Chemical Information Profile for

Alkylanilines

2-Ethylaniline [CAS No. 578-54-1]
3-Ethylaniline [CAS No. 587-02-0]
3,5-Dimethylanilnine [CAS No. 108-69-0]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

May 2009

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/
Basis for Nomination: 2-Ethylaniline (2-EA) [CAS No. 578-54-1], 3-ethylaniline (3-EA) [CAS No. 587-02-0], and 3,5-dimethylaniline (3,5-DMA) [CAS No. 108-69-0] were nominated by the National Institute of Environmental Health Sciences for toxicological characterization because of ubiquitous potential exposure scenarios, the limited availability of published toxicological data for this subclass of alkyl-substituted (ethyl-) anilines, and their structural similarities to the known animal carcinogens 2,6-xylidine, and o-toluidine. The International Agency for Research on Cancer (IARC) classified o-toluidine as carcinogenic to humans (Group 1) and 2,6-xylidine as possibly carcinogenic to humans (Group 2B).

2-EA, 3-EA, and 3,5-DMA are mainly used as reactants or chemical intermediates for the production of other compounds (e.g., azo dyes, pharmaceuticals, curing agents, antioxidants and antiozonants, gasoline additives, detergents, pesticides, wood preservatives, special lacquers, and more). 2-EA also is used as a reactant in the manufacture of conductive polymers. It has been detected in waters near industries and in tar bases within a smoke plume from an acid tar distillation plant. According to the U.S. Environmental Protection Agency Inventory Update Reporting rule, increases in 2-EA production volume from 10-500 thousand pounds in 1990 and 1994 to >1-10 million pounds in 2002 further raises concerns about occupational exposure. Workers in industries that manufacture or use any of these alkylanilines are at risk of exposure via inhalation or dermal contact. All three of these chemicals also have been detected in cigarette smoke and in indoor (e.g., hair salon or game room of a club) and outdoor ambient air. Higher concentrations of each chemical were reported in sidestream compared to mainstream smoke. 2-EA-, 3-EA-, and 3,5-DMA-hemoglobin adducts were higher in smokers vs. non-smokers and in bladder cancer patients vs. controls (the adducts were an independent predictor of bladder cancer risk). In a population-based study of smokers in Italy, no significant relationship between 3-EA- or 3,5-DMA-hemoglobin adduct levels and smoking status was seen. 3,5-DMA-hemoglobin levels were also significantly higher in women vs. men and in permanent hair dye users vs. nonusers. Comparison of the hemoglobin binding index in female rats showed 3,5-DMA (14.0) > 3-EA (12.7) > 2-EA (5.1).

In humans, 2- and 3-EA may cause irritation of the skin, eyes, mucous membranes, and respiratory tract. High levels can interfere with blood oxygenation, causing headache, fatigue, dizziness, methemoglobinemia, or even death. Chronic exposure may cause changes in the liver and nervous system. The mouse oral LD50 for 3,5-DMA was 707 mg/kg. The rat oral LD50 for 2-EA compared to 3,5-DMA was >1000 vs. 421 mg/kg, respectively. Somnolence, blood changes in spleen, and cyanosis in the lungs, thorax, or respiratory tract were observed in rats given 2-EA. Changes in respiratory rate and volume, weakness, in coordination, collapse, and coma were reported when undiluted 2-EA was given orally to rats and intravenously to rabbits. Subchronic exposure of rats to 3,5-DMA via oral administration caused hemolysis in erythrocytes, and liver and kidney damage, including massive liver necrosis (one female) and necrosis of kidney papilla. 2-EA also moderately damaged the cell membranes of human lung fibroblasts.

All three alkylanilines were negative in several strains of Salmonella typhimurium and Escherichia coli. Neither 2- nor 3-EA induced unscheduled DNA synthesis in rodent hepatocytes. 3,5-DMA did not inhibit testicular DNA synthesis in mice in vivo but did induce DNA adducts, as did 3-EA, suggesting carcinogenic potential.
Data Availability Checklist for 2-Ethylaniline [578-54-1]

Abbreviations:  H = human;  L = Lepus (rabbit);  M = mouse;  R = rat
Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

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The above table provides an overview of the data summarized in this profile. From left to right, column 1 and 6 list the endpoints and columns 2-5 and 7-10 identify the four species (human, rat, mouse, and rabbit) that were considered. An "X" is entered in each box that corresponds to an endpoint and species for which data are included in the profile. Blank cells indicate that no data were available in the literature.
2-Ethylaniline Profile

Chemical Name: 2-Ethylaniline  
CAS RN: 578-54-1  
Formula: C₈H₁₁N  
Molecular Wt.: 121.182

A. Chemical Information

Molecular Identification

Chemical Name: 2-Ethylaniline  
CAS RN: 578-54-1  
Synonyms: o-Aminoethylbenzene; Aniline, 2-ethyl-; Aniline, o-ethyl- (8CI); Benzenamine, 2-ethyl- (9CI); o-Ethylaniline; ortho-Ethylaniline; 2-Ethylbenzenamine; 2-Ethylphenylamine  
Trade Names: Not available  
Hill Formula: C₈H₁₁N  
Line Formula: CH₃-CH₂-C₆H₄-NH₂  
Smiles Notation: CCC1=CC=CC=C1N  
PubChem CID: 11357 (PubChem, undated)  
InChI: 1/C₈H₁₁N/c1-2-7-5-3-4-6-8(7)9/h3-6H,2,9H2,1H3  
Molecular Weight: 121.182  
Purity of Commercial Products: >98%  
Additives in Commercial Products: Not available  
Impurities in Commercial Products: Not available  
Mammalian Metabolites: Not available  
Biodegradation Products: Not available  
Environmental Transformation: (HSDB, 2003a)  
- Air: Primarily exists as a vapor (based on vapor pressure) that will degrade by reaction with photochemically produced hydroxyl radicals (half-life of ~3 hours).  
- Soil: Expected to also be present in the protonated form in moist soils (based on pKₐ value) and to strongly bind to soil surfaces and not volatilize. Anilines in general bind to humic material in soil, which decreases their mobility.  
- Water: May adsorb to sediment and suspended solids (based on estimated KₐOC).  

Physical-Chemical Properties

Physical State: colorless or yellow to red or brown clear liquid [darkens with time and air exposure] (Albemarle Corp., 2003; Aldrich Chem. Co., 2001; HSDB, 2003a)  
Specific Gravity or Density Value: 0.982 g/mL @ 20 °C (HSDB, 2003a)  
Boiling Point: 209.65 °C (ChemIDplus, undated; HSDB, 2003a)  
Vapor Pressure  
- 0.11 mm Hg @ 20 °C (Albemarle Corp., 2003)
− 0.17 mm Hg @ 25 °C (ChemIDplus, undated)
− 1 mm Hg @ 38.5 °C (NJ DHSS, 2002)

**Solubility:** 5320 mg/L @ 25 °C in water (estimated) (ChemIDplus, undated); soluble in alcohol (e.g., ethanol), toluene, and ethyl ether; slightly soluble in chloroform; slightly soluble to insoluble in water (HSDB, 2003a)

**Log P = Log K_{ow}:** 1.74 (ChemIDplus, undated)

**Bioconcentration Factor(s) (species):** 4.4 estimated (aquatic organisms) (HSDB, 2003a)

**B. Exposure Potential**

**U.S. Annual Production**
1986: No reports
1990: 10,000 - 500,000 lb
1994: 10,000 - 500,000 lb
1998: >500,000 - 1 million lb
2002: >1 - 10 million lb
(U.S. EPA, 2009 [U.S. EPA IUR database; search by casno = 578541])

**Worldwide Annual Production**
Not available

**Production Processes**
Prepared by the aluminum anilide catalyzed-reaction of aniline with ethylene (U.S. EPA, 2006)

**Uses**
Intermediate for pharmaceuticals, dyestuffs, pesticides, and other products (HSDB, 2003a); reactant/monomer in production of conductive polymers (Leclerc et al., 1989)

**Occupational Exposure**
Potential exposure (dermal contact and inhalation) may occur at workplaces where 2-ethylaniline is produced or used (HSDB, 2003a).

