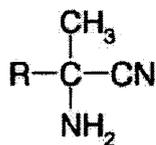


ROBUST SUMMARY FOR AMINOALKYLNITRILE CATEGORY

Summary

For purposes of this HPV submission, the aminoalkylnitrile category is composed of two chemicals with two functional groups, an amino group and a nitrile group, both of which are bonded to the same carbon atom. This carbon atom also bears a methyl group and another alkyl group. This category is composed of discrete materials that change by an incremental increase in carbon number in the alkyl moiety. The aminoalkylnitriles included in this HPV category are 2-amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile. The next higher homologue, 2-amino-2,3-dimethylbutanenitrile has been the subject of a separate HPV submission. Because of the close similarity in the structure and properties of this homologue, it will be considered as a supporting analog, and data on this analog are used to supplement data for the aminoalkylnitrile category.

For purposes of this HPV document, the aminoalkylnitrile chemicals can be represented by the general structural formula:



Information regarding these chemicals is presented in the table below.

<u>Chemical Name</u>	<u>CAS Registry Number</u>	<u>R =</u>
Propanenitrile, 2-amino-2-methyl-	19355-69-2	CH ₃ - (Category Member)
Butanenitrile, 2-amino-2-methyl-	4475-95-0	CH ₃ CH ₂ - (Category Member)
Butanenitrile, 2-amino-2,3-dimethyl-	1089-55-0	

The members of this category are produced solely by DuPont, as company-limited intermediates for the synthesis of the corresponding azonitriles, 2,2'azobis-(2-isobutyronitrile) (AIBN) (CAS # 78-67-1) and 2,2'azobis-(2-methylbutyronitrile) (AMBN) (CAS #13472-08-7). An HPV submission was made to EPA for AMBN, and in this submission AIBN was proposed as an analog to provide data to support AMBN. Because of the similar molecular structures, comparable effects data, and expected similar metabolic pathway, EPA agreed that AIBN is an acceptable analog for AMBN. We believe that similar considerations also justify treating 2-amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile as members of an HPV

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category, and justify using data for 2-amino-2,3-dimethylbutanenitrile to support this aminoalkylnitrile category.

The scientific literature was searched and summarized. Data were identified for the two materials in the category and the analogous substance (Table 1). Each study on category materials was evaluated for adequacy. EPA has already evaluated the HPV submission for the supporting analog. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies that were either considered not adequate but provided information of relevance for hazard identification and evaluation, or covered non-SIDS endpoints (Appendices A-C).

Table 1: Matrix of Available and Adequate Data for Aminoalkylnitrile Category

	Propanenitrile, 2-amino-2-methyl- (Category Member)	Butanenitrile, 2-amino-2-methyl- (Category Member)	Butanenitrile, 2-amino-2,3-dimethyl- (Supporting Analog)
R =	CH ₃ -	CH ₃ CH ₂ -	(CH ₃) ₂ CH-
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	√	√	√
Boiling Point	√	√	√
Vapor Pressure	√	√	√
Partition Coefficient	√	√	√
Water Solubility	√/-	√/-	√
ENVIRONMENTAL FATE			
Photodegradation	√	√	√
Stability in Water	√	√	√
Transport (Fugacity)	√	√	√
Biodegradation	√	√	√
ECOTOXICITY			
Acute Toxicity to Fish (96-hour LC ₅₀)	√	√	√
Acute Toxicity to Invertebrates (48-hour EC ₅₀)	√	-	√
Acute Toxicity to Aquatic Plants	-	-	√
MAMMALIAN TOXICITY			
Acute Toxicity	√	√	√
Repeated Dose Toxicity	√/-	N/A	√
Developmental Toxicity	-	-	-
Reproductive Toxicity	N/A	N/A	N/A
Genetic Toxicity Gene Mutations	-	-	√
Genetic Toxicity Chromosomal Aberrations	-	-	-
√ = Data are available and considered adequate. √/- = Data are available, but considered inadequate. - = No data available. N/A = Not Applicable.			

