Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

Ethyl (3-methylphenyl)-amino acetonitrile (CASRN 63133-74-4) (9th CI and CA Index Name: Acetonitrile, [ethyl (3-methylphenyl)amino]-)

Contents:

BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and 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 an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm.
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level exposure characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm.

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Ethyl (3-methylphenyl)-amino Acetonitrile (CAS No. 63133-74-4)
[9th CI Name: Acetonitrile, [ethyl (3-methylphenyl)amino]-]

September 2008

Prepared by

Risk Assessment Division
Economics, Exposure and Technology Division
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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR Ethyl (3-methylphenyl)-amino Acetonitrile (CAS No. 63133-74-4)

1. Physical-Chemical Properties and Environmental Fate

Ethyl(3-methylphenyl)-amino acetonitrile is a clear, colorless liquid at room temperature. Based on estimated values, the solubility and vapor pressure are considered moderate. It has moderate mobility in soil and low volatility. The rate of atmospheric photooxidation is rapid. Hydrolysis is expected to be negligible since this compound does not possess functional groups that hydrolyze under environmental conditions. The rate of biodegradation is judged to be slow. The persistence of ethyl (3-methylphenyl)-amino acetonitrile is judged to be moderate (P2) and the bioaccumulation potential is ranked low (B1).

2. Hazard Characterization

Aquatic Organism Toxicity. The acute hazard of ethyl (3-methylphenyl)-amino acetonitrile to fish and aquatic invertebrates is low, and to aquatic plants is moderate.

Human Health Toxicity. In animal studies, acute toxicity of ethyl (3-methylphenyl)-amino acetonitrile is moderate via the oral route and low via the dermal route of exposure. Data for repeated-dose toxicity is not required for the HPV Challenge Program because the chemical is considered a closed-system intermediate (CSI). In a combined reproductive/ developmental study in rats via oral gavage, the chemical is considered moderately toxic but there was no evidence of reproductive or developmental toxicity. Ethyl (3-methylphenyl)-amino acetonitrile did not induce gene mutations or chromosomal aberrations.

3. Exposure Characterization

Ethyl (3-methylphenyl)-amino acetonitrile (CAS # 63133-74-4) has an aggregated production and/or import volume in the United States of 10,000 to 500,000 pounds. IUR information for this chemical indicates that it is used as an industrial intermediate in manufacturing of other basic organic compounds. No commercial use is reported in the IUR submissions or other data sources.

Potential for Exposures to Humans and the Environment:
Based on the information considered, including IUR data and information from the HPV Challenge Program, and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for each of the potentially exposed groups (including workers, the general population, consumers and children) and the environment. Persistence and bioaccumulation ratings for this chemical are P2 and B1, respectively. These ratings suggest that this chemical is moderately persistent in the environment and is not bioaccumulative. The Agency has reviewed the information in the original and revised/ updated HPV submission and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed system intermediate. The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental

exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting this chemical in accordance with IUR requirements.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the Chemical Assessment and Management Program (ChAMP).

Risk Statement and Rationale

The Agency has reviewed the information in the HPV submission or test plan and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed system intermediate (CSI). Ethyl (3-methylphenyl)-amino acetonitrile is manufactured and processed in closed systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting this chemical in accordance with IUR requirements. Therefore, there is a low concern for potential risks to aquatic organisms and the general population from environmental releases, and also to workers, consumers, and children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Ethyl (3-methylphenyl)-amino acetonitrile (CAS No. 63133-74-4)
[9th CI Name: Acetonitrile, [ethyl (3-methylphenyl)amino]-]

September 2008

Prepared by

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SCREENING-LEVEL HAZARD CHARACTERIZATION
Ethyl (3-methylphenyl)-amino acetonitrile (CAS No. 63133-74-4)

Introduction

The sponsor, Eastman Chemical Company, submitted a Test Plan and Robust Summaries to EPA for ethyl (3-methylphenyl)-amino acetonitrile (CAS No. 63133-74-4; 9th CI name: acetonitrile, [ethyl (3-methylphenyl)amino]-) on December 10, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 13, 2004 (http://www.epa.gov/chemrtk/pubs/summaries/eth3meth/c14884tc.htm). EPA comments on the original submission were posted to the website on June 3, 2004. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 12, 2004, which were posted to the ChemRTK website on September 20, 2004.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. 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 2003 to May 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical (s) is included in the appendix. The screening-level hazard characterization for environmental and human health effects is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

