

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

2-Amino-2,3-dimethylbutanenitrile (CASRN 13893-53-3)
(9th CI and CA Index Name: Butanenitrile, 2-amino-2,3-dimethyl-)

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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 America¹ 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 Program³. 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 sources⁵ 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 databases⁶ 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 guidance⁷. A more detailed description of the hazard characterization process is available on the EPA website⁸.

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

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 databases¹⁰ 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 characterizations¹¹. 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

2-Amino-2,3-dimethylbutanenitrile (CAS No. 13893-53-3)

[9th CI Name: Butanenitrile, 2-amino-2,3-dimethyl-]

September 2008

Prepared by

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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR 2-Amino-2,3-dimethylbutanenitrile (CAS No. 13893-53-3)

1. Physical-Chemical Properties and Environmental Fate

2-Amino-2,3-dimethylbutanenitrile is a liquid at room temperature that has a high estimated water solubility and moderate estimated vapor pressure. 2-Amino-2,3-dimethylbutanenitrile has high mobility in soil and minimal volatility. The rate of atmospheric photooxidation is considered moderate. The bioaccumulation potential is ranked low (B1). No measured data on the biodegradability of 2-amino-2,3-dimethylbutanenitrile were provided by the sponsor. However, based on professional judgment, EPA judges the persistence of the chemical as moderate (P2).

2. Hazard Characterization

Aquatic Organism Toxicity. The acute toxicity of 2-amino-2, 3-dimethylbutanenitrile to fish and aquatic plants is high, and to aquatic invertebrates is moderate.

Human Health Toxicity. The acute oral toxicity of 2-amino-2, 3-dimethylbutanenitrile in rats is moderate. The acute inhalation toxicity of 2-amino-2, 3-dimethylbutanenitrile in rats and acute dermal in rabbits is high. Mortality was observed following instillation of 2-amino-2,3-dimethylbutanenitrile into the eyes of rabbits. Repeated-dose and reproductive data were not required for the HPV Challenge Program because 2-amino-2, 3-dimethylbutanenitrile is a closed-system intermediate. However, a dermal repeated-dose toxicity study in rats was submitted and showed skin irritation, but there were no signs of toxicity in any treatment group. 2-Amino-2,3-dimethylbutanenitrile did not induce gene mutations.

3. Exposure Characterization

2-amino-2,3-dimethyl-butanenitrile (CAS # 13893-53-3) has an aggregated production and/or import volume in the United States of 1 million to 10 million pounds. Non-confidential IUR information for this chemical indicates that it is used as a site-limited intermediate. No commercial/consumer uses were reported in the IUR or any other data sources.

Potential Exposures to Humans and the Environment:

Based on the information considered, including IUR data and information from the HPV Challenge Program information, and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for the potentially exposed groups (including workers, general population, consumers and children) and the environment. The Agency has reviewed the information in the HPV submission test plan 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 for which this chemical was reported.

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 reviewed the information in the HPV submission and test plan and determined that the HPV chemical satisfied the guidance for a closed system intermediate. 2-Amino-2, 3-dimethylbutanenitrile was determined to be 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 low risk to workers, consumers, and children.

**SCREENING-LEVEL HAZARD CHARACTERIZATION
OF HIGH PRODUCTION VOLUME CHEMICALS**

SPONSORED CHEMICAL

**2-Amino-2,3-dimethylbutanenitrile (CAS No. 13893-53-3)
[9th CI Name: Butanenitrile, 2-amino-2,3-dimethyl-]**

September 2008

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SCREENING-LEVEL HAZARD CHARACTERIZATION 2-Amino-2,3-dimethylbutanenitrile (CAS No. 13893-53-3)

Introduction

The sponsor, Cytec Industries, Inc., submitted a Test Plan and Robust Summaries to EPA for 2-amino-2,3-dimethylbutanenitrile (CAS No. 13893-53-3; 9th CI name: butanenitrile, 2-amino-2,3-dimethyl-) on May 21, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 18, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/2amindi/c13131tc.htm>). EPA comments on the original submission were posted to the website on February 19, 2002. The sponsor submitted updated/revised documents on July 2001 and April 5, 2002, which were posted to the ChemRTK website on July 20, 2001 and April 25, 2002. Public comments were also received and posted to the website.

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. 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 effects testing under the HPV Challenge Program claiming that 2-amino-2,3-dimethylbutanenitrile is a closed-system intermediate (CSI). EPA's evaluation of the original and revised/updated information indicated that the chemical meets the guidance to fully support the CSI status for this chemical – waiving of repeated-dose and reproductive toxicity testing for the purposes of the HPV Challenge Program.

