail skin) 4 hours/day for 4 months. Following the 4-month exposures, some test animals (number unspecified) were examined for pathology and others were mated with untreated rats (number unspecified); no exposures occurred during mating, gestation, or lactation. Offspring were maintained until 2 months of age. The only effects reported in the parental animals consisted of increased estrous length and decreases in the number of primordial follicles in parental females at 80 mg/kg-bw/day. There were no reported effects to the testes or ovaries; or pathological, structural, or functional changes reported in the germ cells. Effects reported in the offspring occurred only at 80 mg/kg-bw/day and included delays in body weight gain in pups from treated females, especially in female pups; increases (at both doses) in mean kidney weight and increases in mean ovarian and heart weight in female pups from treated females; decreases in mean spleen and lung weights in male pups from treated females; increases in lung and adrenal weights in female pups from treated males; and decreases in mean liver and spleen weights in male pups from treated males. All other effects reported occurred in greater frequency at the low dose. No statistical information or other details were provided. This study is considered to be of limited value due to lack of details reported.

LOAEL/NOAEL (reproductive toxicity) = Not Established

m-Toluidine (CASRN 108-44-1, supporting chemical)

In the combined repeated-dose/reproductive/developmental toxicity screening study with Sprague-Dawley rats described previously, *m*-toluidine was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. Signs of reproductive toxicity included increases in implantation losses observed in all animals at 300 mg/kg-bw/day and in 2/10 animals at 100 mg/kg-bw/day, but none at 30 mg/kg-bw/day. No other signs of reproductive toxicity were reported. (<http://cs3-hq.oecd.org/scripts/hpv/>)

LOAEL (reproductive toxicity) = 100 mg/kg-bw/day (based on implantation losses)

NOAEL (reproductive toxicity) = 30 mg/kg-bw/day

Developmental Toxicity

N,N-Diethylaniline (CASRN 91-66-7)

In a prenatal developmental toxicity study, pregnant Sprague-Dawley rats (24 or 29/dose) were administered N,N-diethylaniline via gavage at 0, 50, 250 or 500 mg/kg-bw/day during days 6-15 of gestation. At 50, 250, and 500 mg/kg-bw/day, signs of maternal toxicity consisted of statistically significant decreases in mean food consumption. Clinical signs of toxicity were observed at all doses (excessive salivation); and at 250 and 500 mg/kg-bw/day (excessive lacrimation and staining of the skin/fur in the anogenital area). Dose-response was not indicated. At 500 mg/kg-bw/day, maternal mortality (17%) was observed; two females died and three were killed in a moribund condition. However, maternal mortality was not reported in the dose-range finding study at this same dose, but only at doses ≥ 750 mg/kg-bw/day. Signs of developmental toxicity at 500 mg/kg-bw/day consisted of statistically significant decreases in mean fetal weight and an increased incidence of fetuses with delayed ossification. However, effects in the fetuses at the highest dose group occurred at a concentration in which excessive maternal mortality was also observed; therefore, definitive conclusions cannot be drawn.

LOAEL (maternal toxicity) = 500 mg/kg-bw/day (based on mortality)

NOAEL (maternal toxicity) = 250 mg/kg-bw/day

LOAEL (developmental toxicity) = ≤ 500 mg/kg-bw/day

NOAEL (developmental toxicity) = 250 mg/kg-bw/day (based on no adverse treatment-related effects observed)

Aniline (CASRN 62-53-3, supporting chemical)

In a prenatal developmental toxicity study with postnatal evaluations (Price et al., 1985), two separate groups of pregnant F344 rats were administered aniline via gavage at 0, 10, 30 or 100 mg/kg-bw/day; one group of 21/24 per dose during gestation days 7-20, and another group of 12-15 per dose from gestation day 7 through parturition (postnatal day 0). In the second group, dams were sacrificed on postnatal day 30 for evaluation; litters were culled at postnatal day 0 and the offspring observed and evaluated for a variety of endpoints until postnatal day 60. For the prenatal study, signs of maternal toxicity in the dams consisted of significant dose-dependent decreases in mean absolute body weight gain, with statistical significance at 100 mg/kg-bw/day. A dose-related statistically significant increase in relative spleen weights was observed at doses ≥ 10 mg/kg-bw/day. At 100 mg/kg-bw/day, hematological changes indicative of increased hemopoietic activity were observed in the dams. These consisted of statistically significant increases in methemoglobin, reticulocyte counts, white blood cell counts, red blood cell size, and red blood cell distribution width, as well as significant decreases in red blood cell counts. No other effects were reported. No effects were observed for pregnancy rates, number of corpora lutea, or number of implantation sites. At termination on gestation day 20, fetuses exhibited enhanced hemopoietic activity based on statistically significant decreases in red blood cell distribution width and increases in mean corpuscular volume, and increases in relative liver weight, all at 100 mg/kg-bw/day. No other treatment-related effects were reported in the offspring. A low incidence of malformed fetuses was observed in all groups in a manner unrelated to dose, including controls, and therefore was not considered to be treatment-related. For the postnatal study, signs of toxicity in the dams at termination on postnatal day 30 consisted of statistically significant increases in relative spleen weight, methemoglobin concentrations, and mean corpuscular volume at 100 mg/kg-bw/day. Postnatal signs of toxicity in the litters consisted of statistically significant increases in mean corpuscular volume on postnatal day 0; no