**General Population Exposure**

**Foods and Beverages, Cosmetics, etc.:** Not available

**Ambient Environment**

**Air Limit:** Not available

**Water Limit(s):** Not available

**Soil Limit:** Not available

**Environmental Exposure in the United States:** 2-Ethylaniline has been detected in cigarette smoke: Kentucky reference cigarettes 1R4F, 2R4F, and 1R3 = 3.6-9.32 ng/cigarette and 1R5F, an Ultra Light cigarette = 0.6 ng/cigarette, and Carlton 1 mg cigarettes = 3.94 ng/cigarette (Chen and Moldoveanu, 2003; Forehand et al., 2000 [PMID:11185617]; Smith et al., 2003 [PMID:12703904]). The amount of aromatic amines are reported to be higher in sidestream smoke than in mainstream smoke. [Nine cigarette brands sold commercially in Italy and nine brands sold in Poland contained higher amounts of aromatic amines in sidestream compared to mainstream smoke (e.g., 327.93 vs.10.04 ng/cigarette [mean values] for 2-ethylaniline in the Italian brands.] Aromatic amine levels differed among the brands as well as the types of cigarettes—higher in mainstream smoke of black-tobacco cigarettes than that of light-tobacco cigarettes. Aromatic amines from sidestream smoke were also common in indoor-ambient air; e.g., the concentration of 2-ethylaniline was 0.50 ng/m³ in the office of a non-smoker with smokers in the adjacent rooms, 0.82 ng/m³ in a hair salon, and 1.55 ng/m³ in the game room of a club (Goniewicz and Czogala, 2005; Luceri et al., 1993 [PMID:8367883]).

**Environmental Exposure in Other Countries:** 2-Ethylaniline was detected in a preliminary screening of surface water samples from areas near major textile industries (Asthana et al., 2000 [authors from The Netherlands and India; PMID:11105862]). It was also found in contaminated groundwater from an industrial area near in Milan; concentrations were not given (Longo and Cavallaro, 1996). In the
UK Midlands, 2-ethylaniline was identified in tar bases within a smoke plume from an acid tar distillation plant (Williams et al., 2001 [PMID:11820470]). In ambient air and airborne particulate matters (PMs) collected in Zonguldak province (Turkey) during the winter of 2006-2007, the median concentrations of 2-ethylaniline were 1.39, 1.35, and 1.13 ng/m³ in PM$_{2.5}$, PM$_{10}$, and air, respectively; during the summer, median concentrations were 1.14, 1.99, and 1.19 ng/m³, respectively. 2-Ethylaniline was detected in coal samples and in coal combustion (Akyüz, 2008).

Levels in Tissues, Body Fluids, and Excreta: Arylamine-hemoglobin adducts, including 2-ethylaniline, were higher in smokers than in nonsmokers and in case subjects with bladder cancer from the Los Angeles area [n=298] than in control subjects [n=308]. Among lifelong nonsmokers, the level of 2-ethylaniline-hemoglobin adducts was also significantly higher in case subjects with bladder cancer than control subjects (9.14 vs. 7.90 pg/g hemoglobin [geometric means]) (Gan et al., 2004). Population-based studies of smokers in Italy also reported smoking related increases in 2-ethylaniline-hemoglobin adducts—38 pg/g hemoglobin in nonsmokers compared to 70 pg/g in blond-tobacco smokers, and 80 pg/g in black tobacco smokers (Bryant et al., 1988a [PMID:3198197], 1988b). Non-smoking pregnant women from Germany did not show an increase in 2-ethylaniline-hemoglobin adducts with increased environmental tobacco smoke exposure or cotinine/creatinine ratios (Branner et al., 1998). The hemoglobin binding index (mmol compound/mol hemoglobin)/(mmol compound/kg bw) in female rats dosed with 2-ethylaniline and sacrificed 24 hours later was 5.1 compared to that of aniline (22.0) and 3- and 4-ethylaniline (12.7 and 5.8, respectively) (Sabbioni, 1994).

Environmental Occurrence
Natural Occurrence: 2-Ethylaniline does not occur naturally but has been detected in shale oil (Epler et al., 1979).

U.S. Environmental Releases: Not available

Concentrations in Environmental Media: Not available

C. Regulatory Information

U.S. Regulations
2-Ethylaniline is listed on the TSCA Inventory (Dialog, 2009)

Exposure Limits (Standards and Criteria): Not available

European Union Scientific Committee Regulations
Not available

Canadian Domestic Substances List (DSL) and Non Domestic Substances List (NDSL)
2-Ethylaniline is specified on the public portion of the DSL (published May 4, 1994) but not on the NDSL (Environment Canada, 2009).

D. Toxicological Information

General Toxicity
In humans, 2-ethylaniline can cause irritation of the skin and eyes. Development of a skin allergy is also possible. High levels can interfere with blood oxygenation, causing headache, fatigue, dizziness, and methemoglobinemia; even higher amounts can affect breathing or result in collapse or death. Changes in the liver and nervous system may occur with chronic exposure (NJ DHHS, 2002). 2-Ethylaniline is also irritating to the mucous membranes and upper respiratory tract (Aldrich Chem. Co., 2001).

Chemical Disposition, Metabolism, and Toxicokinetics

Human Studies: An unspecified urinary metabolite was reported (Luom, 1996). 2-Ethylaniline is $N$-acetylated in vitro by human $N$-acetyltransferase 2, but not by $N$-acetyltransferase 1 (Liu et al., 2007 [PMID:17672512]).
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Animal Studies: Arylamines are metabolized by ring oxidation, N-glucuronidation, N-acetylation, and N-oxidation; in the liver of mammals they are metabolized to N-hydroxyarylamines by monooxygenases (usually cytochrome P450) before binding to hemoglobin [see Levels in Tissues, Body Fluids, and Excreta (Sabbioni, 1994) (study is done in rats).

Acute Exposures
Not classified as a skin irritant in rabbits but was a mild eye irritant (U.S. EPA, 2006)

oral LD₅₀ = 1260 mg/kg [rat] (ChemIDplus, undated; U.S. EPA, 2006)
oral LD₅₀ = 1360 mg/kg [male rat] (Ethyl Corp., 1986)
intravenous LD₅₀ = 273 mg/kg [rabbit] (Ethyl Corp., 1986)

Route: oral (gavage)
Species: rat; CD; 5 males and 5 females/group
Dose/Duration: 290, 590, 1170, 2350, and 4700 mg/kg
Observation Time: not provided
Effects: death of 7 animals at 1.17 g/kg and of all animals at 2.35 g/kg; cyanosis observed in animals within 24 hours of dosing, with normal coloration in survivors within 7-10 days; enlarged spleen at necropsy

Route: oral
Species: rat; strain and sex not provided
Dose/Duration: 1260 mg/kg (LD₅₀); duration not provided
Observation Time: not provided
Effects: somnolence (general depressed activity); cyanosis in the lungs, thorax, or respiratory tract; blood changes in spleen
Source(s): ChemIDplus (undated)

Route: oral (gavage)
Species: rat, male, strain not provided
Dose/Duration: "undiluted" (dose not specified); duration not provided
Observation Time: not provided
Effects: changes in respiratory rate and volume; weakness; incoordination; collapse; coma
Source(s): Ethyl Corp. (1986)

Route: inhalation
Species: rat; species not provided; 10 males
Dose/Duration: 1.07 mg/L (220 ppm) for 1 or 4 hours
Observation Time: up to 14-day recovery period
Effects: no signs of toxicity; no significant gross pathology at necropsy

Route: intravenous
Species: rabbit, strain and sex not provided
Dose/Duration: "undiluted" (dose not specified); duration not provided
Observation Time: not provided
Effects: changes in respiratory rate and volume; weakness; incoordination; collapse; coma
Source(s): Ethyl Corp. (1986)
Subchronic Exposures
Not available
Chronic Exposures
Not available
Synergistic/Antagonistic Effects
Not available
Cytotoxicity
2-Ethylaniline (1 mM) had a low inhibitory effect on basal metabolism of brown fat isolated from hamsters: 30% inhibition vs. 11% with aniline (Pettersson et al., 1980 [PMID:7210019]) and on the growth rate of Ascites sarcoma BP8 cells: 14% inhibition vs. 30% with aniline (Pilotti et al., 1975 [PMID:1188959]). At a concentration of 25 mM it also moderately damaged the cell membrane of human lung fibroblasts: 31% nucleotide release vs. 0% with aniline (Thelestam et al., 1980 [PMID:7466833]).
Reproductive and Developmental Toxicity
Not available
Carcinogenicity
Not available
Anticarcinogenicity
Not available
Genetic Toxicity
Microbial Gene Mutation: Negative in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538, G46, C3076, and D3052 and Escherichia coli strains WP2 and WP2uvrA- with or without S9 (CCRIS, 1993a; Thompson et al., 1983 [PMID:6653503]; U.S. EPA, 2006)
Human Studies (in vitro and in vivo): Not available
Animal Studies (in vitro and in vivo)
Gene Mutation: Did not induce unscheduled DNA synthesis in rodent hepatocytes [up to 1000 µM] (CCRIS, 1993a; Thompson et al., 1983 [PMID:6653503])
Cytogenetic Effects: Not available
Germ Cell Effects: Not available
Neurotoxicity
Not available
Immunotoxicity
Not available