In the revised submission, the sponsor provided a robust summary for a chromosomal aberrations study in mammalian cells for two aliphatic nitriles, but did not provide chromosomal aberrations data for the sponsored chemical. The sponsor also provided developmental toxicity robust summaries for the following proposed supporting chemicals: four saturated aliphatic nitriles (acetonitrile, CAS No. 75-05-8; propionitrile, CAS No. 107-12-0; n-butyronitrile, CAS No. 109-74-0 and isobutyronitrile, CAS No. 78-82-0); four unsaturated aliphatic nitriles (acrylonitrile, CAS No. 107-13-1; methacrylonitrile, CAS No. 126-98-7; allylnitrile, CAS No. 109-75-1 and *cis*-2-pentenenitrile, CAS No. 920-37-6) and a chlorine-substituted unsaturated aliphatic nitrile (2-chloroacrylonitrile, CAS No. 920-37-6).

EPA did not consider the submitted data for chromosomal aberrations and developmental toxicity adequate for the following reasons: (1) The sponsor did not provide a rationale for using data for saturated aliphatic nitriles, unsaturated aliphatic nitriles or a chlorine-substituted unsaturated aliphatic nitrile to characterize the chromosomal aberration induction potential or developmental toxicity of the sponsored chemical, an amine-substituted saturated aliphatic nitrile. (2) There is uncertainty that data for the proposed supporting nitriles could be extrapolated to determine the dose-response characteristics of the sponsored chemical because slight changes in the structures of these nitriles produced large differences in effect levels in an inhalation developmental toxicity study (for example, the NOAECs for acetonitrile and propionitrile were different by a factor of 10). (3) Although all of the proposed supporting chemicals produced developmental effects, the sponsor indicated that the mechanism by which nitriles produce developmental effects is uncertain and provided no discussion about whether or not the amine moiety of the sponsored chemical would affect developmental toxicity potential. (4) The sponsor provided no data or discussion to indicate if structural variations in nitriles may affect their potential to induce chromosomal aberrations.

Hazard Characterization

2-Amino-2,3-dimethylbutanenitrile is a liquid at room temperature that has high estimated water solubility and moderate estimated vapor pressure. 2-Amino-2,3-dimethylbutanenitrile has high mobility in soil and minimal volatility. The rate of atmospheric photooxidation is considered moderate. The bioaccumulation potential is ranked low (B1). No measured data on the biodegradability of 2-amino-2,3-dimethylbutanenitrile were provided by the sponsor. However, based on professional judgment, EPA judges the persistence of the chemical as moderate (P2).

The acute toxicity of 2-amino-2,3-dimethylbutanenitrile to fish and aquatic plants is high and to aquatic invertebrates is moderate.

The acute oral toxicity of 2-amino-2,3-dimethylbutanenitrile in rats is moderate. The acute inhalation toxicity of 2-amino-2,3-dimethylbutanenitrile in rats and acute dermal toxicity in rabbits is high. Mortality was observed following instillation of 2-amino-2,3-dimethylbutanenitrile into the eyes of rabbits. Repeated-dose and reproductive data were not required for the HPV Challenge Program because 2-amino-2,3-dimethylbutanenitrile is a closed-system intermediate. However, a dermal repeated-dose study in rats was submitted and showed skin irritation, but there were no signs of toxicity in any treatment group. 2-Amino-2,3-dimethylbutanenitrile did not induce gene mutations.

Ready biodegradation, developmental toxicity and chromosomal aberrations were identified as data gaps under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of 2-amino-2,3-dimethylbutanenitrile 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

2-Amino-2,3-dimethylbutanenitrile is a liquid at room temperature that has high estimated water solubility and moderate estimated vapor pressure.

Table 1a. Physical-Chemical Properties of 2-Amino-2,3-dimethylbutanenitrile¹	
Property	Value
CAS No.	13893-53-3
Molecular Weight	112.18
Physical State	Liquid
Melting Point	Unavailable, liquid at room temperature
Boiling Point	186.88°C (with decomposition) (estimated) ²
Vapor Pressure	23.42 mm Hg (measured; 60% solution of 2-amino-2,3-dimethylbutanenitrile in toluene) 0.69 mm Hg at 25°C (estimated) ²
Water Solubility	1.07×10 ⁵ mg/L at 25°C (estimated) ²
Henry's Law Constant	9.8×10 ⁻⁹ atm·m ³ /mole (estimated) ²
Log K _{ow}	0.87 (estimated) ²

¹CYTEC Industries Inc. 2002. Revised Robust Summary for 2-Amino-2,3-Dimethylbutanenitrile.