statistically significant differences were noted among control and treatment groups for other hematological endpoints on postnatal day 0, or for any parameters in the hematological profile on postnatal days 10, 25 and 50. Statistically significant transient decreases in pup body weight (at 100 mg/kg-bw/day) and in relative liver weight (at 10 and 30 mg/kg-bw/day only) and spleen weights (significant dose response trend) were transient and observed at various times postnatally. A dose-related, statistically nonsignificant increase in the number of litters in which one or more postnatal deaths occurred was also observed during postnatal development. These deaths occurred before postnatal day 30; the cause(s) was not determined. As with the first part of the study, no reported treatment-related effects on pup viability and growth, or on any other developmental parameters in pups surviving to postnatal day 60 were observed. (The Agency obtained most of this information from the published article since the robust summary did not have many details).

LOAEL (maternal toxicity) = 10 mg/kg-bw/day (based on increases in relative spleen weights)

NOAEL (maternal toxicity) = Not established

LOAEL (developmental toxicity) = 100 mg/kg-bw/day (based on increased relative liver weight and on enhanced hematopoietic activity in fetuses sacrificed on gestation day 20; and on transient signs of toxicity (decreased body weight) in pups observed postnatally)

NOAEL (developmental toxicity) = 30 mg/kg-bw/day

N,N-Dimethylaniline (CASRN 121-69-7, supporting chemical)

In a Chernoff/Kavlock assay, pregnant CD-1 mice (50/dose) were administered N,N-dimethylaniline via gavage at 0 and 365 mg/kg-bw/day from gestation day 7-14; pups were delivered and nursed and observations continued until postnatal day 3. Three treatment-related deaths were observed in females during the first 4 days of exposure and 3 dams died during the postnatal period. Maternal body weight was comparable to controls. Three dams in the treated group did not appear to have any implantations. One dam in the treated group had a dead litter which was not delivered as of gestation day 23. No effects were reported for time to delivery or reproductive outcome. The average number of live pups per litter at birth were unaffected by treatment. The average number of live pups per litter, offspring viability, and litter weight at postnatal day 3 were also unaffected by treatment. No other effects were reported, although it is not clear from the summary of this study in the robust summary if any other parameters were measured.

LOAEL (maternal toxicity) = \leq 365 mg/kg-bw/day (based on maternal mortality)

NOAEL (maternal toxicity) = Not Established

NOAEL (developmental toxicity) = \geq 365 mg/kg-bw/day

o-Toluidine (CASRN 95-53-4, supporting chemical)

In a repeated-dose toxicity study, male and female rats (15/sex/group; strain unspecified) were exposed to 0, 8, and 80 mg/kg-bw/day o-toluidine dermally (to 2/3 of the tail skin) 4 hours/day for 4 months. Following the 4-month exposures, some test animals (number unspecified) were examined for pathology and others were mated with untreated rats (number unspecified); no exposures occurred during mating, gestation, or lactation. Offspring were maintained until 2 months of age. The only effects reported in the parental animals consisted of increased estrous length and decreases in the number of primordial follicles in parental females at 80 mg/kg-bw/day. There were no reported effects to the testes or ovaries; or pathological, structural, or functional changes reported in the germ cells. Effects reported in the offspring occurred only at

80 mg/kg-bw/day and included delays in body weight gain in pups from treated females, especially in female pups; increases (at both doses) in mean kidney weight and increases in mean ovarian and heart weight in female pups from treated females; decreases in mean spleen and lung weights in male pups from treated females; increases in lung and adrenal weights in female pups from treated males; and decreases in mean liver and spleen weights in male pups from treated males. All other effects reported occurred in greater frequency at the low dose. No statistical information or other details were provided. This study is considered to be of limited value due to lack of details reported.

LOAEL/NOAEL (maternal/developmental toxicity) = Could not be established

m-Toluidine (CASRN 108-44-1, supporting chemical)

In the combined repeated-dose/reproductive/developmental toxicity study with Sprague-Dawley rats described previously, *m*-toluidine was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. Signs of toxicity in the dams included hematological and histopathological changes in the liver and spleen consistent with hemolytic anemia at 100 and 300 mg/kg-bw/day. Examination of the uterus revealed increases in implantation losses in all animals at 300 mg/kg-bw/day and in 2/10 animals at 100 mg/kg-bw/day, but none at 30 mg/kg-bw/day. Signs of developmental toxicity included an increase incidence of pup deaths at 30 and 100 mg/kg-bw/day; however, the authors attributed the pup mortality a result of lack of nursing activity in the dams. All surviving offspring at 30 and 100 mg/kg-bw/day developed normally during the 4-day lactation observation period.

(<http://cs3-hq.oecd.org/scripts/hpv/>)

LOAEL (maternal toxicity) = 100 mg/kg-bw/day (based on hematological and histopathological changes in the liver and spleen consistent with hemolytic anemia)

NOAEL (maternal) = 30 mg/kg-bw/day

NOAEL (developmental toxicity) = 100 mg/kg-bw/day (based on no treatment-related effects at highest adjusted dose)

Genetic Toxicity – Gene Mutation

In vitro

N-Ethylaniline (CASRN 103-69-5)

In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 were exposed to *N*-ethylaniline up to 1666 µg/plate with and without metabolic activation. The use and performance of controls was not reported.