E. Mechanistic Data

Endocrine Modulation
Not available
Effect on Enzymes
Not available
Modes of Action
Not available
Structure-Activity Relationships
Due to the limited amount of toxicological data available for 2-ethylaniline, the activity of one isomer, 2,4-xylidine [95-68-1], and one close congener, o-toluidine [95-53-4], that have been well studied is summarized here.
Isomer
2,4-Xylidine [CAS No. 95-68-1; PubChem CID:7250 (PubChem, undated)]: In mice, a single oral dose (not specified) released lysosomal enzymes found in the large granule fraction of the liver. In rats, a single intravenous injection increased blood methemoglobin level. Short-term toxic effects of oral studies in rats included hepatomegaly, decreased weight gain, cholangiofibrosis, bile duct
proliferation, hepatic cell necrosis, kidney damage, decreased glycogen content and glucose-6-phosphatase activity, and increased cytochrome P450 content. 2,4-Xylidine inhibited testicular DNA synthesis in male mice. In a two-year oral study, male Sprague-Dawley rats exhibited subcutaneous fibromas and fibrosarcomas; excess hepatomas were also reported. The IARC evaluated 2,4-xylidine "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate human and animal data (IARC, 1987). They evaluated the 2,6-xylidine isomer "possibly carcinogetic to humans" (Group 2B) based on inadequate evidence of carcinogenicity in humans and sufficient evidence in experimental animals (IARC, 1993). 2,4-Xylidine was mutagenic in _S. typhimurium_ strain TA100 with S9, increased the frequency of chromosome aberrations in the presence of S9 in vitro, and was positive in the DNA repair test (HSDB, 2003b).

**Congener**

_**o-Toluidine** [CAS No. 95-53-4; PubChem CID: 7242 (PubChem, undated)]_

_Human Studies:_ Increased risk of bladder cancers was associated with increased duration of work with _o_-toluidine and aniline in a retrospective cohort study of 1749 workers in western New York State. Hematuria was observed in men handling toluidines. Transient hematuria, as well as fetal and maternal methemoglobinemia, can be caused by _o_-toluidine (HSDB, 2003c).

_Animal Studies:_ _o_-Toluidine was metabolized in rats to aminomethylphenols and excreted mainly in the urine as acid-hydrolyzable conjugates within 72 hours. In rabbits, it was metabolized to 4-amino-m-cresol (HSDB, 2003c; IPCS, 1998). Dermal exposure can cause minimal to mild skin irritation. Acute and short-term effects in rats include cyanosis, corneal opacity, prostration, lethargy, pallor, decreased body weight, increased spleen weight, elevated methemoglobin levels, and hemosiderosis (IPCS, 1998). The main signs of toxicity are methemoglobinemia and related effects on the spleen. Albino rats fed _o_-toluidine in the diet for up to 91 days exhibited epithelial changes in bladder (e.g., keratosis), metaplasia, and a tendency to early papillomatosis. In female rats, dermal treatment with _o_-toluidine for four months affected ovarian cycle, ovary morphostructure, reproduction ability, and offspring. In males, treatment stimulated spermatogenesis (HSDB, 2003c). The IARC evaluated _o_-toluidine as "probably carcinogetic to humans" (Group 2A) based on limited evidence of carcinogenicity in humans and sufficient evidence in animals (IARC, 2000). _o_-Toluidine was generally nonmutagenic in bacteria except in the presence of norharman. It was clastogenic in Chinese hamster lung fibroblasts ovary cells and in rat liver cells in vitro (IPCS, 1998).

The reader is referred to the "Chemical Information Profiles" for "3-Ethylaniline" and "3,5-Dimethylaniline" and to Attachment 1 "Summary of Carcinogenicity and Genotoxicity Results for Several Alkylanilines." The Attachment 1 follows the 3,5-dimethylaniline profile and contains a table that includes chemical name of selected alkylanilines and respective CASRN; carcinogenicity classification by the International Agency for Research on Cancer, NTP, and the American Conference of Industrial Hygienists; and results from genotoxicity studies conducted in bacteria, yeast, and mammalian cells.

**Search Strategy**

STN International files MEDLINE, CANCERLIT, NIOSHTIC, AGRICOLA, CABA, EMBASE, BIOTECHNO, ESBIOBASE, IPA, BIOSIS, TOXCENTER, and NTIS were searched simultaneously on April 14, 2005. Search terms included the CAS number and synonyms.
On July 9, 2008, an updated search was conducted on STN. In addition to the above databases (except CANCERLIT and NIOSHTIC, which are no longer available on STN International), FSTA, FROSTI, and PASCAL were also searched. The search was limited to material published between 2005 and 2008.

On April 15, 2009, essentially the same search was conducted in the same files plus PASCAL and limited to publication years 2008 and 2009. From the 28 titles examined, only two full records (from TOXCENTER) were selected for downloading. A CAPLUS search with the CAS No. of 2-ethylaniline was also done on April 15, 2009, in sections covering environmental pollution. There were 16 records (no date limitations); 3 full records were downloaded.
Data Availability Checklist for 3-Ethylaniline [587-02-0]

Abbreviations: H = human; L = Lepus (rabbit); M = mouse; R = rat

Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>H</th>
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</table>

The above table provides an overview of the data summarized in this profile. From left to right, column 1 and 6 list the endpoints and columns 2-5 and 7-10 identify the four species (human, rat, mouse, and rabbit) that were considered. An "X" is entered in each box that corresponds to an endpoint and species for which data are included in the profile. Blank cells indicate that no data were available in the literature.
### 3-Ethylaniline Profile

**Chemical Name:** 3-Ethylaniline  
**CAS RN:** 587-02-0  
**Formula:** C₈H₁₁N  
**Molecular Wt.:** 121.182

#### A. Chemical Information

**Molecular Identification**
- **Chemical Name:** 3-Ethylaniline  
- **CAS RN:** 587-02-0  
- **Synonyms:** 3-Amino-1-ethylbenzene; 3-Ethylbenzenamine; 3-Ethylphenylamine; 3-Aminoethylbenzene; Aniline, m-ethyl- (8CI); Benzenamine, 3-ethyl- (9CI); m-Ethylaniline  
- **Trade Names:** Not available  
- **Hill Formula:** C₈H₁₁N  
- **Line Formula:** CH₃-CH₂-C₆H₄-NH₂  
- **Smiles Notation:** CCC1=CC(=CC=C1)N  
- **PubChem CID:** 11475 (PubChem, undated)  
- **InChI:** 1/C₈H₁₁N/c1-2-7-4-3-5-8(9)6-7/h3-6H,2,9H2,1H3  
- **Molecular Weight:** 121.18  
- **Purity of Commercial Products:** up to 99% pure (ChemExper, 2006)  
- **Additives in Commercial Products:** Not available  
- **Impurities in Commercial Products:** Not available  
- **Mammalian Metabolites:** Not available  
- **Biodegradation Products:** Not available  
- **Environmental Transformation:** Not available

**Physical-Chemical Properties**
- **Physical State:** clear dark brown liquid (Acros Organics, 2008; Shenzhen Conghui, 2004)  
- **Specific Gravity or Density Value:** 0.9896 g/cm³ @ 0 ºC (Shenzhen Conghui, 2004); 0.9750 g/cm³ (Acros Organics, 2008); 0.973±0.06 g/cm³ @ 760 Torr [calculated] (Registry, 2006a)  
- **Boiling Point:** 212 ºC @ 760 Torr (Acros Organics, 2008; Shenzhen Conghui, 2004); 214-215 ºC @ 760 Torr (Registry, 2006a)  
- **Vapor Pressure:** 0.139 Torr @ 25 ºC [calculated] (Registry, 2006a)  
- **Solubility:** slightly soluble in water (Shenzhen Conghui, 2004); 4.6 g/L (mass intrinsic solubility) and 0.038 mol/L (molar intrinsic solubility) @ 25 ºC [calculated] (Registry, 2006a)  
- **Log P = Log Kₐw:** 1.928±0.195 @ 25 ºC [calculated] (Registry, 2006a)  
- **Bioconcentration Factor(s) (species):** 1.0-17.17 @ pH 1-10 @ 25 ºC [calculated] (Registry, 2006a)
B. Exposure Potential

**U.S. Annual Production**
Not available

**Worldwide Annual Production**
Not available

**Production Processes**
- Catalytic hydrogenation of 3′-nitroacetophenone under high pressure (Freedman and Doak, 1955; Kindler and Oelschlager, 1956)
- Vapor phase alkylation of aniline with ethanol at feed rates of 125 or 215 mL reaction mixture/100 mL aluminum oxide/hr; 79-82% yield (Zollner and Marton, 1957)
- Reduction of 4,6-dichloro-3-nitro-1-ethylbenzene at elevated temperature over Raney nickel in acid-binding agents (e.g., alkali-metal oxides) and solvents like methanol (Raab et al., 1951 pat.)