<http://www.epa.gov/chemrtk/pubs/summaries/2amindi/c13131tc.htm>.

²USEPA. 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>.

Environmental Fate Characterization

2-Amino-2,3-dimethylbutanenitrile is expected to partition primarily to soil and water, 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 2-amino-2,3-dimethylbutanenitrile will exist in the vapor phase in the atmosphere. The rate of atmospheric photodegradation of vapor-phase 2-amino-2,3-dimethylbutanenitrile with photochemically generated hydroxyl radicals is considered moderate. Volatilization of 2-amino-2,3-dimethylbutanenitrile is considered minimal based on its Henry's Law constant. It is highly mobile in soil, does not bioaccumulate, and partially hydrolyzes at environmental pH although no rates were provided. No measured data on the ready biodegradability of 2-amino-2,3-dimethylbutanenitrile were provided by the sponsor. Although some simple aliphatic nitriles are readily biodegradable, no data were available to demonstrate that branched amino nitriles or nitriles containing quaternary carbons biodegrade rapidly. In some cases the presence of a quaternary carbon reduces biodegradability. Therefore, based on professional judgment EPA rates the persistence of the chemical as moderate (P2). 2-Amino-2,3-dimethylbutanenitrile was reported to partially hydrolyze in water; however, no rate for this reaction was provided. The bioaccumulation potential is ranked low (B1) based on an estimated BCF of 3.

Property	Value
Photodegradation Half-life	44.4 hours (estimated) ²
Hydrolysis Half-life	Partially hydrolyses in water to HCN
Biodegradation	No data
Bioconcentration	BCF = 3 (estimated) ²
K _{oc}	44 (estimated) ²
Fugacity (Level III Model) ²	Air = 0.16% Water = 46.2% Soil = 53.5% Sediment = 0.09%
Persistence	P2 (moderate) ³
Bioaccumulation	B1 (low) ³

¹CYTEC Industries Inc. 2002. Revised Robust Summary for 2-Amino-2,3-Dimethylbutanenitrile. <http://www.epa.gov/chemrtk/pubs/summaries/2amindi/c13131tc.htm>.

²US 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>.

³Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: 2-Amino-2,3-dimethylbutanenitrile is a liquid at room temperature that has a high estimated water solubility and moderate estimated vapor pressure. 2-Amino-2,3-dimethylbutanenitrile has high mobility in soil and minimal volatility. The rate of atmospheric photooxidation is considered moderate. The bioaccumulation potential is ranked low (B1). No measured data on the biodegradability of 2-amino-2,3-dimethylbutanenitrile were provided by the sponsor. However, based on professional judgment, EPA rates the persistence of the chemical as moderate (P2).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Bluegill sunfish (*Lepomis macrochirus*, 10/concentration) were exposed to 2-amino-2,3-dimethylbutanenitrile at nominal concentrations of 0, 0.10, 0.18, 0.32, 0.56 or 1.0 mg/L under static conditions for 96 hours. All of the fish at 1.0 mg/L died before the end of the 24-hour observation period. No deaths or signs of toxicity occurred at lower concentrations.

96-h LC₅₀ = 0.75 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*, 20/concentration, 10/replicate) were exposed to 2-amino-2,3-dimethylbutanenitrile at nominal concentrations of 0, 0.56, 1.0, 1.8, 3.2, 5.6 or 10 mg/L under static conditions for 48 hours. Concentrations were not measured. No mortality or abnormal effects were noted at concentrations up to 3.2 mg/L. Mortality or immobilization were observed at 5.6 mg/L after 24 and 48 hours of exposure (2/20 and 3/20 dead, respectively) and at 10 mg/L after 24 and 48 hours of exposure (15/20 and 20/20 dead, respectively).

48-h EC₅₀ = 6.9 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to 2-amino-2,3-dimethylbutanenitrile at nominal concentrations of 0, 0.01, 0.1, 0.5, 1.0 or 10 mg/L under static conditions for 96 hours. Concentrations were not measured. Growth was inhibited at concentrations ≥ 0.5 mg/L.

