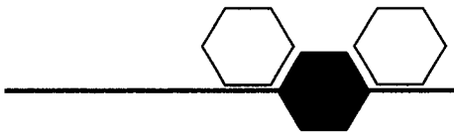


AEE Consortium

BASF Corporation • Huntsman Corporation

U.S. High Production Volume (HPV) Challenge Program

Sponsored Substance: 2-(2-aminoethoxy) ethanol
CAS Number 929-06-6

Sponsor: The AEE Consortium
Members: BASF Corporation and Huntsman Corporation

December 24, 2009

Test Plan

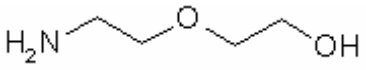
Prepared by: Bergeson & Campbell, P.C.
1203 Nineteenth Street, N.W.
Suite 300
Washington, D.C. 20036

1203 Nineteenth Street, N.W., Suite 300, Washington, D.C. 20036 • Tel. (202) 557-3800, Fax (202) 557-3836

Introduction

The purpose of this test plan is to summarize the available data, identify gaps in the data set, and recommend additional tests, which may be conducted to characterize sufficiently the Screening Information Data Set (SIDS) data elements for the sponsored substance 2-(2-aminoethoxy) ethanol (AEE), CAS Number 929-06-6. The substance is sponsored by the AEE Consortium, which is comprised of BASF Corporation and Huntsman Corporation. AEE, to date, is considered a high production volume (HPV) chemical in the United States with import and manufacture volumes being in excess in 1 million pounds per year. In addition, to the U.S. HPV Challenge Program, AEE has been pre-registered in association with the European Union's (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation. AEE is considered an HPV chemical within the EU. As such, the first registration for AEE in association with REACH is expected to occur in 2010. Due to participating in various global chemical programs, any proposed testing takes into consideration the goals and objectives of each program while also taking into consideration animal welfare issues. Additional testing is proposed to address the reproductive and developmental endpoints while also providing additional information for the repeated dose endpoint via the inhalation route. This testing proposal also supports data gathering requirements in association with REACH. As noted below, AEE is used as a cutting fluid. A study is therefore underway following Organization for Economic Cooperation and Development (OECD) test guideline 422 under Good Laboratory Practice (GLP) conditions via the inhalation route. Once a final report is issued, the AEE Consortium will submit to the U.S. Environmental Protection Agency (EPA) in association with the HPV Challenge Program a robust study summary to address each of the endpoints.

Chemistry: AEE is an organic primary amine compound in which one of the three hydrogen atoms in ammonia is replaced (see structure below). Amines are a derivative of ammonia in which one or more hydrogen atoms are replaced by a substituent such as an alkyl or aryl group. AEE has a formula of $C_4H_{11}NO_2$ with a molecular weight of 105.1. It is typically manufactured with a purity of greater than 98%.



Read-Across: Data sharing is proposed for the biodegradation endpoint to support a conclusion of ready biodegradation. Data are available on the sponsored substance AEE, but available data are only available following inherent biodegradation test guidelines. Data from the close structural analog 2-ethoxyethylamine, CAS Number 110-76-9 with a molecular formula of $C_4H_{11}NO$, a molecular weight of 89.14, and with the below chemical structure is proposed for read-across to support a conclusion of ready biodegradation. The substances have similar physical chemical properties in which environmental fate properties are also considered similar.

Use: Aqueous AEE is a widely used industrial substance for removing carbon dioxide (CO_2) and hydrogen sulfide (H_2S) from natural gas streams and refinery process streams. In addition, it may also be used to remove CO_2 from combustion gases/flue gases and may have potential for abatement of greenhouse gases. As lubrication oil, AEE is used in cutting and metal working fluids and is considered to be a preferred primary amine due to its low volatility and is least likely of the other amines to leach cobalt, aluminum, or copper. In the electronics industry, AEE is used to formulate wafer and PWB cleaning solvents.

Physical Chemical Properties: All endpoints are considered addressed. (*see* Table 1). Detailed information is presented in the submitted robust study summaries.