**Uses**
- Chemical intermediate in the synthesis of several compounds—for example,
  - benzacridines and other nitrogen heterocyclic derivatives (e.g., 7-ethyl-2,4-dimethyl-quinoline and N-(m-ethylphenyl)-2-naphthylamine) (Buu-Hoi et al., 1961)
  - unsymmetrical triarylamines [one-pot synthesis] (Harris and Buchwald, 2000 [PMID:10993362])
  - indole and alkylindolines [vapor-phase synthesis] (Campanati et al., 2005)
- Reactant/monomer in production of conductive polymers (e.g., La Fleur and Wu, 2000 pat.; Leclerc et al., 1989; and Nateghi et al., 2005) [For applications to polymer polyaniline nanofibers, see Huang (2006).]
- Reaction product with polyphosphazenes (e.g., Grune et al., 1993; and White and Singler, 1977)
- Reactant in the preparation of polymerizable thiopheneazo dyes used for nonlinear optical materials or with aminodicyanonaphthoquinone to make optical recording materials (Beckman et al., 1996 pat.; Edokoro et al., 1985 pat.)
- Additive in aviation gasoline (Gaughan 1995 pat.; Gaughan et al., 2005 pat. appl.)

**Occupational Exposure**
Not available in the literature, but potential exposure is likely during use of 3-ethylaniline in the production of other compounds (see Uses).

**General Population Exposure**

**Foods and Beverages, Cosmetics, etc.:** Not available

**Ambient Environment**

**Air Limit:** Not available

**Water Limit(s):** Not available

**Soil Limit:** Not available

**Environmental Exposure in the United States:** 3-Ethylaniline has been detected in cigarette smoke: Kentucky reference cigarettes 1R4F and 2R4F = 10.09-15.3 ng/cigarette, 1R5F = 2.5 ng/cigarette, and 1R3 = 38.4 ng/cigarette; and Carlton 1 mg cigarettes = 5.93 ng/cigarette (Chen and Moldoveanu, 2003; Forehand et al., 2000 [PMID:11185617]; Smith et al., 2003 [PMID:12703904]).

The amount of aromatic amines were reported to be higher in sidestream smoke than in mainstream smoke. [Nine cigarette brands sold commercially in Italy and nine brands sold in Poland contained higher amounts of aromatic amines in sidestream compared to mainstream smoke (for 3-ethylaniline 356.33 vs. 4.20 ng/cigarette [mean values] and 110-5200 vs. ≤310 ng/cigarette, respectively). Aromatic amine levels differed among the brands as well as the types of cigarettes; higher in mainstream smoke of black-tobacco cigarettes than that of light-tobacco cigarettes. Aromatic amines from sidestream smoke were also common in indoor-ambient air; e.g., the concentration of 3-ethylaniline was 0.20 ng/m³ in the office of a non-smoker with smokers in the adjacent rooms, 1.02 ng/m³ in a hair salon, and 2.25 ng/m³ in the game room of a club (Luceri et al., 1993 [PMID:8367883]).
Levels in Tissues, Body Fluids, and Excreta: Arylamine-hemoglobin adducts, including 3-ethylaniline, were higher in smokers than in nonsmokers and in case subjects with bladder cancer from the Los Angeles area \([n=298]\) than in control subjects \([n=308]\). Among lifelong nonsmokers, the level of 3-ethylaniline-hemoglobin adducts was also significantly higher in case subjects with bladder cancer than control subjects \((23.54 \text{ vs. } 18.02 \text{ pg/g hemoglobin})\). 3-Ethylaniline was an independent predictor of bladder cancer risk \((\text{Gan et al.}, 2004)\). Population-based studies of smokers in Italy did not show a significant relationship between 3-ethylaniline-hemoglobin adduct levels and smoking status or tobacco type \((\text{nonsmokers}: 102 \text{ pg/g hemoglobin}; \text{blond-tobacco smokers}: 115 \text{ pg/g hemoglobin}; \text{and black-tobacco smokers}: 129 \text{ pg/g hemoglobin})\) \((\text{Bryant et al.}, 1988b)\). The hemoglobin binding index \((\text{mmol compound/mol hemoglobin})/(\text{mmol compound/kg bw})\) in female rats dosed with 3-ethylaniline and sacrificed 24 hours later was 12.7, which was lower than that of aniline \((22.0)\) but higher than that of 2- or 4-ethylaniline \((5.1 \text{ and } 5.8, \text{ respectively})\) \((\text{Sabbioni}, 1994)\).

Environmental Occurrence
Natural Occurrence: 3-Ethylaniline does not occur naturally but has been detected in shale oil \((\text{Epler et al.}, 1979)\).
U.S. Environmental Releases: Not available
Concentrations in Environmental Media: Not available

C. Regulatory Information

U.S. Regulations
None available (for EPA, FDA, or OSHA)

Exposure Limits (Standards and Criteria): Not available

European Union Scientific Committee Regulations
None available

Canadian Domestic Substances List (DSL) and Non Domestic Substances List (NDSL)
3-Ethylaniline is not specified on the DSL or NDSL \((\text{Environment Canada}, 2009)\).

D. Toxicological Information

General Toxicity
In humans, ingestion of 3-ethylaniline may cause gastrointestinal irritation with nausea, vomiting, and diarrhea. Inhalation may cause respiratory tract irritation, leading to pulmonary edema. Skin contact may cause irritation, dermatitis, and cyanosis (including of the extremities). In the eyes, it may cause irritation, chemical conjunctivitis, and corneal damage. Chronic exposure may cause methemoglobinemia (characterized by brown-colored blood, headache, weakness, dizziness, shortness of breath, cyanosis, rapid heart rate, unconsciousness, and possible death) and liver and kidney damage \((\text{Acros Organics}, 2008; \text{Shenzhen Conghui}, 2004)\).

Chemical Disposition, Metabolism, and Toxicokinetics

Absorption and Clearance: In mice administered 145 \(\mu\text{g} 3\text{-ethylaniline/kg bw intraperitoneally, 45% of the dose was detected in the urine (amount may be underestimated due to difficulty in collecting samples). Plasma clearance showed a half-life of 33 hours. These results suggest that metabolism and elimination of metabolites was complete in <8 hours (Skipper et al., 2006 [PMID:16918249])}\).

Human Studies: 3-Ethylaniline is \(N\)-acetylated \textit{in vitro} by human \(N\)-acyetyltransferase 1 and 2, preferentially by \(N\)-acyetyltransferase 2 \((\text{Liu et al.}, 2007 [PMID:17672512])\).

Animal Studies: Arylamines are metabolized by ring oxidation, \(N\)-glucuronidation, \(N\)-acetylation, and \(N\)-oxidation; in the liver (of mammals) they are metabolized to \(N\)-hydroxyarylamines by monooxygenases (usually cytochrome P450) before binding to hemoglobin \([\text{see Levels in Tissues, Body Fluids, and Excreta}]\) \((\text{Sabbioni}, 1994)\) \([\text{study is done in rats}]\). A novel rat \(N\)-acyetyltransferase isoform (termed Nat3) catalyzes \(N\)-acyetylation of 3-ethylaniline \((\text{Walraven et al.}, 2006)\).
Acute Exposures
Not available

Subchronic Exposures
Not available

Chronic Exposures
Not available

Synergistic/Antagonistic Effects
Not available

Cytotoxicity
N-Hydroxylated-3-ethylamine (potential metabolite of 3-ethylaniline) was cytotoxic to human lymphoblastoid TK6 and HCT116 colon cancer cells (Jang et al., 2006 abstr.).