The sponsor proposed reduced health testing, claiming that ethyl (3-methylphenyl)-amino acetonitrile is a closed-system intermediate (CSI). EPA's evaluation of the original and revised/updated information indicated that the chemical failed to meet some of the guidance to fully support the CSI status for this chemical. In its revised/updated submission the sponsor provided additional information that supported the CSI claim. Therefore, EPA has determined that the chemical qualifies for reduced testing – waiving of repeated-dose and developmental toxicity testing.

Hazard Characterization

Ethyl (3-methylphenyl)-amino acetonitrile is a clear, colorless liquid at room temperature. Based on estimated values, the solubility and vapor pressure are considered moderate. It has moderate mobility in soil and low volatility. The rate of atmospheric photooxidation is rapid. Hydrolysis is expected to be negligible since this compound does not possess functional groups that hydrolyze under environmental conditions. The rate of biodegradation is judged to be slow. The persistence of ethyl (3-methylphenyl)-amino acetonitrile is judged to be moderate (P2) and the bioaccumulation potential is ranked low (B1).

The evaluation of available toxicity data indicate that the potential acute hazard of ethyl (3-methylphenyl)-amino acetonitrile to fish and aquatic invertebrates is low and to aquatic plants is moderate.
In animal studies, acute toxicity of ethyl (3-methylphenyl)-amino acetonitrile is moderate via the oral route and low via the dermal route of exposure. Data for repeated-dose toxicity is not required for the HPV Challenge Program because the chemical is considered a closed-system intermediate (CSI). In a combined reproductive/ developmental study in rats via oral gavage, the chemical is considered moderately toxic, but there was no evidence of reproductive or developmental toxicity. Ethyl (3-methylphenyl)-amino acetonitrile did not induce gene mutations or chromosomal aberrations.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of ethyl (3-methylphenyl)-amino acetonitrile are summarized in Table 1a, while its environmental fate properties are given in Table 1b. The structure of the compound is provided in the Appendix.

Physical-Chemical Properties Characterization

Ethyl (3-methylphenyl)-amino acetonitrile is a clear, colorless liquid at room temperature. Using estimated values, the solubility and vapor pressure are considered moderate.

Table 1a. Physical-Chemical Properties of Ethyl (3-methylphenyl)-amino acetonitrile[1]

Property	Value
CAS No.	63133-74-4
Molecular Weight	174.27
Physical State	Liquid
Melting Point	<0ºC (measured)
Boiling Point	>250ºC (measured)
Vapor Pressure	0.021 mm Hg (estimated)
Water Solubility	252 mg/L (estimated)
Dissociation Constant (pKa)	0.80 (estimated)[2]
Henry's Law Constant	5.21×10^{-8} atm-m^3/mol (estimated)
Log K_{ow}	2.73 (estimated)

[1] Eastman Chemical Company. 2003. Robust Summary for 3,4-Dichlorotrifluorotoluene. http://www.epa.gov/chemrtk/pubs/summaries/eth3meth/c14884tc.htm.
[2] Estimated by Sparc, May 2008 release w4.21405-s4.21408 (http://ibmlc2.chem.uga.edu/sparc).

Environmental Fate Characterization

Ethyl (3-methylphenyl)-amino acetonitrile is expected to partition primarily to soil, according to the results of a Level III fugacity model that assumes equal emissions to air, water, and soil. Based on its estimated vapor pressure ethyl (3-methylphenyl)-amino acetonitrile will exist in the vapor phase in the ambient atmosphere. The rate of atmospheric photooxidation of vapor-phase ethyl (3-methylphenyl)-amino acetonitrile with photochemically generated hydroxyl radicals is rapid. Volatilization of ethyl (3-methylphenyl)-amino acetonitrile is considered minimal based on its Henry's Law constant. It has moderate mobility in soil. Hydrolysis is expected to be negligible since this compound does not possess functional groups that hydrolyze under environmental conditions. The rate of biodegradation is judged to be slow. The persistence potential of ethyl (3-methylphenyl)-amino acetonitrile is judged to be moderate (P2) and the bioaccumulation potential is ranked low (B1) based on an estimated BCF of 25.

