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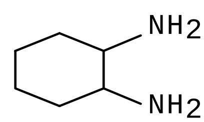
ROBUST SUMMARY FOR AMINE HEADS CATEGORY

Summary

Identification of a structure and functional based category

The amine heads category is composed of related members of the class of six carbon aliphatic diamines characterized as colorless, water soluble or miscible, strong bases possessing ammmoniacal odors. Amine heads included in this group are 1,6-hexanediamine (HMD), 1,2-cyclohexanediamine (DCH), and 2-methyl-1,5-pentanediamine - (MPMD or Dytek A). Structures of these amine heads are presented below.

Chemical Name	CAS Registry Number	Structure
1,6-Hexanediamine (9CI)	124-09-4	$NH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-NH_2$
1,2-Cyclohexanediamine (9CI)	694-83-7	
2-methyl- 1,5-Pentanediamine, (9CI)	15520-10-2	$NH_2-CH_2-CH(CH_3)-CH_2-CH_2-CH_2-NH_2$

These three materials occur together naturally in the manufacture of hexamethylenediamine, which is purified and used to produce Nylon-6,6. The “heads” designation is a result of a mixture of these three amines, plus other compounds, being the lower boiling fraction (heads) of the crude hexamethylenediamine. These lower boiling materials are removed by fractional distillation and are either discarded as waste, sold as a mixture (Solutia), or further purified (DuPont) to give the products listed above. The composition of the “amine heads” fraction varies depending on the manufacturer’s process for synthesis of HMD, on the relative yields of the various compounds dependent upon reaction conditions, and on the “cut” (fraction) removed. Thus, much of the material produced and handled is a mixture of these three major amines and a lesser quantity of the material is the purified DCH or MPMD. Therefore, data on the crude mixture and data on the purified components are all relevant. In addition, the high similarity of the toxicity of these three analogs suggests that the category “read across” procedure for filling data gaps has a high reliability.

Scientific literature was searched and summarized (Table 1). HMD is not in the HPV program as it has previously been submitted under the Organization for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) Program (IPCS, n.d.); however, data will be presented in this document to lend overall support to the amine heads category.

Each study on category materials was evaluated for adequacy. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies 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 on Amine Heads Category

	HMD	DCH	MPMD
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	√	√	√
Acute Toxicity to Invertebrates	√	√/*	√/*
Acute Toxicity to Aquatic Plants	√	√/*	√/*
MAMMALIAN TOXICITY			
Acute Toxicity	√	√	√
Repeated Dose Toxicity	√	√	√
Developmental Toxicity	√	–/*	–/*
Reproductive Toxicity	√	–/***	–/**
Genetic Toxicity Gene Mutations	√	√	√
Genetic Toxicity Chromosomal Aberrations	√	√	√

√ = Data are available and considered adequate.
√/* = Modeled data are available, but no empirical data are available.
–/* = No studies were available; however, we expect similar results to HMD.
–/** = Data on a 28-day repeated dose study were available but considered inadequate to cover the reproductive endpoint. However, we expect similar results to HMD.
–/*** = Data on reproductive organs are available in a 13-week repeated dose study on a mixture that contains DCH. For DCH, we expect similar results to HMD.

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Evaluation of Data Matrix Patterns

The available adequate data were broken out by discipline (physical chemical, environmental fate, ecotoxicology, and mammalian toxicology). These comparisons were conducted to determine if a pattern existed among the materials and to determine if additional testing needed to be conducted to complete the data set for the category.

Melting (or freezing) points are most affected by structural variations such as the cyclic ring (DCH) or branching (MPMD) while basicity, boiling points, etc. remain relatively similar within the family. Complete and adequate data (Table 2) generally correlate with structure, and validate the category proposal.