All three nitriles have roughly equivalent physical chemical properties (Table 2). Molecular weights range from 84.12 to 112.17. They are all liquids at room temperature, with melting points ranging from -4.7 to 7.7°C , and all three decompose with heat. Measured vapor pressure values are 30 mm Hg at 66°C , 14 mm Hg at 68°C , and 23.42 mm Hg at 25°C for 2-amino-2-methylpropanenitrile, 2-amino-2-methylbutanenitrile, and 2-amino-2,3-dimethylbutanenitrile, respectively. Estimated vapor pressures are also included at the standard temperature of 25°C , where measured data at this temperature were not available. Estimated vapor pressures were used when needed in modeling environmental fate data. Although no density was reported for 2-amino-2,3-dimethylbutanenitrile, the density for 2-amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile are similar, with values of 0.9 and 0.886, respectively. Partition coefficients are similar with estimated values of -0.04, -0.25, and 0.87 for 2-amino-2-methylpropanenitrile, 2-amino-2-methylbutanenitrile, and 2-amino-2,3-dimethylbutanenitrile, respectively. All three aminoalkylnitriles show appreciable water solubility with values greater than or equal to 27 g/L. The available data show similarity between the three nitriles for physical and chemical characteristics, thus supporting the category approach. **No further physical/chemical testing is recommended.**

Table 2: Physical and Chemical Characteristics

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2,3-dimethyl
Physical Appearance	Brown liquid with an ammonia-like odor	Yellow liquid with an ammonia-like odor	Liquid
Molecular Weight	84.12	98.15	112.17
Water Solubility	> 100 g/L	27.0 g/L	1.07×10^5 mg/L @ 25°C
Melting Point	-4.7°C	7.1°C	7.7°C
Boiling Point	Decomposes	Decomposes	Decomposes
Vapor Pressure	30 mm Hg @ 66°C (measured) 4 mm Hg @ 20°C (measured) 2.84 mm Hg @ 25°C (estimated)	14 mm Hg @ 68°C (measured) 1.03 mm Hg @ 25°C (estimated)	23.42 mm Hg @ 25°C (measured) 0.6 mm Hg @ 25°C (estimated)
Density/ Specific Gravity	0.9 @ 25°C	0.886	No Data
Partition Coefficient (log Kow)	-0.04 (estimated)	0.45 (estimated)	0.87 (estimated)

Members of the aminoalkylnitrile category have similar environmental fate behavior (Table 3). At acidic to neutral environmental pH, all three aminoalkylnitriles may be ionized due to the presence of the amino group, then subject to cation exchange reactions. Although somewhat volatile, with vapor pressures above 0.1 mm Hg (Table 2), they have Henry's Law constants less than $10e-8$ atm-m³/mole, so there will be a tendency to rain out of the atmosphere and not to volatilize from surface waters. Based on the atmospheric oxidation models, the two substances in the category have estimated half-lives of greater than 10 days, due to hydroxyl radical oxidation. The category analog is subject to the same oxidation mechanism, but with a higher hydrogen:carbon ratio is oxidized more rapidly, with an estimated half-life of 1.85 days. All three aminoalkylnitriles show appreciable water solubility with values greater than or equal to 27 g/L (Table 2). They are likely to be unstable in water, however, because they show a tendency to disproportionate to the corresponding ketone, cyanide, and ammonium when dissolved in water in the absence of excess ammonia (Kirk-Othmer, 1978). Biodegradation is estimated to be fast for 2-amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile. Because of the presence of a dimethyl group, the model estimates that the supporting analog is not as readily biodegradable. The category shows little tendency to bioaccumulate based on low estimated BCF values. Consistent with behavior described above, and assuming equal emissions to air, water, and soil, any residual of the aminoalkylnitrile category is expected to be distributed primarily in water and soil, based on the Mackay Level III fugacity model. Therefore, with regard to expected environmental distribution, the aminoalkylnitriles behave in a similar manner, justifying their classification as a category. **No further environmental fate testing is recommended.**

Table 3: Environmental Fate

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2,3-dimethyl-
Bioaccumulation*	log BCF = 0.5	log BCF = 0.5	log BCF = 0.5
Biodegradation*	Readily degradable	Readily degradable	Not readily biodegradable
Fugacity*	Air 1% Water 45.9% Soil 53.9% Sediment 0.089%	Air 0.1% Water 44.8% Soil 55% Sediment 0.09%	Air 0.127% Water 42.2% Soil 57.6% Sediment 0.087%
* Modeled data.			