Reproductive and Developmental Toxicity
Not available

Carcinogenicity
Not available

Anticarcinogenicity
Not available

Genetic Toxicity

Microbial Gene Mutation: Negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, G46, C3076, and D3052 and *Escherichia coli* strains WP2 and WP2uvrA- with or without S9 (Epler et al., 1979; Thompson et al., 1983 [PMID: 6653503])

Human Studies (*in vitro and in vivo*): Not available

Animal Studies (*in vitro and in vivo*)

Gene Mutation: Negative for induction of unscheduled DNA synthesis in rat hepatocytes [0.5-1000 nmol/mL] (Thompson et al., 1983 [PMID: 6653503]); formed DNA adducts *in vivo* in the bladder and liver of mice (detected less frequently in colon, kidney, lung, and pancreas) (Skipper et al., 2006 [PMID: 16918249]).

Cytogenetic Effects: Not available

Germ Cell Effects: Not available

Neurotoxicity
Not available

Immunotoxicity
Not available

E. Mechanistic Data

Target Organs/Tissues
Human: Blood, blood-forming organs, central nervous system, kidneys, and liver (Acros Organics, 2008)

Animal: Not available

Endocrine Modulation
Not available

Effect on Enzymes
Not available

Modes of Action
Not available

Structure-Activity Relationships
The reader is referred to the "Chemical Information Profiles" for "2-Ethylaniline" and "3,5-Dimethylaniline" and to Attachment 1 "Summary of Carcinogenicity and Genotoxicity Results for Several Alkylanilines." The Attachment 1 follows the 3,5-dimethylaniline profile and contains a table that includes chemical name of selected alkylanilines and respective CASRN; carcinogenicity
classification by the International Agency for Research on Cancer, NTP, and the American Conference of Industrial Hygienists; and results from genotoxicity studies conducted in bacteria, yeast, and mammalian cells.

**Search Strategy**

Most general Internet searches for several alkylanilines were done June 21-23, 2006, with the Google/Google Scholar search engine. The most significant retrieval was the 1993 Government of Canada review on 3,5-xylidine. Several reviews on the toluidines were found at the web site [http://www.inchem.org](http://www.inchem.org). STN International files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, and NTIS were searched simultaneously on June 23, 2006. Search terms included the CAS numbers and synonyms for the three ethylbenzenes and six xylidines. Reviews were sought in the results for the two groups as well as for the toluidines.