96-h EC₅₀ (growth) = 0.36 mg/L

Conclusion: The acute toxicity of 2-amino-2,3-dimethylbutanenitrile to fish and aquatic plants is high, and to aquatic invertebrates is moderate.

3. Human Health Effects

Acute Oral Toxicity

Sprague-Dawley rats (10 males/dose) were administered 2-amino-2,3-dimethylbutanenitrile via gavage at 31.3, 62.5 or 125 mg/kg-bw in corn oil and were observed for 14 days. Signs of toxicity included tremors, tonic convulsions, salivation and prostration at the highest dose and in one rat at 62.5-mg/kg-bw. All of the rats administered 125 mg/kg-bw and one rat at 62.5 mg/kg-bw died within 8 hours of exposure.

LD₅₀ = 83 mg/kg-bw

Acute Inhalation Toxicity

(1) Rats (5/sex/concentration) were exposed to 2-amino-2,3-dimethylbutanenitrile vapor at measured concentrations of 21, 58, 71 or 77 ppm (approximately 0.10, 0.27, 0.33 or 0.35 mg/L, respectively) for 4 hours and observed for 14 days. Deaths occurred at ≥ 0.33 mg/L, all during the first day of exposure. Clinical signs included hypoactivity, ataxia, prostration and respiratory irritation on the day of exposure at concentrations ≥ 0.27 mg/L. No clinical signs were seen in rats of any exposure group for the rest of the 14-day post-exposure period. No macroscopic abnormalities were observed in rats that died during the exposure or in rats sacrificed at the end of the 14-day observation period.

LC₅₀ ~ 0.33 mg/L

(2) Rats (5/sex/concentration) were exposed to 2-amino-2,3-dimethylbutanenitrile vapor at mean measured concentrations of 63, 75 or 109 ppm (approximately 0.29, 0.34 or 0.5 mg/L, respectively) for 1 hour and observed for 14 days. Deaths occurred at 0.5 mg/L, all during the first day of exposure. Clinical signs included hypoactivity, ataxia, prostration and respiratory irritation on the day of exposure at concentrations ≥ 0.34 mg/L. No clinical signs were seen in rats at any exposure concentration for the rest of the 14-day post-exposure period. No macroscopic abnormalities were observed in rats that died during the exposure or in rats sacrificed at the end of the 14-day observation period.

LC₅₀ (1-h) ~ 0.42 mg/L

Acute Dermal Toxicity

New Zealand White rabbits (5 males/dose) were administered 2-amino-2,3-dimethylbutanenitrile dermally to shaved skin at 12.5, 25, 50, 100 or 200 mg/kg-bw under occlusive conditions for 24 hours and observed for 14 days. All rabbits died after exposure to ≥ 50 mg/kg-bw and 3/5 rabbits died after exposure to 25 mg/kg-bw. Signs of toxicity included ataxia and prostration.

LD₅₀ = 23 mg/kg-bw

The following information was submitted to EPA under TSCA 8(e):

In an eye irritation study, the instillation of 2-amino-2,3-dimethylbutanenitrile of greater than 95% purity (89 mg) into the eyes of rabbits resulted in the deaths of five of six animals tested.

Repeated-Dose Toxicity

2-Amino-2, 3-dimethylbutanenitrile is a closed-system intermediate (CSI); therefore, repeated-dose toxicity testing is waived for this chemical under the HPV Challenge Program. However, the sponsor has submitted a robust summary for a 28-day repeated-dose dermal toxicity study which is summarized below.

Charles-River CD rats (5/sex/dose) were administered 2-amino-2, 3-dimethylbutanenitrile dermally to unabraded skin at 0, 3, 10 or 30 mg/kg-bw/day (6 hours/day, 5 days/week) under occlusive conditions for 28 days. After 6 hours of daily exposure, the patch was removed and the treated area was cleansed. No clinical signs of toxicity were seen at any dose, and body weight gain, food consumption and clinical chemistry values were comparable among all groups. No treatment-related changes were seen in the liver, kidney, heart, brain or gonads weights. Increased absolute and relative thyroid weights (dose-response data not provided) were observed in males and females in all doses; however, no corroborative thyroid pathology was observed upon microscopic examination. No treatment-related gross or microscopic lesions were observed in other organs. Skin irritation, consisting of erythema, eschar formation, dry and/or flaky skin and small sores, was observed at the application site in rats at 10- and 30-mg/kg-bw/day.