N-Ethylaniline was not mutagenic in this assay.

N-Ethyl-m-toluidine (CASRN 102-27-2)

(1) *S. typhimurium* strains TA97, TA98, TA100 and TA1535 were exposed to *N*-ethyl-*m*-toluidine up to 5000 µg/plate with and without metabolic activation. Without metabolic activation, cytotoxicity was observed at 2500 µg/plate (3330 µg/plate in TA100). Otherwise, no mutagenic activity was observed without metabolic activation. With metabolic activation, cytotoxicity was observed at 5000 µg/plate (3330 µg/plate in TA100). *N*-Ethyl-*m*-toluidine was considered positive when tested with metabolic activation.

N-Ethyl-m-toluidine was not mutagenic without metabolic activation, but was mutagenic with metabolic activation in this assay.

(2) *S. typhimurium* strains TA98, TA100, TA1535 and TA 1537 were exposed to N-ethyl-*m*-toluidine up to 200 µg/plate with and without metabolic activation. Information on controls was not provided.

N-Ethyl-*m*-toluidine was mutagenic (with and without metabolic activation) in this assay.

(3) *Escherichia coli* strain WP2uvrA was exposed to N-ethyl-*m*-toluidine up to 5000 µg/plate with and without metabolic activation. Cytotoxicity was observed at 5000 µg/plate.

N-Ethyl-*m*-toluidine was not mutagenic in this assay.

***N,N*-Dimethyl-*p*-toluidine (CASRN 99-97-8)**

S. typhimurium strains (TA 98, TA100, TA1537 and TA1538) were exposed to N,N-dimethyl-*p*-toluidine up to 5000 µg/plate with and without metabolic activation. Without metabolic activation, cytotoxicity was observed at 1000 µg/plate. In a similar assay using concentrations up to 100 µg/plate, the cytotoxic concentration was 100 µg/plate. It is not clear if positive controls were used.

N,N-Dimethyl-*p*-toluidine was not mutagenic in these assays.

***N,N*-Diethylaniline (CASRN 91-66-7)**

In several bacterial mutagenicity tests (one with *E. Coli* strains and the others with *S. typhimurium* strains), N,N-diethylaniline was tested up to 5000 µg/plate with and without metabolic activation. No mutagenic activity was observed in all but one Ames assay.

N,N-Diethylaniline was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Aniline (CASRN 62-53-3, supporting chemical)

In several cytogenetic assays, aniline was tested in Chinese hamster lung fibroblast, ovary and v79 cells at concentrations up to 5000 µg/mL with and without metabolic activation.

Aniline induced chromosomal aberrations in these assays.

***N,N*-Dimethylaniline (CASRN 121-69-7, supporting chemical)**

(1) In an *in vitro* chromosomal aberration study, cultured Chinese hamster ovary cells were exposed up to 1010 µg/mL N,N-dimethylaniline with and without metabolic activation. The induction of chromosomal aberrations was positive without metabolic activation at the highest dose.

N,N-Dimethylaniline induced chromosomal aberrations in this assay.

(2) *N,N*-Dimethylaniline (CASRN 121-69-7, supporting chemical)

Cultured Chinese hamster V79 cells were exposed up to 0.14 mg/ml N,N-dimethylaniline without metabolic activation in an *in vitro* micronuclei induction assay and was found to be weakly positive.

N,N-Dimethylaniline induced chromosomal aberrations in this assay.

m-Toluidine (CASRN 108-44-1, supporting chemical)

Cultured Chinese hamster lung (CHL/IU) cells were exposed to *m*-toluidine up to 1.1 mg/mL with and without metabolic activation. The positive controls gave expected responses. Structural chromosomal aberrations were not induced up to the highest concentrations tested. Polyploidy was significantly increased ($p < 0.05$), but remained within historical controls and was not considered positive. (<http://cs3-hq.oecd.org/scripts/hpv/>)

m-Toluidine did not induce chromosomal aberrations in this assay.

p-Toluidine (CASRN 106-49-0, supporting chemical)

In an *in vitro* chromosomal aberration study, cultured Chinese hamster lung cells were exposed to *p*-toluidine up to 1000 $\mu\text{g/mL}$ with and without metabolic activation. The positive controls gave expected responses. The cytotoxic concentration in the presence of metabolic activation was 25 $\mu\text{g/mL}$. The induction of chromosomal aberrations was only observed in the presence of metabolic activation at concentrations $> 12.5 \mu\text{g/mL}$. No chromosomal aberrations were observed in the absence of metabolic activation.

p-Toluidine induced chromosomal aberrations in these assays.

N,N-Dimethyl-p-toluidine (CASRN 99-97-8)

In a cytogenetic assay, Chinese Hamster V79 cells were exposed to N,N-dimethyl-*p*-toluidine up to 1.2mM without metabolic activation. Cytotoxicity was observed at 1.2 mM, where $> 10\%$ survival was estimated by colony formation. It is not clear if positive controls were used.