History of the online session is the following. [Database tallies are included for only MEDLINE (MED), TOXCENTER (TXC), and EMBASE (EMB).]

```
L1  280 S 2(W)ETHYLANILINE OR O(W)ETHYLANILINE OR 578-54-1
L2  10 S O(W)AMINOETHYLBENZENE OR 2(W)(ETHYLPHENYLAMINE OR ETHYLBENZENAMINE)
L3  147 S 3(W)ETHYLANILINE OR M(W)ETHYLANILINE OR 587-02-0
L4  3 S 3(W)AMINOETHYLBENZENE OR 3(W)(ETHYLPHENYLAMINE OR ETHYLBENZENAMINE)
L5  296 S 4(W)ETHYLANILINE OR P(W)ETHYLANILINE OR 589-16-2
L6  8 S 4(W)AMINOETHYLBENZENE OR 4(W)(ETHYLPHENYLAMINE OR ETHYLBENZENAMINE)
L7  281 S L1 OR L2
L8  148 S L3 OR L4
L9  297 S L5 OR L6
L10 492 S L7 OR L8 OR L9
SET DUPORDER FILE
L11 451 DUP REM L10 (41 DUPLICATES REMOVED) [9, MED; 401, TXC; 23, EMB]
      SAVE L11 X391TO393BIO/A
L12 133 DUP REM L8 (15 DUPLICATES REMOVED) [1, MED; 130, TXC; 19, EMB]
      SAVE L13 X391BIOSORT/A
L13 133 SORT L12 1-133 TI
L14  7 S L10 AND (REVIEW? OR REVIEW/DT)
L15  7 SORT L14 1-7 TI
L16  5886 S XYLYLAMINE? OR DIMETHYLANILINE? OR AMINODIMETHYLBENZENE?
L17  67 S DIMETHYLAMINOETHYLBENZENE? OR DIMETHYLBENZENAMINE? OR AMINO(2A)DIMETHYLBENZENE
L18  86 S XYLYLAMINE? OR AMINO(2A)XYLENE
L19  6031 S L16 OR L17 OR L18
L20  1219 S 1300-73-8 OR 87-59-0 OR 95-68-1 OR 95-78-3 OR 87-62-7 OR 95-6
L21  1280 S L20 OR 108-69-0
L22  1280 S L20 OR L21
L23  6271 S L19 OR L21
L24  3772 DUP REM L23 (2499 DUPLICATES REMOVED) [1010, MED; 1645, TXC; 543, EMB]
      SAVE L24 X393TOX399/A
L25  178 S L23 AND (REVIEW? OR REVIEW/DT)
L26  129 DUP REM L25 (49 DUPLICATES REMOVED)
L27  129 SORT L26 1-129 TI
L28  93 S L27 NOT N(W)N
L29  93 SORT L28 1-93 TI
L30  393 S TOLUIDINE? AND (REVIEW? OR REVIEW/DT)
L31  121 S L30 AND (2000-2007)/PY
L32  13 S L31 AND (2005-2007)/PY
L33  10 DUP REM L32 (3 DUPLICATES REMOVED) [7, MED; 3, EMB]
L34  10 SORT L33 1-10 TI
L35  182 S 3(W)5(W)(XYLIDINE OR DIMETHYLANILINE OR DIMETHYLBENZENAMINE OR AMINO(2A)DIMETHYLPHENYLAMINE OR ETHYLBENZENE)
L36  169 S 3(W)5(W)DIMETHYLBENZENE OR 108-69-0
L37  0 S 5(W)AMINO(W)1(W)3(W)(DIMETHYLBENZENE OR XYLENE)
L38  222 S L35 OR L36
L39  192 DUP REM L38 (30 DUPLICATES REMOVED) [7, MED; 167, TXC; 5, EMB]
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On April 13, 2009, STN International database files MEDLINE, AGRICOLA, CABA, BIOSIS, IPA, TOXCENTER, EMBASE, PASCAL, and NTIS were searched simultaneously for publications published in 2006 (year of previous STN International searches) to 2009. Twelve publications were on both 3-ethylaniline and 3,5-dimethylaniline, 32 were on 3-ethylaniline, and 39 were on 3,5-dimethylaniline. Titles were compared with those in EndNote files containing the references already cited. Most of the nonsynthetic studies were on aquatic toxicity. Only five full records were downloaded, and two were discarded because they pertained to aquatic toxicity. The edited history of the online session is reproduced below.

A CAPLUS search with the CAS No. of 3-ethylaniline was also done on April 15, 2009, in sections covering environmental pollution. There were 4 records (no date limitations); no full records were downloaded.
Data Availability Checklist for 3,5-Dimethylaniline [108-69-0]

Abbreviations:  H = human; L = *Lepus* (rabbit); M = mouse; R = rat

Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

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<th>ENDPOINT</th>
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<td><strong>Subchronic Toxicity (1 to &lt;26 weeks)</strong></td>
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<td><strong>Structure-Activity Relationships</strong></td>
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</tbody>
</table>

The above table provides an overview of the data summarized in this profile. From left to right, column 1 and 6 list the endpoints and columns 2-5 and 7-10 identify the four species (human, rat, mouse, and rabbit) that were considered. An "X" is entered in each box that corresponds to an endpoint and species for which data are included in the profile. Blank cells indicate that no data were available in the literature.
3,5-Dimethylaniline Profile

Chemical Name: 3,5-dimethylaniline  
CAS RN: 108-69-0  
Formula: C₈H₁₁N  
Molecular Wt.: 121.182

A. Chemical Information

Molecular Identification
Chemical Name: 3,5-Dimethylaniline (3,5-DMA)  
CAS RN: 108-69-0  
Synonyms: 1-Amino-3,5-dimethylbenzene; 3,5-Dimethyl-1-aminobenzene; 3,5-Dimethylbenzeneamine; 3,5-Dimethylbenzeneamine; 3,5-Dimethylphénylamine; 3,5-Xylidene (8CI); 3,5-Xylylamine; 5-Amino-1,3-dimethylbenzene; 5-Amino-1,3-xylene; Benzenamine, 3,5-dimethyl- (9CI); Benzene, 1-amino-3,5-dimethyl-
Trade Names: Not available  
Hill Formula: C₈H₁₁N  
Line Formula: (CH₃)₂-C₆H₄-NH₂  
Smiles Notation: CC1=CC(=CC(=C1)N)C  
PubChem CID: 7949 (PubChem, undated)  
InChI: 1/C₈H₁₁N/c1-6-3-7(2)5-8(9)4-6/h3-5H,9H2,1-2H3  
Molecular Weight: 121.18
Purity of Commercial Products: 98-99% (ChemExper, 2006)
Additives in Commercial Products: Not available
Impurities in Commercial Products: Not available
Mammalian Metabolites: Not available
Biodegradation Products: Converted by Escherichia coli to the corresponding (phenylazo) naphthal in the presence of nitrate within 24 hours (HSDB, 2005)
Environmental Transformation: In the vapor phase was degraded in air by reacting with photochemically produced hydroxyl radicals (2 hour estimated half-life). In activated sludge inoculum under aerobic conditions, degraded by 53% in 6 hours. Expected to volatilize from water surfaces (estimated model half-lives for river [1 m deep, flowing 1 m/sec, wind velocity 3 m/sec] and lake [1 m deep, flowing 0.05 m/sec, wind velocity 0.5 m/sec] were 16 and 120 days, respectively) (HSDB, 2005). Using a different method, the half-life for volatilization from surface waters [same river properties] to atmosphere at 20 °C was estimated at 29.5 hours (Government of Canada, 1993).

Physical-Chemical Properties
Physical State: pale to yellow oily liquid (Government of Canada, 1993; HSDB, 2005)
**Specific Gravity or Density Value:** 0.9706 g/cm³ @ 20 ºC (Registry, 2006b)  
**Boiling Point:** 220.5 ºC (ChemIDplus, undated; Registry, 2006b)  
**Vapor Pressure:** 0.126-0.128 Torr @ 25 ºC [calculated] (ChemIDplus, undated; Registry, 2006b)  
**Solubility:** 2050 mg/L in water @ 25 ºC [calculated] (ChemIDplus, undated); 5.0 g/L (mass intrinsic solubility) and 0.041 mol/L (molar intrinsic solubility) @ 25 ºC [calculated] (Registry, 2006b)  
**Log P = Log K\text{ow}:** 3.04 [measured] (Government of Canada, 1993); 2.170 [calculated] (ChemIDplus, undated); 1.856±0.200 @ 25 ºC [calculated] (Registry, 2006b)  
**Bioconcentration Factor(s) (species):** 1.0-15.16 @ pH 1-10 @ 25 ºC [calculated] (Registry, 2006b)

**B. Exposure Potential**

**U.S. Annual Production**  
1986: 10,000 – 500,000 pounds  
1990: No reports  
1994: No reports  
1998: No reports  
2002: No reports  
(U.S. EPA, 2009 [U.S. EPA IUR database; search by casno = 108690])

**Worldwide Annual Production**  
Not available

**Production Processes**  
Reduction of 3,5-dimethylnitrobenzene with iron in strong acid; can also be produced in various coal conversion processes (Government of Canada, 1993) or by nitration and reduction of xylene followed by separation of the 3,5-isomer by conversion to the formyl derivative that is then hydrolyzed to the free base (HSDB, 2005)

**Uses**  
Intermediate in the manufacture of azo dyes, pharmaceuticals, curing agents, antioxidants and antiozonants, gasoline additives and detergents, wood preservatives, wetting agents for textiles, frothing agents for ore dressing, special lacquers and metal complexers (Government of Canada, 1993)

**Occupational Exposure**  
Inhalation and dermal exposures may occur during production and use in other manufacturing processes (HSDB, 2005).

**General Population Exposure**  
3,5-DMA was reported for indoor (0.60 to 4.71 µg/m³) and outdoor (0.60 µg/m³) air samples collected from 75 residential homes and immediate surroundings in Ottawa, Canada, during the winter months (Zhu et al., 2005 [PMID:15984771]).

**Foods and Beverages, Cosmetics, etc.:** Not available

**Ambient Environment**  
**Air Limit:** Not available  
**Water Limit(s):** Not available  
**Soil Limit:** Not available

**Environmental Exposure in the United States:** 3,5-DMA has been detected in cigarette smoke: Kentucky reference cigarettes 1R4F = 9.05 ng/cigarette and 2R4F = 6.77 ng/cigarette, and Carlton 1 mg cigarette = 3.11 ng/cigarette (Chen and Moldoveanu, 2003; Smith et al., 2003 [PMID:12703904]). It was identified in the aqueous phase of groundwater obtained from a well nearby the site of the former coal-tar distillation plant in Saint Louis Park, MN (Pereria et al., 1983). 3,5-DMA was also identified in biosolids from a wastewater treatment plant in South Carolina serving a textiles and refractory industry (Xia and Pillar, 2003).

**Environmental Exposure in Other Countries:** 3,5-DMA has been determined in the range 0.5-50 µg/L in real samples such as the Yamuna river water and underground water in India (Singh et al.,
Alkylaniline Chemical Information Profiles

2003 [PMID:12974294]). It was also detected in the Cape Town brown haze; most of the volatile organic compounds were combustion products of petrol and diesel fuel (Burger et al., 2004).