The nitriles are moderately to highly toxic to aquatic life (Table 4). 2-Amino-2-methylpropanenitrile, 2-amino-2-methylbutanenitrile, and 2-amino-2,3-dimethylbutanenitrile are highly toxic to fish with a 96-hour LC₅₀ of 0.71 to 0.75 mg/L. 2-Amino-2-methylpropanenitrile and 2-amino-2,3-dimethylbutanenitrile are moderately toxic to *Daphnia* with 48-hour EC₅₀'s of 6.9 and 7.1 mg/L, respectively. 2-Amino-2,3-dimethylbutanenitrile is highly toxic to algae with a 96-hour EC₅₀ of 0.36 mg/L. The three chemicals appear to have somewhat similar toxicity to the individual species. Some differences exist, with algae appearing to be more sensitive than

fish or invertebrates. The available data are similar for all three nitriles, supporting the category approach for ecotoxicity. **Since the database indicates that there is strong agreement in aquatic toxicity across the category and analog chemicals, and data exists for each study type, no additional ecotoxicity testing is recommended.**

Table 4: Ecotoxicity

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2,3-dimethyl-
Toxicity to Fish (96-hour LC ₅₀ value)	0.71 mg/L (N) 468.3 mg/L (E)	0.71 mg/L (N) 744.5 mg/L (E)	0.75 mg/L (N) 163.343 mg/L (E)
Toxicity to Invertebrates (48-hour EC ₅₀ value)	7.1 mg/L (N) 26.6 mg/L (E)	41.1 mg/L (E)	6.9 mg/L (N) 10.4 mg/L (E)
Toxicity to Algae (96-hour EC ₅₀ value)	24.8 mg/L (E)	35.7 mg/L (E)	0.36 mg/L (N) 13.3 mg/L (E)
N = value based on nominal test concentrations E = estimate value; log Kow values used in the ECOSAR model are listed in Table 2.			

Acute toxicity data indicate that the three chemicals exhibit similar acute toxicity (Table 5). 2-Amino-2-methylpropanenitrile is very toxic to mammals with an oral LD₅₀ in rats of 10-30 mg/kg; while 2-amino-2-methylbutanenitrile and 2-amino-2,3-dimethylbutanenitrile are toxic with oral LD₅₀s of 74 and 83 mg/kg, respectively. All three chemicals are toxic via the inhalation route with a 1-, 2-, and/or 4-hour ALC (approximate lethal concentration) or LC₅₀ ranging from 71-111 ppm. Dermal, 2-amino-2-methylpropanenitrile and 2-amino-2,3-dimethylbutanenitrile are very toxic with an ALD (approximate lethal dose) and LD₅₀ in rabbits of 30-100 and 23 mg/kg, respectively. The test substances produced slight to mild skin irritation. 2-Amino-2-methylpropanenitrile and 2-amino-2,3-dimethylbutanenitrile produced mortality when tested in rabbit eyes. 2-Amino-2-methylbutanenitrile did not cause death of rabbits, but was a severe eye irritant. 2-Amino-2-methylbutanenitrile was not a skin sensitizer when tested in guinea pigs. No data regarding the acute dermal toxicity of 2-amino-2-methylbutanenitrile, or dermal sensitization potential of 2-amino-2-methylpropanenitrile and 2-amino-2,3-dimethylbutanenitrile were available. The available acute toxicity data are similar for the three nitriles, thus supporting the category approach for acute toxicity. **All required SIDS acute toxicity data points are complete for the category, and no further acute mammalian testing is recommended.**

Table 5: Acute Mammalian Toxicity

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2,3-dimethyl-
Oral LD₅₀ (rat)	10-30 mg/kg	74 mg/kg	83 mg/kg
Inhalation (rat)	2- and 4-hour ALC (rats) = 71 ppm	1-hour LC ₅₀ (male rats) = 111 ppm 1-hour LC ₅₀ (female rats) = 104 ppm 1-hour LC ₅₀ (rats – combined sexes) = 107 ppm	4-hour LC ₅₀ = 73 ppm; 1-hour LC ₅₀ = 92 ppm
Dermal (rabbit)	ALD = 30-100 mg/kg	No Data	LD ₅₀ = 23 mg/kg
Dermal Irritation	Slight to mild	Slight	Mild
Eye Irritation	Death	Severe	Death
Dermal Sensitization	No Data	Not a sensitizer	No Data