N,N-Dimethyl-p-toluidine induced chromosomal aberrations in this assay.

In vivo

Aniline (CASRN 62-53-3, supporting chemical)

In several cytogenetic assays with mice (oral and intraperitoneal administration) and rats (gavage) tested up to 1000 mg/kg, aniline tested positive.

Aniline induced chromosomal aberrations in these assays.

p-Toluidine (CASRN 106-49-0, supporting chemical)

In an *in vivo* mouse micronucleus test, CD-1 male and female mice were administered 43.75, 87.50 and 175.0 mg/kg-bw/day *p*-toluidine via the intraperitoneal route of exposure. Signs (not stated) of clinical toxicity and mortality were observed. No cytotoxicity was seen. One hundred immature erythrocytes were scored per animal instead of 2000.

p-Toluidine did not induce chromosomal aberrations in this assay.

N,N-Diethylaniline (CASRN 91-66-7)

In an *in vivo* micronucleus assay, Bor:NMRI mice were administered N,N-diethylaniline via intraperitoneal injection at 600 mg/kg-bw. There was an altered ratio between polychromatic and normochromatic erythrocytes. No increase in micronuclei was observed.

N,N-Diethylaniline did not induce micronuclei in this assay.

Genetic Toxicity – Other

In vitro

N,N-Diethylaniline (CASRN 91-66-7)

In an unscheduled DNA synthesis assay *in vitro*, primary cultured rat hepatocytes were exposed to N,N-diethylaniline at 0.15 – 150 µg/mL. No unscheduled DNA synthesis was observed in this assay.

N,N-Diethylaniline did not induce unscheduled DNA synthesis in this assay.

In vivo

Aniline (CASRN 62-53-3, supporting chemical)

In a dominant lethal study, Wistar-derived rats were administered 75, 150 and 200 mg/kg-bw aniline via the intraperitoneal route of exposure over 5 days. The positive control gave an appropriate response. No evidence of a dominant lethal effect was observed.

Aniline did not induce dominant lethal effects in this assay.

p-Toluidine (CASRN 106-49-0, supporting chemical)

In an *in vivo* alkaline elution assay, male Swiss CD-1 mice were administered *p*-toluidine via a single intraperitoneal injection of 35 mg/kg-bw. Solvent was used as the negative control. Single strand breaks were observed in the DNA of liver and kidney nuclei. *p*-Toluidine was considered positive for this assay.

***p*-Toluidine did induce chromosomal effects in this assay.**

N,N-Dimethyl-p-toluidine (CASRN 99-97-8)

In two *in vivo* alkaline elution assays, Sprague-dawley rats were administered N,N-dimethyl-*p*-toluidine via oral or intraperitoneal injection at up to 1080 mg/kg-bw for up to 24 hours. DNA fragmentation increased in liver cells to about 2.4 times the control at the highest dose only and suggested that N,N-dimethyl-*p*-toluidine was weakly positive in this assay. Negative results were obtained when N,N-dimethyl-*p*-toluidine was tested in Balb/c mice.

N,N-Dimethyl-p-toluidine induced chromosomal effects in these assay.

Additional Information

Eye Irritation

N-Ethyl-m-toluidine (CASRN 102-27-2)

New Zealand White rabbits (6 females) eyes were exposed to 0.1 mL of undiluted N-ethyl-*m*-toluidine without rinsing. The animals were scored at 24 hours and all signs of irritation had cleared by 72 hours. N-ethyl-*m*-toluidine was not considered irritating to the eye under these conditions.

N-Ethyl-m-toluidine was not irritating to rabbit eyes in this assay.

N,N-Diethylaniline (CASRN 91-66-7)

N,N-diethylaniline was not irritating to the eyes when tested on rabbits. No additional information was provided.

N,N-Diethylaniline was not irritating to rabbit eyes in this assay.

Skin Irritation

N-Ethyl-m-toluidine (CASRN 102-27-2)

New Zealand White rabbits (3/sex) were exposed to undiluted N-ethyl-*m*-toluidine for 4 hours under an occlusive dressing. All animals were scored after unwrapping and at day 7. N-Ethyl-*m*-toluidine was slightly irritating to the skin under these conditions.

N-Ethyl-*m*-toluidine was slightly irritating to rabbit skin in this assay.

N,N-Diethylaniline (CASRN 91-66-7)

Several skin irritation studies conducted with N,N-Diethylaniline were slightly to severely irritating to the skin when tested in rabbits, but not irritating when tested in rats. No additional information was provided.

N,N-Diethylaniline was slightly to severely irritating to rabbit skin, but not in rats.

Skin Sensitization

N-Ethyl-m-toluidine (CASRN 102-27-2)

An undiluted sample of 0.3 mL N-ethyl-*m*-toluidine in acetone was tested in rabbits (10/sex) via dermal application in a Buehler skin sensitization test. The rabbits were challenged with a 50% solution of N-ethyl-*m*-toluidine. Irritation was observed in some control animals at 24 hours. The irritation had resolved by 48 hours. The response of the challenged animals was comparable to the controls. N-Ethyl-*m*-toluidine was not considered a sensitizer under these conditions.