Table 2: Physical and Chemical Characteristics

	HMD	**DCH**	**MPMD**
Physical Appearance	white crystalline solid	colorless liquid	colorless liquid
Molecular Formula	$C_6H_{16}N_2$	$C_6H_{14}N_2$	$C_6H_{16}N_2$
Molecular Weight	116.2	114.2	116.2
Water Solubility	960 g/ 100g H_2O @ 30ºC	904.4 g/L @ 25ºC	617.3 g/L @ 25ºC
Melting Point (Freezing Point)	42ºC	2ºC (cis), 15ºC (trans)	-50 to -60ºC
Boiling Point	205ºC @ 760 mm Hg	191ºC @ 760 mm Hg	193ºC @ 760 mm Hg
Vapor Pressure	3 mm Hg @ 60ºC	0.387 mm Hg @ 20ºC	0.22 mm Hg @ 20ºC 0.25 mm Hg @ 25ºC
Density/ Specific Gravity	0.833 g/cm^3 @ 60ºC	Specific gravity: 0.94	Density: 0.86 g/mL
Partition Coefficient (Log Kow)	0.35 estimated	0.09 estimated	0.27 estimated

Environmental fate data are essentially equivalent for the category members (Table 3). The data indicate that HMD, DCH, and MPMD are ready biodegradable. The low octanol/water partition coefficients for the three category members indicate a low potential for bioaccumulation. Fugacity model predictions indicate that these materials will act similarly in regards to partitioning in the environment. When emitted under a standard scenario of equal emission to air, water, and soil, they will partition primarily into soil and water. All category members will be positively charged at environmental pH ranges. These cations will tend to stick to soil.

Table 3: Environmental Fate

	HMD	**DCH**	**MPMD**
Bioaccumulation*	Low BCF = 1	Low BCF = 3	Low BCF = 3
Biodegradation	Ready Biodegradable	Ready Biodegradable	Ready Biodegradable
Fugacity*	Air: 0.016% Water: 38% Soil: 61.9% Sediment: 0.71%	Air: 0.031% Water: 38.9% Soil: 61% Sediment: 0.072%	Air: 0.0874% Water: 46.1% Soil: 53.7% Sediment: 0.078%
* = Modeled data			

Actual and estimated data on ecotoxicology support a category approach for these chemicals (Table 4). Modeling of physical-chemical parameters (i.e., Kow) and aquatic toxicity was conducted to help provide insight into the behavior in the environment and the aquatic toxicity of HMD, DCH, and MPMD. Syracuse Research Corporation models for estimating physical-chemical properties were used to estimate $\log_{10}$ Kow (Meylan and Howard, 1995) for the amine head chemicals for subsequent use in the ECOSAR program. ECOSAR (Meylan and Howard, 1999) was used to estimate the missing aquatic toxicity data for the three amine head chemicals to green algae, daphnids (planktonic freshwater crustaceans), and fish. ECOSAR predictions are based on actual toxicity test data for classes of compounds with similar modes of action. Predicted $\log_{10}$ Kow values were used as input for the ECOSAR model (see Table 4 for values).

Experimentally, HMD has exhibited low to slight acute toxicity towards freshwater fish species and moderate acute toxicity to *Daphnia magna* and towards the algal species *Selenastrum capricornutum*. The estimated aquatic toxicity data for DCH and MPMD are consistent with the available experimental data for the acute toxicity of these two compounds to fish. The estimated data for DCH and MPMD are also consistent with the experimental data for HMD and support a low to moderate level of concern for these compounds.

Table 4: Aquatic Toxicity

	HMD	**DCH**	**MPMD**
Log Kow	0.35 (E)	0.09 (E)	0.27 (E)
Toxicity to Fish (LC_{50} value)	96-hour (fathead minnow): 1435 mg/L (N) 96-hour: 364 mg/L (E)	48-hour (orfe): 200 mg/L (N) 525 mg/L (E)	48-hour (orfe): 130 mg/L (N) 409.7 mg/L (E)
Toxicity to Invertebrates (48-hour EC_{50} value)	23.4 mg/L (N) 21.8 mg/L (E)	30.3 mg/L (E)	24.2 mg/L (E)
Toxicity to Algae (96-hour EC_{50} value)	14.8 mg/L (N) 23.2 mg/L (E)	29.6 mg/L (E)	25.1 mg/L (E)
E = estimated value, N = value based on nominal test concentrations			

Acute toxicity data indicate that all three chemicals exhibit similar acute toxicity (Table 5) and thus support the category approach. All three members of the category were slightly toxic via the acute oral route and moderately toxic via the acute inhalation route. HMD and a mixture containing DCH were both moderately toxic via the acute dermal route. HMD and MPMD were not skin sensitizers, while DCH was a weak skin sensitizer. All three chemicals are severe irritants or corrosive to the skin. HMD, MPMD, and a mixture containing HMD and DCH are all severely irritant or corrosive to the eye.