Table 1b. Environmental Fate Characteristics of Ethyl (3-methylphenyl)-amino acetonitrile[1]	
Property	**Value**
Photodegradation Half-Life	0.6 hours (estimated)
Hydrolysis Half-Life	Functional groups are not subject to hydrolysis
Biodegradation	9-13% after 28 days (not readily biodegradable)
Bioconcentration	BCF = 25 (estimated)[2]
K_{oc}	162.9 (estimated)[2]
Fugacity (Level III Model)[2]	Air = 0.08%, Water = 31.4%, Soil = 68.2%, Sediment = 0.33%
Persistence[3]	P2 (moderate)
Bioaccumulation[3]	B1 (low)

[1] Eastman Chemical Company. 2003. Chemical Challenge Program. Robust Summary for 3,4-Dichlorotrifluoro-toluene. http://www.epa.gov/chemrtk/pubs/summaries/eth3meth/c14884tc.htm.
[2] US 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.
[3] FR. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194-60204.

Conclusion: Ethyl (3-methylphenyl)-amino acetonitrile is a clear, colorless liquid at room temperature. Based on estimated values, the solubility and vapor pressure are considered moderate. It has moderate mobility in soil and low volatility. The rate of atmospheric photooxidation is rapid. Hydrolysis is expected to be negligible since this compound does not possess functional groups that hydrolyze under environmental conditions. The rate of biodegradation is judged to be slow. The persistence of ethyl (3-methylphenyl)-amino acetonitrile is judged to be moderate (P2) and the bioaccumulation potential is ranked low (B1).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Fathead minnows (*Pimephales promelas*) were exposed to ethyl (3-methylphenyl)-amino acetonitrile at nominal concentrations of 0, 10, 15, 22.5, 33.8 or 50.6 mg/L under semi-static conditions for 96 hours. The measured concentrations were 0, 9.1, 14, 21.5, 35.6 or 58.8 mg/L, respectively. At 21.5 mg/L, all fish showed depressed activity after 4 hours of exposure. All fish exposed to the two highest doses died after 4 hours of exposure. None of the control fish or fish exposed to 9.1 or 14 mg/L died or demonstrated abnormal behavior during the study.
96-h LC_{50} = 27.7 mg/L

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to ethyl (3-methylphenyl)-amino acetonitrile at nominal concentrations of 0, 10, 15, 22.5, 33.8 or 50.6 mg/L under semi-static conditions for 48 hours. The measured concentrations were 0, 9.1, 14, 21.7, 34.1 or 51.6 mg/L, respectively. At 21.7, 34.1 and 51.6 mg/L, 10, 30 and 70% immobilization was noted at 48 hours, respectively. None of the daphnia exposed to the control, 9.1 or 14 mg/L were affected during the study.
48-h EC_{50} = 40.0 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to ethyl (3-methylphenyl)-amino acetonitrile at nominal concentrations of 0, 0.625, 1.25, 2.5, 5.0 or 10.0 mg/L for 72 hours. The measured concentrations were 0, 0.37, 0.68, 1.37, 3.16 or 6.51 mg/L, respectively. Exposure to 0.37 and 0.68 mg/L had no significant effect on the biomass or growth rate at any point during the study. At $\geq$ 1.37 mg/L, a concentration- and time-dependant reduction in biomass and inhibition of growth rate were seen.

72-h EC_{50} (biomass) = 1.40 mg/L
72-h EC_{50} (growth) = 2.88 mg/L

Conclusion: The evaluation of available toxicity data indicates that the potential hazard of ethyl (3-methylphenyl)-amino acetonitrile to fish and aquatic invertebrates is low and to aquatic plants is moderate.