N-Ethyl-*m*-toluidine was not a skin sensitizer in rabbit in this study

N,N-Diethylaniline (CASRN 91-66-7)

A 10% solution of N,N-diethylaniline was tested in guinea pigs via dermal application. The dermal challenge exposure using 1 or 2% solutions of N,N-diethylaniline did not elicit a response. N,N-Diethylaniline was not considered a skin sensitizer under these conditions.

N,N-Diethylaniline was not a skin sensitizer in guinea pig in this study.

Carcinogenicity

There were no cancer bioassays for any of the four sponsored chemicals; however, carcinogenicity bioassays conducted by the National Toxicology Program (NTP) for the supporting chemical N,N-dimethylaniline, chronic toxicity studies on the supporting chemicals *m*-toluidine, and *p*-toluidine, as well as NTP carcinogenicity bioassays on aniline hydrochloride and *o*-toluidine hydrochloride provide insights regarding the potential carcinogenicity of the monocyclic aromatic amines category members.

Aniline Hydrochloride (CASRN 142-04-1; the hydrochloride of aniline [CASRN 62-53-3])

In a National Toxicology Program carcinogenicity bioassay, groups of 50 male and female Fischer 344 rats and B6C3F₁ mice were fed high and low dietary concentrations of aniline hydrochloride of 0.6 and 0.3 percent for rats and 1.2 and 0.6 percent for mice. After a 103-week period of compound administration, observation of the rats and mice continued for up to an additional 5 weeks. In male rats the incidences of several types of tumors were associated with administration of the compound. In mice of both sexes no tumors occurred in statistically

significant increased incidences among dosed groups when compared to controls. [http://ntp-apps.niehs.nih.gov/ntp_tox/]

Under the conditions of this bioassay, dietary administration of aniline hydrochloride was carcinogenic to male and female Fischer 344 rats. There was no evidence of compound-induced carcinogenicity in B6C3F₁ mice of either sex.

N,N-Dimethylaniline (CASRN 121-69-7; supporting chemical)

In a National Toxicology Program carcinogenicity bioassay, groups of 50 male and female Fischer 344 rats and B6C3F₁ mice were administered N,N-dimethylaniline in corn oil by gavage at 0, 3, or 30 mg/kg for rats and 0, 15, or 30 mg/kg for mice, 5 days per week for 103 weeks. Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenic activity of N,N-dimethylaniline for male F344/N rats, as indicated by the increased incidences of sarcomas or osteosarcomas (combined) of the spleen. There was no evidence of carcinogenic activity of N,N-dimethylaniline for female F344/N rats given 3 or 30 mg/kg body weight by gavage for 2 years. There was no evidence of carcinogenic activity of N,N-dimethylaniline for male B6C3F₁ mice given 15 or 30 mg/kg body weight by gavage for 2 years. There was equivocal evidence of carcinogenic activity of N,N-dimethylaniline for female B6C3F₁ mice, as indicated by an increased incidence of squamous cell papillomas of the forestomach. Both rats and mice could have tolerated doses higher than those used in these studies. [http://ntp-apps.niehs.nih.gov/ntp_tox/]

Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenic activity of N,N-dimethylaniline for male F344/N rats, there was no evidence of carcinogenic activity of N,N-dimethylaniline for female F344/N rats, there was no evidence of carcinogenic activity of N,N-dimethylaniline for male B6C3F₁ mice and there was equivocal evidence of carcinogenic activity of N,N-dimethylaniline for female B6C3F₁ mice.

o-Toluidine Hydrochloride (CASRN 636-21-5; the hydrochloride of o-toluidine [CASRN 95-53-4])

In a National Toxicology Program carcinogenicity bioassay, groups of 50 male and female F344 rats and B6C3F₁ mice were administered *o*-toluidine hydrochloride at one of several doses, either 3000 or 6000 ppm for rats and either 1000 or 3000 ppm for the mice, for 101 to 104 weeks. In rats, the administration of the test chemical induced several types of sarcomas of the spleen and other organs in both males and females, mesotheliomas of the abdominal cavity or scrotum in males, and transitional-cell carcinomas of the urinary bladder in females. Administration of the *o*-toluidine hydrochloride also resulted in increased incidences of fibromas of the subcutaneous tissue in the males and fibroadenomas or adenomas of the mammary gland in females. In mice, hemangiosarcomas were induced at various sites in males, and hepatocellular carcinomas or adenomas were induced in females. [http://ntp-apps.niehs.nih.gov/ntp_tox/]

Under the conditions of this bioassay, o-toluidine hydrochloride was carcinogenic in both male and female F344 rats and B6C3F₁ mice, producing a significant increased incidence of one or more types of neoplasms.

m-Toluidine Hydrochloride (CASRN 638-03-9; the hydrochloride of m-toluidine [CASRN 108-44-1])

(1) In a chronic toxicity study, 25 Sprague-Dawley rats per dose group (sex unspecified) were administered *m*-toluidine hydrochloride in the diet at 8000 and 16000 ppm (400 and 800 mg/kg-

bw/day) for 13 weeks, then 4000 and 8000 ppm (200 and 400 mg/kg-bw/day) for 65 weeks. A greater than 10% reduction in body weight gain and death was observed at 400 and 800 mg/kg-bw/day following 13 weeks, therefore the dosages were reduced to 200 and 400 mg/kg-bw/day for the remaining 65 weeks. No increase in tumors was observed. No other details were provided.