Table 5: Acute Mammalian Toxicity

	HMD	DCH	MPMD
Oral LD_{50}	792 mg/kg (fasted rat) 1127 mg/kg (non-fasted rat)	ALD = 2300 mg/kg (non-fasted rat) 1100 mg/kg (non-fasted rat)*	1690 mg/kg (non-fasted rat)
Inhalation LC_{50}	4-hour LC_{50} > 0.95 mg/L	4-hour ALC: 3.2 mg/L	1-hour LC_{50}: 2.9-4.1 mg/L
Dermal LD_{50}	1110 mg/kg	501-794 mg/kg*	No Data
Dermal Irritation	Corrosive	Severe skin irritant	Corrosive
Eye Irritation	Corrosive	Severe irritant**	Corrosive
Dermal Sensitization	Not a sensitizer	Weak sensitizer	Not a sensitizer

* = Data on a mixture containing 30-50% HMD, 5-10% DCH, and 5-10% MPMD.
** = Data on a mixture containing 69.5% HMD and 30.5% DCH.

A summary of the available data on repeated dose, developmental, and reproductive toxicity is shown in Table 6. Upon repeated administration of HMD to rats and mice via inhalation for 13 weeks, HMD produced nasal irritation with accompanying histological alterations at 1.6 mg/m^3 and above. Likewise, 2-week inhalation studies of DCH and MPMD produced nasal lesions at levels of 10 mg/m^3 and higher. Repeated oral administration of HMD for 13 weeks produced body weight effects at levels of 150 mg/kg and above. In a repeated dose oral study of a mixture that contained HMD, DCH, and MPMD, the NOEL was 125 mg/kg (the highest level tested). In a 28-day oral study of MPMD, a NOEL of 10,000 ppm (745 mg/kg) (the highest level tested) was determined for male rats. Body weight, body weight gains, and food consumption of female rats was depressed leading to a NOEL of 3000 ppm (276 mg/kg) in the female rats. HMD is not a developmental or reproductive toxin in the rat. There were no organ weight effects for MPMD in a 28-day oral study, and no organ weight effects in a 13-week oral study for a mixture containing HMD, DCH, and MPMD. Because of the similarities observed between the 3 materials in their structures, physical and chemical characteristics, acute toxicity, environmental fate, and aquatic toxicity, and the similar NOELs observed in the repeated dose studies, it is reasonable to conclude that DCH and MPMD would have similar toxicity to HMD in developmental and reproductive toxicity.

Table 6: Repeated Dose, Developmental, and Reproductive Toxicity

	HMD	**DCH**	**MPMD**
Repeated Dose Toxicity (NOAEL)	13-week inhalation study in rats: NOEL = 12.8 mg/m^3 13-week inhalation study in rats and mice: NOAEL = 5 mg/m^3 HDDC** (corresponding to 1.6 mg/m^3 HDC) 13-week oral study in rats: NOEL = 50 mg/kg	2-week inhalation study in rats: NOEL < 10 mg/m^3 13-week oral study in rats*: NOEL = 125 mg/kg	2-week inhalation study in rats: NOEL < 10 mg/m^3 28-day oral study in rats: NOEL = 10,000 ppm (745 mg/kg) (males) and 3000 ppm (276 mg/kg) (females)
Developmental Toxicity	Maternal and Fetal NOEL = 112 mg/kg Maternal and Fetal LOEL = 184 mg/kg Not a developmental toxin	No Data	No Data
Reproductive Toxicity	Not a reproductive toxin in a 2-generation study	No effects on reproductive organs in a 13-week study*	No effects on reproductive organs in a 28-day study

* = Data on a mixture which contains approximately 41% HMD, 6% DCH, and 7% MPMD.
** = HDDC is 1,6-hexanediamine dihydrochloride.