A summary of the available data on repeated dose, developmental, and reproductive toxicity is shown in Table 6. Repeated administration of 2-amino-2-methylpropanenitrile to rats via inhalation for 2 weeks at vapor concentrations of 0, 1.4, 7.3, or 22 ppm produced neither deaths nor differences in body weights or clinical observations. In addition, no toxicologically significant changes in hematology, clinical chemistry, urine analysis, organ weight, gross observations, or microscopic observations were seen. The NOEL for the study was 22 ppm. 2-Amino-2,3-dimethylbutanenitrile was tested in a 28-day dermal study in rats at doses of 3, 10, and 30 mg/kg. Although increased thyroid weights were observed at all dose levels, no pathologic changes to account for this finding were observed. Based on skin irritation observed at ≥ 10 mg/kg, the NOEL was 3 mg/kg. However, the authors state that the intent of the repeated exposure dermal study was to assess systemic toxicity, and since no evidence of systemic toxicity was observed, the NOEL for systemic toxicity for the study was 30 mg/kg. No effects were observed in the reproductive organs (testes, epididymides, prostate, and seminal vesicle) of the male rats treated with 2-amino-2-methylpropanenitrile for 2 weeks or in male and female rats (testes and uterus) treated with 2-amino-2,3-dimethylbutanenitrile for 28 days. **Since the category constituents are DuPont limited intermediates, repeated dose and reproductive**

toxicity data are not required. Since no data are available regarding developmental toxicity, a developmental toxicity test with 2-amino-2-methylpropanenitrile following OECD guideline 414 is recommended.

Table 6: Repeated Dose, Developmental, and Reproductive Toxicity

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2,3-dimethyl-
Repeated Dose Toxicity (NOAEL)	2-week inhalation (rats) NOEL = 22 ppm	N/A	28-day dermal (rat) NOEL = 3 mg/kg (based on irritation) or 30 mg/kg (based on systemic toxicity)
Developmental Toxicity	No Data	No Data	No Data
Reproductive Toxicity	N/A	N/A	N/A

No information was found regarding genetic toxicity for 2-amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile. 2-Amino-2,3-dimethylbutanenitrile was not mutagenic when tested in an Ames assay with *Salmonella typhimurium*, with and without exogenous metabolic activation. **Since no data are available regarding the clastogenic effects of the category members or the analog chemical, a chromosome aberration study with 2-amino-2-methylpropanenitrile following OECD guideline 473 is recommended.**

Table 7: Genetic Toxicity

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2,3-dimethyl-
Mutagenic	No Data	No Data	Negative (with and without activation)
Clastogenic	No Data	No Data	No Data

Human Exposure

2-Amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile are DuPont-limited intermediates. These two aminoalkylnitriles are manufactured at one DuPont plant and are shipped by DOT 412 tank truck to another DuPont facility for conversion into the corresponding 2,2'-azobis(alkylnitriles), 2,2'-azobis-(2-isobutyronitrile) (AIBN) and 2,2'-azobis-(2-methylbutyronitrile) (AMBN). The aminoalkylnitriles are not sold to third parties and are not consigned to toll manufacturers for conversion to the final products.

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The aminoalkylnitriles are produced in a closed system using ammonia, the appropriate ketone (acetone or 2-butanone), and HCN. The aminoalkylnitriles are hard piped to dedicated storage tanks and stored under an ammonia blanket. Off-gases associated with the aminoalkylnitrile process are vented to a flare stack. Each batch is sampled during manufacture and each storage tank is sampled daily and before loading. All sampling is done using a closed system that utilizes a container with a septum seal on the top with a needle type injector to prevent human exposure to both liquid and vapors. Sample analysis is conducted in a ventilated laboratory hood. Each aminoalkylnitrile has a required percentage of excess ketone for product quality control. The excess ketone is used as a marker for potential exposure during personnel air monitoring at the manufacturing site, since it is more volatile than the corresponding aminoalkylnitrile.

During loading at the manufacturing site, the trailer and the storage tank are connected to form a closed system to prevent exposure. Flex hose is connected to the liquid valve on the trailer and the liquid is fed through an induction pipe to the bottom of the trailer. The aminoalkylnitrile in liquid form is pumped into the trailer and the vapor from the container is vented back, through a separate vent line, into the storage tank that is being emptied. Both lines are purged before disconnecting from the trailer. There is no operator exposure during the loading operation.