There was no evidence of carcinogenicity in this assay.

(2) In a chronic toxicity study, HaM/ICR mice (25/sex/dose) were administered *m*-toluidine hydrochloride in the diet at 16000 and 32000 ppm (2400 and 4800 mg/kg-bw/day) for 22 weeks, then reduced to 4000 and 8000 ppm (600 and 1200 mg/kg-bw/day) for 56 weeks for males, and 8000 and 16000 ppm (1200 and 2400 mg/kg-bw/day) for 56 weeks for females. A greater than 10% reduction in body weight gain and death was observed at 2400 and 4800 mg/kg-bw/day following 22 weeks, therefore the dosages were reduced for the remaining 56 weeks. An increase in liver tumors was observed in male mice at 600 mg/kg-bw/day. No other details were provided.

There was evidence of carcinogenicity in this assay.

***p*-Toluidine Hydrochloride (CASRN 540-23-8; the hydrochloride of *p*-toluidine [CASRN 106-49-0]).**

In a chronic toxicity study, Sprague-Dawley rats and HaM/ICR mice (25/dose; sex unspecified) were administered *p*-toluidine hydrochloride in the diet at 1000 and 2000 ppm for 18 months. An increase in liver tumors was observed in mice but not in rats. No other details were provided.

There was evidence of carcinogenicity in this assay.

Conclusion: The acute toxicity by the oral and dermal routes is low for three sponsored category members and moderate for one sponsored category member (CASRN 103-69-5). The acute toxicity by the inhalation route is high for all four sponsored category members. Repeated-dose subchronic toxicity studies in rats with the sponsored category chemicals CASRNs 91-66-7 via the oral route and 102-27-2 via the inhalation route showed hematological and histopathological changes in the spleen and liver consistent with hemolytic anemia at 10 mg/kg-bw/day (lowest dose) and 0.18 mg/L, respectively; the NOAEL for systemic toxicity was not established by the oral route and was 0.03 mg/L by the inhalation route. Repeated-dose subchronic toxicity studies in rats and/or mice by the oral route with the supporting chemicals CASRNs 62-53-3, 121-69-7, 95-53-4, and 108-44-1 showed changes in the bone marrow and spleen between 31.25 and 225 mg/kg-bw/day; with mortality observed at 110 and 225 mg/kg-bw/day for CASRNs 62-53-3 and 95-53-4, respectively. Among the supporting chemicals, the only study reporting a NOAEL for systemic toxicity (30 mg/kg-bw/day) was CASRN 108-44-1. Reproductive toxicity studies were not available for any sponsored chemical; however, chronic toxicity studies in rats and mice by the oral route with the supporting chemical CASRN 62-53-3, showed no treatment-related effects to reproductive organs; the NOAEL for reproductive toxicity was 72 mg/kg-bw/day. A combined repeated-dose/reproductive/developmental toxicity screening study with limited postnatal evaluations by the oral route in rats with the supporting chemical, CASRN 108-44-1, showed adult systemic toxicity as demonstrated by hematological and histopathological changes in the liver and spleen consistent with hemolytic anemia, and reproductive toxicity as demonstrated by implantation losses, all at 100 mg/kg-bw/day; the NOAEL for adult systemic and reproductive toxicity was 30 mg/kg-bw/day. There was no

evidence of developmental toxicity in this study (NOAEL 100 mg/kg-bw/day). A prenatal developmental toxicity study in rats by the oral route with the sponsored chemical CASRN 91-66-7 showed mortality in the dams at 500 mg/kg-bw/day; the NOAEL for maternal and developmental toxicity was 250 mg/kg-bw/day. An oral prenatal developmental toxicity study in rats with the supporting chemical, CASRN 62-53-3, which included extensive postnatal evaluations, showed increases in relative spleen weights in the dams at 10 mg/kg-bw/day, the lowest dose; the NOAEL for maternal toxicity was not established. In the same study, there was developmental toxicity at 100 mg/kg-bw/day as demonstrated by increased relative liver weight and enhanced hematopoietic activity in fetuses sacrificed on gestation day 20; and transient decreases in postnatal pup body weight; the NOAEL for developmental toxicity was 30 mg/kg-bw/day. A Chernoff/Kavlock assay by the oral route in mice with the supporting chemical CASRN 121-69-7 showed mortality in the dams at doses \leq 365 mg/kg-bw/day, the only dose tested; the NOAEL for maternal toxicity was not established. There was no evidence of developmental toxicity in this study and the NOAEL was \geq 365 mg/kg-bw/day. Sponsored category members, CASRNs 103-69-5, 91-66-7 and 99-97-8, were not mutagenic when tested *in vitro*; whereas CASRN 102-27-2 was mutagenic *in vitro*. Supporting chemicals CASRNs 62-53-30, 121-69-7, 121-69-7, 106-49-0, and the sponsored chemical CASRN 99-97-8 induced chromosomal aberrations when tested *in vitro*; whereas the supporting chemical CASRN 108-44-1 did not. Supporting chemical CASRN 62-53-3 did induce chromosomal aberrations when tested *in vivo*, while sponsored chemical CASRN 91-66-7 and supporting chemical CASRN 106-49-0 did not. The sponsored category members were not irritating to rabbit eyes; were slightly-to-severely irritating to rabbit, but not rat skin; and are not sensitizing. Chronic/carcinogenicity studies with the supporting chemical CASRN 121-69-7, with aniline hydrochloride (CASRN 142-04-1), *o*-toluidine hydrochloride (CASRN 636-21-5), *m*-toluidine hydrochloride (CASRN 638-03-9), and *p*-toluidine hydrochloride (CASRN 540-23-8) showed evidence of carcinogenicity in rats and/or mice. (Based on these cancer data – and the concern for cancer for this class of chemicals - the sponsor proposed to conduct low pH Syrian Hamster Embryo (SHE) cell transformation assays with two of the sponsored chemicals (CASRNs 102-27-2 and 103-69-5).