3. Human Health Effects

Acute Oral Toxicity

(1) Rats (8; sex and strain not specified) were administered ethyl (3-methylphenyl)-amino acetonitrile in corn oil via gavage at 100 – 800 mg/kg-bw and were observed for 14 days. Mortality occurred from 3 hours to 1 day after dosing. Clinical signs of toxicity included weakness, vasodilation, sides caved in and ataxia. No significant findings were noted at necropsy.
LD_{50} = 200 – 400 mg/kg-bw

(2) Mice (10; sex and strain not specified) were administered undiluted ethyl (3-methylphenyl)-amino acetonitrile via gavage at 50 – 800 mg/kg-bw and observed for 14 days. Mortality occurred within 1 day of treatment. Clinical signs of toxicity included weakness, vasodilation, rolling, convulsions when handled, tremor and rough coat.
LD_{50} = 400 – 800 mg/kg-bw

Acute Dermal Toxicity

Guinea pigs (3; sex and strain not specified) were administered undiluted ethyl (3-methylphenyl)-amino acetonitrile dermally at 5 – 20 mL/kg-bw (approximately 4910 – 19,640 mg/kg-bw) under occluded conditions for an unspecified period and observed for 14 days. No animals died. Slight erythema and edema were observed and cleared by 1 week.
LD_{50} > ~ 19,640 mg/kg-bw

Repeated-Dose Toxicity

Data for this endpoint is not required because this chemical is a closed-system intermediate.

Reproductive/Developmental Toxicity

In a combined reproductive/developmental toxicity study, Sprague-Dawley rats (12/sex/dose) were administered ethyl (3-methylphenyl)-amino acetonitrile via gavage at 0, 25, 75 or 150 mg/kg-bw/day for 14 days prior to mating, throughout mating, gestation and early lactation. Mean body weight and body weight gains were decreased in mid- and high-dose males. At the high dose, clinical signs included reduced activity, vasodilation, rapid respiration, wet fur, transient convulsions and tremors in parental males and fur wet with saliva and vasodilation in parental females. Transient vasodilation was observed in all males and one female at the mid-dose. No treatment-related changes in sperm motility, epididymal spermatozoa counts or testicular spermatid counts were observed. There were no effects on histopathology of reproductive organs, sperm morphology, motility and counts, reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, numbers of implants, number of corpora lutea, pre- and post-implantation loss, pup survival, number of live and dead pups, pup sex ratio and pup body weight. Absolute testes weights were lower in high-dose males, but the biological significance is unclear since there were no effects on histopathological or sperm parameters.
LOAEL (systemic toxicity) = 75 mg/kg-bw/day (based on decreased body weight in males)
NOAEL (systemic toxicity) = 25 mg/kg-bw/day
NOAEL (maternal toxicity) = 150 mg/kg-bw/day (based on no effects at the highest dose tested)
NOAEL (reproductive/developmental toxicity) = 150 mg/kg-bw/day (based on no effects at the highest dose tested)

Genetic Toxicity – Gene Mutation

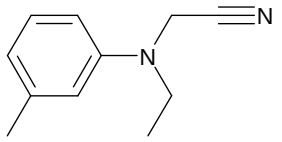
In vitro
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to ethyl (3-methylphenyl)-amino acetonitrile at concentrations of 1 – 1000 μg/plate without metabolic activation and 3.33 – 5000 μg/plate with metabolic activation. *Escherichia coli* WP2 *uvr*A(pKM101) were exposed to concentrations of 10 – 5000 μg/plate with and without metabolic activation. Positive controls were tested concurrently, but the control responses were not provided. The cytotoxic concentration was 333 μg/plate for *Salmonella* with and without metabolic activation and 1000 μg/plate for *E. coli* with metabolic activation and 3330 μg/plate for *E. coli* without metabolic activation. In one assay, no increases in the number of revertants were observed for any strain with or without metabolic activation. In a second assay, a 3-fold increase was observed in *Salmonella* strain TA1537 without metabolic activation, but the increase was not concentration-dependent and was within the range of historical controls. A confirmatory assay conducted with only TA1537 without metabolic activation showed no increase in the mean number of revertants.
Ethyl (3-methylphenyl)-amino acetonitrile was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Chinese hamster ovary (CHO) cells were exposed to ethyl (3-methylphenyl)-amino acetonitrile at concentrations up to 600 μg/mL in the presence and absence of metabolic activation for 3 hours in one assay and 19.8 hours in a second assay. Positive controls were tested concurrently and responded appropriately. The cytotoxic concentration was between 300 and 400 μg/mL and precipitation of the test substance was noted at concentrations $\geq$ 420 μg/mL.
Ethyl (3-methylphenyl)-amino acetonitrile did not induce chromosomal aberrations in these assays.