**Levels in Tissues, Body Fluids, and Excreta:** Arylamine-hemoglobin adducts, including 3,5-DMA, were higher in smokers than in nonsmokers and in case subjects with bladder cancer from the Los Angeles area \[n=298\] than in control subjects \[n=308\]. 3,5-DMA-hemoglobin adduct levels were statistically significantly higher in nonsmoking case subjects (at blood draw) than in nonsmoking controls subjects (29.36 vs. 22.43 pg/g hemoglobin [geometric means]); among lifelong nonsmokers, the same was seen (28.70 vs. 21.73 pg/g hemoglobin). 3,5-DMA was also an independent predictor of bladder cancer risk. A statistically significant difference in 3,5-DMA-hemoglobin levels was also observed between women and men (27.8 vs. 23.2 pg/g hemoglobin, respectively) and between users of permanent hair dyes and nonusers (35.0 vs. 29.0 pg/g hemoglobin) (Gan et al., 2004). Population-based studies of smokers in Italy did not show smoking-related increases in 3,5-DMA-hemoglobin adduct levels—931 pg/g hemoglobin in nonsmokers compared to 112 pg/g in blond-tobacco smokers and 135 pg/g in black tobacco smokers (Bryant et al., 1988b). In female rats dosed with 3,5-DMA (killed after 24 hours), the hemoglobin binding index \[(mmol compound/mol hemoglobin)/(mmol compound/kg bw)\] (14.0) was lower than that of aniline (22.0) but higher than that of 2-, 3-, and 4-ethylaniline (5.1, 12.7, and 5.8, respectively) (Sabbioni, 1994). Human adipose tissue samples (7 of 46) collected from the north, central, south, and west regions of the United States were positive for 3,5-DMA (HSDB, 2005).

**Environmental Occurrence**

**Natural Occurrence:** 3,5-DMA does not occur naturally (Government of Canada, 1993).

**U.S. Environmental Releases:** Not available

**Concentrations in Environmental Media:** Not available

**C. Regulatory Information**

**U.S. Regulations**

3,5-DMA is listed on the TSCA Inventory (Dialog, 2009)

**Exposure Limits (Standards and Criteria):** Not available

**European Union Scientific Committee Regulations**

None available [Note: A maximum allowable concentration of 1 mg 3,5-DMA/m³ was determined in Romania based on data from indices of monophasic and biphasic relative toxicity, histopathological studies, methemoglobin and sulhemoglobin measurements, and blood catalase activity and cerebral succinic dehydrogenase activity (Goldstein, 1975).]

**Canadian Domestic Substances List (DSL) and Non Domestic Substances List (NDSL)**


**D. Toxicological Information**

**General Toxicity**

Not available

**Chemical Disposition, Metabolism, and Toxicokinetics**

**Absorption and Clearance:** In mice administered 100 µg/kg 3,5-DMA intraperitoneally (i.p.), 45% of dose was detected in urine (amount may be underestimated due to difficulty in collecting samples). Plasma clearance was biphasic. Authors indicate that metabolism and elimination of metabolites was complete in ≤8 hours (Skipper et al., 2006 [PMID:16918249]).

**Human Studies:** 3,5-DMA is \(N\)-acetylated in vitro by human \(N\)-acetyltransferase 1 and 2, preferentially by \(N\)-acetyltransferase 2 (Liu et al., 2007 [PMID:17672512]).

**Animal Studies:** Arylamines are metabolized by ring oxidation, \(N\)-glucuronidation, \(N\)-acetylation, and \(N\)-oxidation; in the liver they are metabolized to \(N\)-hydroxyarylamines by monoxygenases (usually cytochrome P450) before binding to hemoglobin [see Levels in Tissues, Body Fluids, and...
Excreta] (Sabbioni, 1994). A novel rat N-acetyltransferase isoform (termed Nat3) catalyzes
N-acetylation of 3,5-DMA (Walraven et al., 2006).

**Acute Exposures**
oral LD₅₀ = 421 mg/kg [mouse] (ChemIDplus, undated)
oral LD₅₀ = 707 mg/kg [rat] (ChemIDplus, undated)

**Subchronic Exposures**
Route: oral (gavage)
Species: rats, Crj:CD (SD), 6 males and 6 females
Dose/Duration: 10, 60, or 360 mg/kg/day for 28 days
Observation Time: not provided
Effects: erythrocytes—hemolysis; significant increase in methemoglobin levels
liver—medium and strong effects in males and females, respectively, given high
dose; massive necrosis of hepatocytes in one female
kidneys—strong effects in both sexes given the high dose; necrosis of the papilla
in 3 males and 6 females
Notes: NOEL = 10 mg/kg/day was reported for both males and females based on
hemolysis in both sexes and unspecified effect on thyroid in males; a strong
correlation was found between the change in erythrocyte count and the calculated
hemoglobin binding index (see Levels in Tissues, Body Fluids, and Excreta)
Source: Sakuratani et al. (2008 [PMID:19061084])

**Chronic Exposures**
Not available

**Synergistic/Antagonistic Effects**
Not available

**Cytotoxicity**
N-Hydroxylated-3,5-DMA and 3,5-dimethylanilinophenol (potential metabolites of 3,5-DMA) were
cytotoxic to human lymphoblastoid TK6 and HCT116 colon cancer cells (Jang et al., 2006 abstr.).

**Reproductive and Developmental Toxicity**
Not available

**Carcinogenicity**
Not available

**Anticarcinogenicity**
Not available

**Genetic Toxicity**

**Microbial Gene Mutation:** Negative in *Salmonella typhimurium* strains TA97, TA98, TA100,
TA1535, and TA1537 and in the *Bacillus subtilis* Rec-assay (CCRIS, 1993b; HSDB, 2005; Zimmer
et al., 1980 [PMID:6990249]); weak activity in *S. typhimurium* in presence of metabolic activation
reported in one study (Zeiger et al., 1988; cited by Government of Canada, 1993).

**Human Studies** (*in vitro and in vivo*): Not available

**Animal Studies** (*in vitro and in vivo*): Induced chromosomal aberrations in Chinese hamster lung
cells (JETOC, 1999; cited by Government of Canada, 2002). Testicular DNA synthesis was not
inhibited in male mice administered 100 mg/kg 3,5-DMA i.p. (Seiler, 1977). DNA adducts were
formed *in vivo* in mouse bladder and liver [detected less frequently in colon, kidney, lung, and
pancreas] (Skipper et al., 2006 [PMID:16918249]).

**Gene Mutation:** N-Hydroxylated-3,5-DMA (potential metabolite of 3,5-DMA) was mutagenic in
human lymphoblastoid TK6 cells (Jang et al., 2006 abstr.).

**Cytogenetic Effects:** Not available

**Germ Cell Effects:** Not available
Neurotoxicity
Not available

Immunotoxicity
Not available

Cardiovascular Effects

Human Studies: Not available

Animal Studies: Significantly induced methemoglobinemia in Sprague-Dawley rat red blood cells in vitro in the presence of active hepatic fractions (0.06-1 mM 3,5-DMA), but a single oral dose (4.8 mmol/kg) in one study of rats did not significantly induce methemoglobinemia (Cauchon and Krishnan, 1997 [PMID:9418948]). In a second study, blood samples from rats given 0.06, 0.12, 0.24, 0.48, or 0.60 mmol 3,5-DMA/kg bw intravenous (i.v.) or 0.24, 0.48, 0.72, 0.96, 1.2, 1.8, 2.4, or 4.8 mmol/kg orally showed dose-dependent induction of methemoglobinemia up to 28.90 ± 0.34%, by i.v. route, and 32.67 ± 2.14%, by oral route, at the top doses (Shardonofsky and Krishnan, 1997 [PMID:15279032]).

E. Mechanistic Data

Target Organs/Tissues

Human: Not available

Animal: Erythrocyte, liver, kidney, and thyroid of rats (Sakuratani et al., 2008 [PMID:19061084])

Endocrine Modulation
Not available

Effect on Enzymes
Not available

Modes of Action
Formation of nitrenium ion from N-acetoxy-3,5-dimethylanaline in vitro leads to DNA adduct formation, suggesting a role in carcinogenic mechanism of action (Cui et al., 2007 abstr., 2007).

Structure-Activity Relationships
The reader is referred to the "Chemical Information Profiles" for "2-Ethylaniline" and "3-Ethylaniline" and to Attachment 1 "Summary of Carcinogenicity and Genotoxicity Results for Several Alkylanilines." The Attachment 1 follows this document and contains a table that includes chemical name of selected alkylanilines and respective CASRN; carcinogenicity classification by the International Agency for Research on Cancer, NTP, and the American Conference of Industrial Hygienists; and results from genotoxicity studies conducted in bacteria, yeast, and mammalian cells.

Search Strategy
Most general Internet searches for several alkylanilines were done June 21-23, 2006, with the Google/Google Scholar search engine. The most significant retrieval was the 1993 Government of Canada review on 3,5-xylidine. Several reviews on the toluidines were found at the web site http://www.inchem.org. STN International files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, and NTIS were searched simultaneously on June 23, 2006. Search terms included the CAS numbers and synonyms for the three ethylbenzenes and six xylidines. Reviews were sought in the results for the two groups as well as for the toluidines.

History of the online session. [Database tallies are included for only MEDLINE (MED), TOXCENTER (TXC), and EMBASE (EMB).]
On April 13, 2009, STN International database files MEDLINE, AGRICOLA, CABA, BIOSIS, IPA, TOXCENTER, EMBASE, PASCAL, and NTIS were searched simultaneously for publications published in 2006 (year of previous STN International searches) to 2009. Twelve publications were on both 3-ethylaniline and 3,5-dimethylaniline, 32 were on 3-ethylaniline, and 39 were on 3,5-dimethylaniline. Titles were compared with those in EndNote files containing the references already cited. Most of the nonsynthetic studies were on aquatic toxicity. Only five full records were downloaded, and two were discarded because they pertained to aquatic toxicity. The edited history of the online session is reproduced below.