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Summary of Human Health Data

Endpoints	Aniline (supporting chemical) 62-53-3	<i>o</i> -toluidine (supporting chemical) 95-53-4	<i>m</i> -Toluidine (supporting chemical) 108-44-1	<i>p</i> -Toluidine (supporting chemical) 106-49-0	N-Ethylaniline 103-69-5	N-Ethyl- <i>m</i> - toluidine 102-27-2	N,N- Dimethylaniline (supporting chemical) 121-69-7	N,N-Dimethyl- <i>p</i> - toluidine 99-97-8	N,N-Diethyl aniline (91-66-7)
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	—**	—**	—**	—**	363 – 478	650 – 787	—**	1650	606
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	—**	—**	—**	—**	1347 – 1915 (rat) > 2000 (rabbit)	> 2000	—**	> 2000	> 5000 (rat) < 935 (rabbit)
Acute Inhalation Toxicity LC ₅₀ (mg/L/6h/day)	—**	—**	—**	—**	1.13 – 1.48	2.4	—**	1.4	1.92
Repeated-Dose Toxicity Oral NOAEL/LOAEL (mg/kg-bw/day)	NOAEL = NE LOAEL ≤ 110	NOAEL = NE LOAEL ≤ 225	NOAEL = 30 LOAEL = 100	—**	No Data NOAEL = NE LOAEL = 10 (RA)	No Data NOAEL = NE LOAEL = 10 (RA)	NOAEL = NE LOAEL = 31.25	No Data NOAEL = NE LOAEL = 10 (RA)	NOAEL = NE LOAEL = 10
Repeated-Dose Toxicity Inhalation NOAEL/LOAEL (mg/L/day)	—**	—**	—**	—**	No Data NOAEL = 0.038 LOAEL = 0.114 (RA)	NOAEL = 0.03 LOAEL = 0.18	—**	No Data NOAEL = 0.03 LOAEL = 0.18	No Data NOAEL = 0.03 LOAEL = 0.18
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)	(26 week) NOAEL = 72	—**	NOAEL = 30 LOAEL = 100	—**	No Data NOAEL = 30 LOAEL = 100 (RA)	No Data NOAEL = 30 LOAEL = 100 (RA)	—**	No Data NOAEL = 30 LOAEL = 100 (RA)	No Data NOAEL = 30 LOAEL = 100 (RA)

Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) Maternal Toxicity Developmental Toxicity	NOAEL = NE LOAEL = 10 NOAEL = 30 LOAEL = 100	—**	NOAEL = 30 LOAEL = 100 NOAEL = 100 (highest adjusted dose)	—**	No Data NOAEL = NE LOAEL = 10 NOAEL = 30 LOAEL = 100 (RA)	No Data NOAEL = 30 LOAEL = 100 NOAEL = 100 (highest adjusted dose) (RA)	NOAEL = NE LOAEL ≤ 365 NOAEL ≥ 365	No Data NOAEL = 250 LOAEL = 500 NOAEL = -250 LOAEL ≤ 500 (RA)	NOAEL = 250 LOAEL = 500 NOAEL = -250 LOAEL ≤ 500
Genetic Toxicity – Gene Mutation <i>In vitro</i>	—**	—**	—**	—**	Negative	Positive	Positive	Negative	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Positive	—**	Negative	Positive	No Data Positive (RA)	No Data Negative (RA)	—**	Positive	No Data Positive (RA)
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Positive	—**	—**	Negative	No Data Positive (RA)	No Data Positive (RA)	—**	No Data Positive (RA)	Negative
Genetic Toxicity – Other Unscheduled DNA synthesis <i>(in vitro)</i> Alkaline elution assay <i>(in vivo)</i> Dominant lethal assay <i>(in vivo)</i>	—** —** Negative	—** —** —**	—** —** —**	—** Positive —**	—* —* —*	—* —* —*	—** —** —**	—* Weak positive —*	Negative —* —*
Additional Information Skin Irritation Eye Irritation Skin Sensitization Carcinogenicity	—** —** —** Positive	—** —** —** Positive	—** —** —** Positive	—** —** —** Positive	—* —* —*	Slightly irritating Not irritating Negative	—** —** —** Positive	—* —* —*	Slightly-severely irritating Not irritating Negative

Measured data in bold; (RA) = Read-Across; — indicates endpoint not addressed for this chemical; * indicates endpoint not necessary for non-SIDS endpoint; ** indicates endpoint not necessary for supporting chemical, NE indicates Not Established

4 Hazards to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

N,N-Diethylaniline (CASRN 91-66-7)

Fathead minnows (*Pimephales promelas*, 10/concentration) were exposed to N,N-diethylaniline at measured concentrations of 6.15, 13.1, 20.6, 27.9 and 33.9 mg/L under flow-through conditions for 96 hours. Observations were made at 4, 24, 48, 72 and 96 hours.