Conclusion: In animal studies, acute toxicity of ethyl (3-methylphenyl)-amino acetonitrile is moderate via the oral route and low via the dermal route of exposure. Data for repeated-dose toxicity is not required for the HPV Challenge Program because the chemical is considered a closed-system intermediate (CSI). In a combined reproductive/ developmental study in rats via oral gavage, the chemical is considered moderately toxic, but there was no evidence of reproductive or developmental toxicity. Ethyl (3-methylphenyl)-amino acetonitrile did not induce gene mutations or chromosomal aberrations.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** **Ethyl (3-methylphenyl)-amino acetonitrile** **(63133-74-4)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	27.7
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	40
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)** **(biomass)**	 2.88 1.40
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	200 – 400 (rat) 400 – 800 (mice)
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	> ~ 19,640
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	NA; data not required because chemical is a closed system intermediate.
Reproductive/Developmental Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)** **Systemic Toxicity (male)** **Maternal Toxicity** **Reproductive/Developmental Toxicity**	 NOAEL = 25 LOAEL = 75 NOAEL = 150 NOAEL = 150
Genetic Toxicity – Gene Mutation ***In vitro***	Negative
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Negative

Screening Level Exposure Characterization for HPV Challenge Chemical

Ethyl (3-methylphenyl)-amino acetonitrile

CAS # 63133-74-4

September 2008

Prepared by

Exposure Assessment Branch
Chemical Engineering Branch
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Screening Level Exposure Characterization

Ethyl (3-methylphenyl)-amino acetonitrile (CAS # 63133-74-4)

Non-CBI Executive Summary

Ethyl (3-methylphenyl)-amino acetonitrile (CAS # 63133-74-4) has an aggregated production and/or import volume in the United States of 10,000 to 500,000 pounds.[12] Non-confidential information in the Inventory Update Reporting (IUR) indicates that this chemical was manufactured and/or imported at the following companies and sites: Eastman Chemical Company/Kingsport, TN. There may be other companies and sites that are claimed confidential. Non-confidential IUR information for this chemical indicates that it is used as an industrial intermediate. No commercial use is reported in the IUR submissions or other data sources.

Potential for Exposures to Humans and the Environment:

Based on the information considered (including IUR data and information from the HPV Challenge Program information cited above) and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for each of the potentially exposed groups (including workers, general population, consumers and children) and the environment. Persistence and bioaccumulation ratings for this chemical are P2 and B1. These ratings suggest that this chemical is moderately persistent in the environment and is not bioaccumulative.[13] The Agency has reviewed the information in the original and revised/ updated HPV submission or test plan and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed system intermediate.[14] The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting this chemical in accordance with IUR requirements.

[12] USEPA, 2006 Partial Updating of TSCA Chemical Inventory.
[13] USEPA, 2008. Screening Level Hazard Characterization for High Production Volume Chemicals, N-Ethyl-N-(3-methylphenyl)-aminoacetonitrile.
[14] USEPA, 2008. Screening Level Hazard Characterization for High Production Volume Chemicals, N-Ethyl-N-(3-methylphenyl)-aminoacetonitrile.

Non-Confidential IUR Data Summary: Ethyl (3-methylphenyl)-amino acetonitrile (CAS # 63133-74-4)

Manufacturing/Import Information

Production and import volume:	10,000 to 500,000 pounds
List of non-CBI companies/sites:	Eastman Chemical Company/Kingsport, TN*
Maximum number of exposed workers:	1,000 or greater (including those of manufacturing, industrial processing and use) **
Highest non-CBI maximum concentration:	up to 90% by weight*
Non-CBI physical forms:	liquid *

* There may be other companies/sites, concentrations and physical forms that are claimed confidential.
** There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.

Table 1
Industrial Processing and Use Information
Reported in 2006 IUR

Processing Activity	Industrial Sector	Functional Use
Processing as a reactant	Other Basic Organic Chemical Manufacturing	Intermediates

Table 2
Commercial/Consumer Uses
Reported in 2006 IUR

Commercial/ Consumer Product Category Description	Highest maximum concentration range	Use in Children's Products
None reported		