Genetic toxicity data are similar between the 3 amine heads, supporting a category approach (Table 7). HMD was not active genetically in a series of tests developed to detect either point mutations or clastogenicity. A compound containing 31% DCH was negative in the Ames Test and in an *in vitro* chromosome aberration test using Chinese hamster ovary cells. MPMD was negative in the Ames test and in an *in vitro* chromosome aberration test conducted in human lymphocytes.

Table 7: Genetic Toxicity

	HMD	**DCH**	**MPMD**
Mutagenicity	Negative	Negative*	Negative
Clastogenicity	Negative	Negative*	Negative
* = Data on a mixture which contains approximately 31% DCH and 6% HMD.			

Overall, the toxicologic database for HMD is complete and the information available. The toxicologic database for DCH and MPMD are somewhat limited, but the information available and the modeled data suggests a level of toxicity comparable to HMD. The 3 chemicals are similar in chemical structure, physical and chemical characteristics, environmental toxicity, aquatic toxicity, acute toxicity, repeated dose toxicity, and genetic toxicity. Because of these similarities, it is reasonable to conclude that the category members would behave similarly in the area where a data gap exists: developmental toxicity and reproductive toxicity.

TEST PLAN: No additional toxicity testing will be conducted.

Exposure Assessment

Exposure Assessment for 1,2-Diaminocyclohexane (DCH) – DuPont & Solutia

1,2-Diaminocyclohexane is a DuPont co-product produced in the manufacture of hexamethylenediamine (HMD) at two sites in the United States, one in Canada, and one in the United Kingdom. Crude DCH is manufactured at all four DuPont facilities. Crude DCH contains mainly HMD and 2-methyl-1,5-pentanediamine. One US and the Canadian site ship their material to the other US site where it is refined to DCH-99%. Some Crude DCH is sold directly, but most is refined to DCH-99 and sold into epoxy curing applications. The crude DCH manufactured in the UK is not further refined and a small percentage is also sold into epoxy curing applications. Three customers account for 75% of the sales with the other 25% spread across several small customers. Waste is disposed of in an approved and permitted incinerator or deepwell.

Amine Heads is Solutia's name for crude DCH and it is also a co-product from Solutia's manufacture of HMD at two sites, both in the United States. Solutia does not further refine the crude product that typically contains 25-55% proportion of DCH. The composition varies depending on operating conditions, feedstock composition and catalyst activity. A typical composition of the current Solutia Amine Heads co-product is:

DCH	25-55%
HMD	10-30%
1,4-Butanediamine	10-20%
3-Aminopropan-1-ol	7-20%
2-Aminocyclopentane,-2-methylamine	1-5%
MPMD	1-5%
Water	10-20%

This Amine Heads co-product is sold into a resin application. Waste Amine Heads is either injected into deep wells or incinerated.

The potential for exposure is the greatest during truck loading for production and during line equipment breaks for maintenance. Exposure is very limited during production as these are closed systems. The sites can have from 430 to 2000 total personnel working (construction, contractor, and plant employees). The areas where the substance is manufactured will have 4 to 5 operators during normal operations and 30 to 60 people during a shutdown or major construction activity. Routine exposure of personnel is limited to operators sampling product for quality control and to workers loading materials into tank trucks. The sites have effective safety, health, and environmental practices and procedures in addition to engineering controls, environmental controls, and personal protective equipment to control exposure. Adequate safety equipment, such as safety showers, eyewash fountains, and washing facilities, are available in the event of an occupational exposure.

Individuals handling DCH wear safety glasses and impervious clothing to prevent contact, such as gloves, apron, boots, or whole bodysuit made from butyl rubber. When the possibility exists for eye and face contact due to splashing or spraying of material, coverall, chemical splash goggles, and a face shield should be worn. A NIOSH approved full-face air purifying respirator with an organic vapor with dust filter cartridge or canister may be permissible under certain circumstances where airborne concentrations are expected to exceed exposure limits. Protection provided by air purifying respirators is limited. Use a positive pressure air supplied respirator if there is any potential for an uncontrolled release or any other circumstances where air purifying respirators may not provide adequate protection.