96-h LC₅₀ = 16.4 mg/L

N,N-Dimethyl-p-toluidine (CASRN 99-97-8)

In two separate studies, fathead minnow (*P. promelas*, 20/concentration) were exposed to N,N-dimethyl-p-toluidine at measured concentrations of 11.1 – 71.3 mg/L under flow-through conditions for 96 hours. Observations were made at 4, 24, 48, 72 and 96 hours.

96-h LC₅₀ (study 1) = 52 mg/L

96-h LC₅₀ (study 2) = 46 mg/L

96-h LC₅₀ (geometric mean of studies) = 48.9 mg/L

N-Ethyl-m-toluidine (CASRN 102-27-2)

Fathead minnows (*P. promelas*) were exposed to N-ethyl-m-toluidine (measured concentrations not stated) under flow-through conditions for 96 hours.

96-h LC₅₀ = 49.5 mg/L

N-Ethylaniline (CASRN 103-69-5)

Medaka (*Oryzias latipes*) were exposed to N-ethylaniline (nominal concentrations not stated) under static conditions for 48 hours. A 96-hour LC₅₀ for fish, estimated by ECOSAR v 1.00, was used to support evaluation of the acute toxicity of N-ethylaniline.

48-h LC₅₀ = 33 mg/L

96-h LC₅₀ = 74.1 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

N,N-Diethylaniline (CASRN 91-66-7)

Daphnia (*Daphnia magna*) were exposed to N,N-diethylaniline (measured concentrations not stated) under static conditions for 48 hours.

48-h EC₅₀ = 1.3 mg/L

Toxicity to Aquatic Plants

N,N-Diethylaniline (CASRN 91-66-7)

Green algae (*Scenedesmus subspicatus*) were exposed to N,N-diethylaniline at nominal concentrations (not stated) for 72 hours. A 96-hour EC₅₀ for green algae, estimated by ECOSAR v 1.00, was used to support evaluation of the acute toxicity of N,N-diethylaniline.

72-h EC₅₀ = 5.6 mg/L

96-h EC₅₀ = 5.8 mg/L (estimated)

N-Ethylaniline (CASRN 103-69-5)

Green algae (*Chlorella pyrenoidosa*) were exposed to N-ethylaniline at nominal concentrations (not stated) for 96 hours under static conditions (Maas-Diepeveen & Van Leeuwen, 1986). A 96-hour EC₅₀ for green algae, estimated by ECOSAR v 1.00, was used to support evaluation of the acute toxicity of N-ethylaniline.

96-h EC₅₀ = 22 mg/L

96-h EC₅₀ = 21.2 mg/L (estimated)

Conclusion: The measured 96-hour LC₅₀ for the monocyclic aromatic amines category members for fish ranges from 16.4 to 49.5 mg/L. The measured 48-hour EC₅₀ for aquatic invertebrates is 1.3 mg/L, and the measured 72-hour/96-hour EC₅₀ for aquatic plants is 5.6 to 22 mg/L.

Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Summary of Environmental Effects – Aquatic Toxicity Data				
Endpoints	N,N-Diethyl aniline (91-66-7)	N,N-Dimethyl-<i>p</i>-toluidine (99-97-8)	N-Ethyl-<i>m</i>-toluidine (102-27-2)	N-Ethylaniline (103-69-5)
Fish				
96-h LC₅₀ (mg/L)	16.4 (m)	48.9 (m)	49.5 (m)	33 (m)
Aquatic Invertebrates		No Data	No Data	No Data
48-h EC₅₀ (mg/L)	1.3 (m)	1.3 (RA)	1.3 (RA)	1.3 (RA)
Aquatic Plants		No Data	No Data	
72-h EC₅₀ (mg/L)	5.6 (m)	5.6 (RA)	5.6 (RA)	22 (m) (96-h)

(m) = measured data (i.e., derived from testing); (RA) = Read Across

5 References

Maas-Diepeveen, J.L., and C.J. Van Leeuwen. 1986. Aquatic Toxicity of Aromatic Nitro Compounds and Anilines to Several Freshwater Species. Lab. For Ecotoxicology, Institute for Inland Water Management and Waste Water Treatment, Report No. 86-42: p 10.

Price, C., R. Tyl, T. Marks, L. Paschke, T. Ledoux, and J. Reel. 1985. Teratologic and Postnatal Evaluation of Aniline Hydrochloride in the Fischer 344 Rat. *Toxicol. Appl. Pharmacol.*, 77: 465-478).