Table 1: Summary of Physical Chemical Properties

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA ADDRESSED
Melting Point	FP: -12.5^{0}C		2	Hawley, 1981	Y
Boiling Point	222. 5 – 223.8^{0}C		2	BASF AG, 1996a	Y
Vapor Pressure	1.54E-03 mmHg (2.05E-001) hPa at 25^{0}C	Data are cited in the Experimental Database in EPISUITE/EPIWEB 4.0.	2	US EPA; Daubert and Danner as cited in HSDB (1989)	Y
Partition Coefficient (log K_{ow})	-1.89	Estimated using EPISUITE/EPIWEB 4.0 (KOWWIN v1.67)	2	US EPA, 2009	Y
Water Solubility	1E+006 mg/L at 25^{0}C	Estimated using EPISUITE/EPIWEB 4.0 (WSKOW v1.41)	2	US EPA, 2009	Y

Environmental Fate and Transport: All endpoints are considered addressed. In the case of the biodegradation endpoint, data are available on AEE following inherent biodegradation protocols resulting in a conclusion of inherently biodegradable. In order to conclude the test substance (AEE) as being readily biodegradable, read-across is performed from the close structural analog 2-ethoxyethylamine (CAS No. 110-76-9). *See* Table 2.

Table 2: Environmental Fate and Transport

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA ADDRESSED
Photodegradation	OH Rate Constant 69.57782 E-12 cm3/mol-sec T1/2 = 1.845 hours	Estimated using EPISUITE/EPIWEB 4.0 (AOPWIN v 1.92)	2	US EPA, 2009	Y
Stability in Water	No hydrolysable groups		2	Kollig *et al*. (1993), Boethling and Mackay (2000) and Harris (1990)	Y
Biodegradation	Readily biodegradable	Data from the structure analog 2-ethoxyethylamine (110-76-9) is proposed. OECD 301 A (1996) Die Away Test	1	BASF AG, 1996b	Y
	Inherently biodegradable	OECD 302B Inherent Biodegradability: Modified Zahn Wellen Test	2	BASF SE, 1980	Y
Transport/ Distribution	Air = 0.00228 % Water = 37.8% Soil = 62.1% Sed = 0.0706	Level III Fugacity Model	2	US EPA, 2009	Y

Acute Aquatic Toxicity: All endpoints are considered addressed. Data are available for the acute fish, acute aquatic invertebrate, and aquatic plant endpoints. Tests were conducted using acceptable guidelines in which the tests were initially conducted using a non-neutralized test substance; however, based on the pH of the substance, at a minimum the highest test concentration was adjusted for pH. Initial results of non-neutralized test substance show that all experimental LC_{50} and EC_{50} values are greater than 100 mg/L with the most sensitive species identified as algae with a ErC_{50} of 261 mg/L, which was adjusted for pH. Estimated values are presented, but in the case of the aquatic plant species, the estimated value is inconsistent with results achieved in the well-conducted studies. Based on no deficiencies noted in the experimental results, the experimental values are preferred. *See* Table 3 for a summary of the reliable data.

Table 3: Acute Aquatic Toxicity

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA ADDRESSED
Acute Toxicity to Fish	96h LC50 = >681 (neutralized)	DIN 38412 part 15 *Leuciscus idus*	2	BASF SE, 1981	Y
	96h LC50 = 4023 mg/L	ECOSAR v1.0 class: aliphatic amines* fresh water	2	US EPA, 2009	Y
Acute Toxicity to Aquatic Invertebrates	48h EC50 = >500 mg/L (neutralized)	EU Method C.2	2	BASF SE, 1990a	Y
	48h LC50 = 181 mg/L	ECOSAR v1.0 class: aliphatic amines* fresh water	2	US EPA, 2009	Y
Toxicity to Aquatic Plants	72h EC50 = 261 mg/L (neutralized)	DIN 38412 Part 9	2	BASF SE, 1990b	Y
	96h EC50 = 22 mg/L	ECOSAR v1.0 class: aliphatic amines* fresh water	2	US EPA, 2009	Y

Human Health

Acute Toxicity: All endpoints are considered addressed. Reliable acute toxicity data are available with AEE via the oral and dermal routes. The oral LD_{50} for male and female rats following OECD test guideline 401 under GLP conditions is 2,558 mg/kg bw (Mallory, 1991). In OECD test guideline 402 under GLP conditions, the dermal LD_{50} in male and female New Zealand White rabbits is > 3,000 mg/kg bw/day (the highest concentration tested) (Mallory, 1991).