DuPont and Solutia practice Responsible Care and assess the ability of potential customers to safely handle DCH prior to commencing a commercial relationship. The Product Stewardship System works with customers to understand their applications and any issues associated with PPE (personal protective equipment), safety equipment (safety showers, eyewash stations, ventilation needs, etc.), storage concerns, disposal requirements, and MSDS questions.

The DuPont Acceptable Exposure Limit (AEL) for DCH is 5 mg/m^3 (1 ppm) (8- and 12-hour TWA). No other limits have been established. Air monitoring has been conducted on DCH and results are shown in the table below. None of the samples taken suggest the probability of exposure in excess of the current recommended AEL. The sampling method used is the Clayton Environmental analytical method validation based on NIOSH Aliphatic Amine Method 2010. LOGAN (lognormal analysis) is a computerized statistical method for characterizing occupational exposures to chemicals, noise, and other environmental hazards. LOGAN uses sequential collection of data and makes decisions on the minimum amount of data. It helps make cost-effective, accurate decisions that ensure a healthy workplace. LOGAN uses inferential statistics to estimate the true workplace conditions, in the same way that public polling estimates opinions by sampling a representative percentage of the public. LOGAN is designed to limit the risk of employee occupational overexposure to less than 5%.

EXPOSURE DATA - DuPont

Area: Operators and Maintenance

People	No. of Results	Avg. of TWA (ppm)	Min. of Results (ppm)	Max. of Results (ppm)
Operators	100	0.09	0.01	0.20
Mechanics	26	0.03	0.01	0.09
Lab Analysts	24	0.01	0.01	0.04

<u>Exposure Assessment for Dytek A (2-Methyl-1,5-pentanediamine) – DuPont</u>

Dytek A is a co-product produced in the manufacture of hexamethylenediamine (HMD). Dytek A is manufactured at one DuPont facility. The majority of Dytek A is sold internally to be used as a chemical intermediate in the production of polyamide plastics, films, and fibers and to one customer for use as a pharmaceutical intermediate in the production of vitamin B for animal feed. A small percentage is sold to a few customers who use the chemical as an epoxy curing agent or a chemical intermediate.

The site can have 430 personnel working (construction, contractor, and plant employees). The area where the substance is manufactured has 1 operator during normal operations and 5 people during a shutdown or major construction activity. The potential for exposure is the greatest greatest during shutdown work and loading and unloading of the Dytek A since the processes used are closed.

The site has effective safety, health, and environmental practices and procedures in addition to engineering controls, environmental controls, and personal protective equipment to control exposure. Adequate safety equipment, such as safety showers, eyewash fountains, and washing facilities, are available in the event of an occupational exposure.

Individuals handling Dytek A should wear safety glasses and impervious clothing such as gloves, apron, boots, or whole bodysuit made from butyl rubber, as appropriate. When the possibility exists for eye and face contact due to splashing or spraying of material, coverall chemical splash goggles and a face shield should be worn. A NIOSH approved full-face air purifying respirator with combination high efficiency particulate (HEPA/P100) filter and organic vapor cartridge or canister may be permissible under certain circumstances where airborne concentrations are expected to exceed exposure limits. Protection provided by air purifying respirators is limited.

Use a positive pressure air supplied respirator if there is any potential for an uncontrolled release or any other circumstances where air purifying respirators may not provide adequate protection.

DuPont practices Responsible Care and assesses the ability of potential customers to safely handle Dytek A prior to commencing a commercial relationship. The Product Stewardship System works with customers to understand their applications and any issues associated with PPE (personal protective equipment), safety equipment (safety showers, eyewash stations, ventilation needs, etc.), storage concerns, disposal requirements, and MSDS questions.

The DuPont Acceptable Exposure Limit for Dytek A is 0.4 ppm (8- and 12-hour TWA) – vapor; 2 mg/m^3 (8- and 12-hour TWA) - particulate. No other limits have been established. Air monitoring has not been conducted on Dytek A.

References for the Summary:

Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92.

Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).

IPCS (n.d.). International Programme on Chemical Safety, SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).