Safety equipment used depends on the task being performed. During routine monitoring of manufacturing operations, operators wear chemical goggles, a hard hat, and full-body Nomex[®] garments. In the course of laboratory work in a vented hood, safety glasses with sideshields and rubber gloves are worn. During loading operations at the manufacturing site, operators wear appropriate personal protective equipment to protect themselves from liquid and vapor contact while on the trailer. PPE consists of Nomex[®] clothing, hardhat, chemical splash goggles, HCN personal monitor, radio, and neoprene gloves. Safety showers, eyewash stations and self-contained breathing apparatus (SCBA) are available in close proximity to the operations area. All first breaks into equipment that cannot be confirmed as having been decontaminated require, at a minimum, the use of a full acid suit and self-contained breathing apparatus (SCBA), such as the Scott Air Pack or air-line respirators.

At the DuPont use site, aminoalkylnitrile tank trucks are close-dome unloaded under a nitrogen blanket, and may be vented to a flare as needed. The stainless steel storage tanks and associated piping are designed to code to contain the aminoalkylnitrile, and have redundant hi-hi level interlocks to prevent overfilling. The aminoalkylnitrile is pumped through an air stripper to remove excess ammonia. The air exiting the stripper is routed to a flare. The stripped liquid aminoalkylnitrile flows to a reactor below liquid level and is completely converted to the corresponding Vazo[®] product in the subsequent reaction.

During unloading of the aminoalkylnitrile tank trucks at the DuPont use site, operators wear personal protective equipment consisting of neoprene chemical gloves sealed to an acid suit, boots, acid hood, and air supplied positive pressure respirator. During sampling of aminoalkylnitriles, chemical gloves and chemical acid hood are required. Safety showers, eyewash stations and self-contained breathing apparatus (SCBA) are available in close proximity to the operations area.

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The DuPont Acceptable Exposure Limit (AEL) for acetone in 2-amino-2-methylpropanenitrile is 500 ppm as an 8- and 12-hour TWA (time-weighted average); the AEL for 2-butanone in 2-amino-2-methylbutanenitrile is 200 ppm as an 8- and 12-hour TWA. Air monitoring at the manufacturing site has shown that ketone concentrations are well below their respective AELs. At the use site, air monitoring is conducted for the aminoalkylnitriles *per se*. Levels of the aminoalkylnitriles measured in short term air monitoring during unloading operations have been consistently below 0.5 ppm, the limit of quantitation, and well below the DuPont AEL for 2-amino-2-methylpropanenitrile, which is 5 ppm (15-minute TWA). Results are shown in the table below:

Exposure Data:

Job Sampled	No. of Results	Average (ppm)	Minimum (ppm)	Maximum (ppm)
<u>DuPont Manufacturing Site</u> Operators (full shift) – acetone	6	<0.82	0.75	1.04
<u>DuPont Manufacturing Site</u> Operators (full shift) – 2-butanone	6	<0.81	0.67	1.56
<u>DuPont End Use Site</u> Operators during unloading of aminoalkylnitrile – as 2-amino- 2-methylpropanenitrile or 2-amino-2-methylbutanenitrile	23	All < 0.5		

Conclusion

2-Amino-2-methylpropanenitrile and 2-amino-2-methylbutanenitrile may be considered as members of an HPV category based on the similarities in their molecular structures, reactivity, use, physical/chemical characteristics, and hazards. These two substances are nearest homologues and have the same functional groups. The use of supporting data from the next higher homologue, 2-amino-2,3-dimethylbutanenitrile, is consistent with the Agency's directive to HPV participants to maximize the use of scientifically appropriate data for related chemicals. Although some chemical and biological differences among these homologues may be expected, we believe these differences are minor. Generation of the additional data noted in the following test plan should be adequate to complete the HPV characterization of both members of the aminoalkylnitrile category.

Table 8: 2-Aminoalkylnitrile Category Proposed SIDS Test Plan

	Propanenitrile, 2-amino-2-methyl-	Butanenitrile, 2-amino-2-methyl-
Developmental Toxicity	Y	N
Genetic Toxicity Chromosomal Aberrations	Y	N

Reference for Summary

Kirk-Othmer Encyclopedia of Chemical Technology (1978). 3rd edition, Wiley-Interscience.