NOAEL = 30 mg/kg-bw/day (based on no systemic effects at the highest dose tested)

Reproductive Toxicity

Based on the closed-system intermediate (CSI) status of 2-amino-2,3-dimethylbutanenitrile, reproductive toxicity testing is waived for this chemical under the HPV Challenge Program.

Developmental Toxicity

No data were submitted for this endpoint. Data gap.

Genetic Toxicity – Gene Mutation

In vitro

Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to 2-amino-2,3-dimethylbutanenitrile at concentrations of 0.1, 1, 10 or 100 µg/plate in the presence and absence of metabolic activation. Positive and negative controls were used which responded appropriately. In the preliminary study concentrations were tested up to 5000 µg/plate. Cytotoxicity was observed at 1000 µg/plate and above.

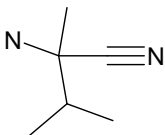
2-Amino-2,3-dimethylbutanenitrile was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

No data were submitted for this endpoint. Data gap.

Conclusion: The acute oral toxicity of 2-amino-2, 3-dimethylbutanenitrile in rats is moderate. The acute inhalation toxicity of 2-amino-2, 3-dimethylbutanenitrile in rats and acute dermal in rabbits is high. Mortality was observed following instillation of 2-amino-2,3-dimethylbutanenitrile into the eyes of rabbits. Repeated-dose and reproductive data were not required for the HPV Challenge Program because 2-amino-2, 3-dimethylbutanenitrile is a closed-system intermediate. A dermal repeated-dose study in rats showed skin irritation, but there were no signs of toxicity in any treatment group. 2-Amino-2,3-dimethylbutanenitrile did not induce gene mutations.

Appendix

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL 2-Amino-2,3-dimethylbutanenitrile (13893-53-3)
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC ₅₀ (mg/L)	0.75
Aquatic Invertebrates 48-h EC ₅₀ (mg/L)	6.9
Aquatic Plants 72-h EC ₅₀ (mg/L) (growth)	0.36 (96-h)
Summary of Human Health Data	
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	83
Acute Inhalation Toxicity LC ₅₀ (mg/L)	~ 0.33
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	23
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	N/A this chemical is a Closed System Intermediate.
Repeated-Dose Toxicity NOAEL/LOAEL Dermal (mg/kg-bw/day)	NOAEL = 30 (28-day)
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	N/A this chemical is a Closed System Intermediate.
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	— Data Gap
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	— Data Gap

– Indicates that endpoint was not addressed for this chemical.

Screening Level Exposure Characterization for HPV Challenge Chemical

Butanenitrile, 2-amino-2,3-dimethyl-

CAS # 13893-53-3

September 2008

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Screening Level Exposure Characterization Butanenitrile, 2-amino-2,3-dimethyl- (CAS # 13893-53-3)

Non-CBI Executive Summary

Butanenitrile, 2-amino-2,3-dimethyl- (CAS # 13893-53-3) has an aggregated production and/or import volume in the United States of 1 million to 10 million pounds.¹² Non-confidential IUR information for this chemical indicates that it is used as a site-limited intermediate. No commercial/consumer uses were reported in the IUR or any other data sources. Information submitted as part of the HPV Challenge Program indicates that butanenitrile, 2-amino-2,3-dimethyl- is used solely as an intermediate for the production of a class of herbicides.¹³ A pre-manufacture notification for this chemical was submitted to EPA and contains data and information that are claimed confidential.

Potential 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 the potentially exposed groups (including workers, general population, consumers and children) and the environment. The Agency has reviewed the information in the HPV submission 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 for which this chemical was reported.

¹² USEPA, 2006. Partial Updating of TSCA Chemical Inventory.

¹³ USEPA, 2008. High Production Volume Information System (HPVIS). Accessed June 17, 2008.
<http://www.epa.gov/hpv/hpvis/index.html>.

¹⁴ USEPA, 2002. EPA Comments on Chemical RTK HPV Challenge Submission. Letter dated January 30, 2002.
<http://www.epa.gov/chemrtk/pubs/summaries/2amindi/c13131rt.pdf>.

Non Confidential IUR Data Summary Butanenitrile, 2-amino-2,3-dimethyl-
(CAS # 13893-53-3)

Manufacturing/Import Information

Production and import volume: 1 million to 10 million pounds
List of non-CBI companies/sites:* Cytec Industries Inc./Wagganam, LA
Maximum number of potentially exposed workers:** less than 100 (including those in manufacturing, industrial processing and use)
Highest non-CBI maximum concentration:* greater than 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
None reported		

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		