Google Scholar searches on April 13, 2009, found two additional references because of its full-text search capabilities: Sugamori et al. (2008 [PMID:17403913]) and Farmer and Singh (2008 [PMID:18468947]). No results were found for either compound in the 2006 Inventory Update Rule database: http://cfpub.epa.gov/iursearch/index.cfm?s=chem.

A limited effort was made to identify drugs or other derivatives to which the U.S. population might be exposed that could be metabolized to 3,5-dimethylaniline. This search was prompted by the knowledge that 2,6-dimethylaniline is a known metabolite of certain local anesthetics such as lidocaine (CAS No. 137-58-6; PubChem CID:3676) (Marques et al., 1997 [PMID:9403181]) and possibly of other drugs with similar substructures, in which the amino group of the aniline is attached to a carbonyl group [a potentially hydrolyzable bond], such as the antiangiinal drug ranolazine (CAS No. 95635-55-5; PubChem CID:56959). Google searches with the name fragments "35 dimethylacetanilide," "3 5 xylidine," "35 dimethylphenyl acetamide," "3 5 dimethylanilino carbonyl," "3 5 acetoxy xylidine," and "3 5 dimethylphenyl" did not lead to the identification of compounds with potential for widespread exposure. Many drug and amino acid derivatives were found that included the fragment "3 5 dimethylanilide" because 3,5-dimethylaniline is one of the chemicals used to derivatize the compounds for chiral separations. The hemoglobin modifier drug efaproxiral (RSR13; CAS No. 131179-95-8; PubChem CID:122335) was found by use of the name fragment "3 5 dimethylanilino carbonyl." Efaproxiral has been tested in clinical trials as a radiation sensitizer for brain tumors and has the potential for abuse as a potential performance-enhancing agent for endurance athletes because in animal tests, it increased maximum oxygen uptake potential (Breidbach and Catlin, 2001 [PMID:11746905]; WADA [World Anti-Doping Agency], 2009). The only metabolite of efaproxiral that was identified by Google searches was the acylglucuronide (RSR13AG).

A CAPLUS search with the CAS No. of 3,5-dimethylaniline was done also on April 15, 2009, in sections covering environmental pollution. There were 22 records (no date limitations) and 8 full records were downloaded.
References


Dialog. 2009. TSCA Inventory [search results]. Internet address: [searched for "578-54-1 or 587-02-0 or 108-69-0"]. Last accessed on April 29, 2009.


Alkylaniline Chemical Information Profiles


PubChem. Undated. Compound Summary for the following:

Last accessed on May 1, 2009.


Registry. 2006a. RN 587-02-0. Database available from the American Chemical Society on STN International. Record entered STN on November 16, 1984.


Acknowledgements
## Attachment 1. Summary of Carcinogenicity and Genotoxicity Results for Several Alkylanilines

<table>
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<tr>
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<th>CASRN</th>
<th>Structure</th>
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<th>Carcinogenicity Classification c</th>
<th>Genotoxicity d</th>
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<tr>
<td><strong>2-Ethylaniline f [CID: 11357]</strong></td>
<td>578-54-1</td>
<td><img src="image1" alt="Structure" /></td>
<td>10 - &lt;50 million lbs</td>
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<td>R</td>
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<td><img src="image3" alt="Structure" /></td>
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### Notes:
- a: Chemical Name
- b: CASRN
- c: 2006 IUR Production Volume
- d: Carcinogenicity Classification
- e: Genotoxicity
- f: Bacteria
- g: Yeast
- h: In vitro
- i: In vivo
- j: Mam +
- k: ANU, CA, CT, G/L, MN, MUT, & SCE
- l: Rd SCE +
- m: Rd MN -
- n: Rd SM -
<table>
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<tr>
<th>Chemical Name [a] [PubChem CID]</th>
<th>CASRN</th>
<th>Structure</th>
<th>2006 IUR Production Volume [b]</th>
<th>Carcinogenicity Classification [c]</th>
<th>Genotoxicity [d]</th>
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<td><img src="image" alt="Structure" /></td>
<td>500,000 - &lt;1 million lbs</td>
<td>A4</td>
<td></td>
</tr>
<tr>
<td>p-Toluidine [l] [CID: 7813]</td>
<td>106-49-0</td>
<td><img src="image" alt="Structure" /></td>
<td>1 - &lt;10 million lbs</td>
<td>A3</td>
<td></td>
</tr>
<tr>
<td>3,5-Dimethylaniline [g,m,n] [CID: 7949]</td>
<td>108-69-0</td>
<td><img src="image" alt="Structure" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,4-Xylidine [m] [CID: 7248]</td>
<td>95-64-7</td>
<td><img src="image" alt="Structure" /></td>
<td>&lt;500,000 lbs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Chemical Name  
<table>
<thead>
<tr>
<th>[PubChem CID]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3-Xylidine [CID: 6893]</td>
</tr>
<tr>
<td>2,4-Xylidine m,o,p [CID: 7250]</td>
</tr>
<tr>
<td>2,5-Xylidine m,p [CID: 7259]</td>
</tr>
<tr>
<td>2,6-Xylidine h,m,q [CID: 6896]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CASRN</th>
<th>Structure</th>
<th>2006 IUR Production Volume</th>
<th>Carcinogenicity Classification</th>
<th>Genotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IARC</td>
<td>NTP</td>
</tr>
<tr>
<td>87-59-2</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>500,000 - &lt;1 million lbs</td>
<td>3</td>
<td>A3</td>
</tr>
<tr>
<td>95-68-1</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>&lt;500,000 lbs</td>
<td>3</td>
<td>Bac +</td>
</tr>
<tr>
<td>95-78-3</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>&lt;500,000 lbs</td>
<td>3</td>
<td>Bac -</td>
</tr>
<tr>
<td>87-62-7</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>&lt;500,000 lbs</td>
<td>2B</td>
<td>NS +/-</td>
</tr>
</tbody>
</table>

Bac = Bacillus, Mm = Mouse, DA = Dermal Application, SCE = Sister Chromatid Exchange, CA = Chromosomal Aberration
<table>
<thead>
<tr>
<th>Chemical Name &lt;sup&gt;a&lt;/sup&gt; [PubChem CID] &lt;sup&gt;e&lt;/sup&gt;</th>
<th>CASRN</th>
<th>Structure</th>
<th>2006 IUR Production Volume &lt;sup&gt;b&lt;/sup&gt;</th>
<th>Carcinogenicity Classification &lt;sup&gt;c&lt;/sup&gt;</th>
<th>Genotoxicity &lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylidine (unspecified locants; mixed isomers)</td>
<td>1300-73-8</td>
<td><img src="image1" alt="Xylidine Structure" /></td>
<td>&lt;500,000 lbs</td>
<td>A3</td>
<td></td>
</tr>
<tr>
<td>2,6-Diethylaniline &lt;sup&gt;s&lt;/sup&gt; [CID: 11369]</td>
<td>579-66-8</td>
<td><img src="image2" alt="2,6-Diethylaniline Structure" /></td>
<td>10 - &lt;50 million lbs</td>
<td>Sal +/-</td>
<td>Mam CA - Mam CT - Mm MN -</td>
</tr>
<tr>
<td>2-Methyl-6-ethylaniline &lt;sup&gt;s&lt;/sup&gt; [CID: 32485]</td>
<td>24549-06-2</td>
<td><img src="image3" alt="2-Methyl-6-ethylaniline Structure" /></td>
<td>10 - &lt;50 million lbs</td>
<td>Sal +/-</td>
<td>Mam MUT - Mm MN -</td>
</tr>
</tbody>
</table>

<sup>a</sup> Chemical Information Profiles are available for compounds in bold.

<sup>b</sup> U.S. Environmental Protection Agency. 2006. Inventory Update Reporting (IUR). Non-confidential 2006 IUR records by chemical, including manufacturing, processing, and use information. Internet address: [http://cfpub.epa.gov/iursearch/index.cfm?s=chem](http://cfpub.epa.gov/iursearch/index.cfm?s=chem) [searched by CAS Number]. Last updated on May 1, 2009. Last accessed on May 1, 2009.

<sup>c</sup> Carcinogenicity data:
IARC (International Agency for Research on Cancer): Group 2A – probably carcinogenic to humans; Group 2B – possibly carcinogenic to humans; Group 3 – not classifiable as to its carcinogenicity to humans
NTP (National Toxicology Program):  R – reasonably anticipated to be a human carcinogen

ACGIH (American Conference of Governmental Industrial Hygienists):  A3 – confirmed animal carcinogen with unknown relevance to humans;  
A4 – not classifiable as a human carcinogen

d Genotoxicity data:
Results:
-, negative
+, positive
+/-, conflicting or mixed results
E, equivocal

Test Systems:
Bac, Bacillus subtilis
Chl, Chinese hamster lung
Esc, Escherichia coli
Mam, cultured mammalian cells
Mm, mouse
NS, not specified
Rd, rodent (not specified)
Rn, rat or rat hepatocytes
Sac, Saccharomyces cerevisiae
Sal, Salmonella typhimurium

Endpoints:
ANU, aneuploidy
CA, chromosomal aberrations
CT, cell transformation
DA, DNA adduct or binding
DS, inhibition of testicular DNA synthesis
G/L, chromosome gain or loss
MN, micronuclei
MUT, mitochondrial DNA or gene mutations
SCE, sister chromatid exchange
SM, sperm morphology
UDS, unscheduled DNA synthesis

References:
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Last accessed on May 1, 2009.


h The Ohio State University. 2006. Table 9. Carcinogens Table: OSHA, IARC, NTP, ACGIH (October 2004). The Ohio State University Office of Environmental Health & Safety Chemical Hygiene Plan. Internet address: http://www.ehs.ohio-state.edu/docs/labsafe/Table9.pdf. Last accessed on May 1, 2009. [Note: p-Toluidine (CAS No. 106-49-0) is designated as "reasonably anticipated to be a human carcinogens" under NTP. This is, however, not true according to the NTP.]


Alkylation Chemical Information Profiles