Table 4. Acute Toxicity

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
Acute toxicity	LD50(m/f) = 2557.9 mg/kg bw	Oral - gavage (rat – SD m/f) similar to OECD 401 (equivalent to EPA *Federal Register*, Vol. 50, No. 188, 1985), GLP	1	Mallory, V.T. 1991a	Y
	LD50(m/f) = 3400 mg/kg bw	Oral – OECD 401 (rat)(m/f)	2	BASF, 1969	Y

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
	LD50 = 5660 mg/kg bw (no data on sex)	Other test method: Oral – gavage 14-day post observation period (rat)	2	Smyth *et al*. 1951	Y
	LD50 = >3000 mg/kg bw LD50= > 3000 mg/kg bw	Dermal (occlusive)(rabbit – New Zealand White, m/f) OECD 402, GLP	1	Mallory, V.T. 1991b	Y
	LD50 (male) = 1260 mg/kg bw	Other test method (rabbit – New Zealand White, m)	2	Smyth *et al*. 1951	Y

Repeated Dose: Existing reliable data are available on AEE to address the repeated dose endpoint. An existing 90-day study is available following OECD test guideline 411 (dermal route) in which dermal irritation was noted at the lowest dose tested (17 mg/kg/day). The systemic no observed adverse effect level (NOAEL) was determined to be 175 mg/kg/day (highest dose tested). Although existing data are available for this endpoint, in order to address the reproductive and developmental endpoints while also providing supplemental data via the inhalation route, a study is proposed following OECD test guideline 422, combined repeated dose, reproductive and developmental toxicity study. The inhalation route was selected based on the desire to obtain additional information applicable to AEE's use as a cutting fluid, which has the possibility of being aerosolized.

Table 5. Repeat Dose

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
Repeat Dose	NOAEL (dermal) = 17 mg/kg/day NOAEL (systemic) = 175 mg/kg/day (highest dose tested)	90-day Dermal study in Rats (Sprague-Dawley, m/f); OECD 411 (GLP) (occlusive)	1	Zeiders, J.L. (2002) (rpt number 0470RH11.001)	Y
	NOAEL (dermal) = 250 mg/kg/day LOEL (dermal) = 500 mg/kg/day (nominal)	Subchronic – range finding (14-day exposure) (dermal) (rat, Sprague-Dawley, m/f) (occlusive)	2	Chyrsalis Preclinical Services, Inc. (2000)	Y

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
		An OECD 422 is proposed via the inhalation route to support existing data for this endpoint			

Genetic Toxicity: All endpoints are considered addressed. Reliable experimental data are available with the test substance (AEE) in the Ames Assay, *in vitro* cell transformation assay (BALB/3T3 Assay), *in vitro* Unscheduled DNA Synthesis (UDS) Assay and the *in vivo* Mouse Micronucleus Assay. In each case, a guideline method was followed under GLP conditions which resulted in negative findings. (*See* Table 6.)

Table 6. Genetic Toxicity

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
Genetic Toxicity					
Mutations	Negative	OECD 471; Ames Assay; GLP; *S. typhimurium* TA 1535, TA 1537; TA 98 and TA 100; with and without S-9	1	Pharmakon Research International, Inc. (1982)	Y
	Negative	OECD 471; Ames Assay; *S. typhimurium* TA 1535, TA 1537; TA 98 and TA 100; with and without S-9	2	BASF AG, 1990	Y
Gene Toxicity					
Cell Transformation Assay	Negative	*In vitro* transformation (BALB/3T3 Assay) EU Guideline B21; GLP	1	Rundell, J.O. (1982) Litton Bionetics (Rpt number 20992)	Not required
UDS Assay (*In vitro*)	Negative	OECD 482 (rat hepatocytes); not GLP; no analytical; without activation	2	American Health Foundation (1982) (rpt number: 030882 Texaco Testing)	Not required
Chromosome Aberration					
Mouse Micronucleus Test (*In vivo*)	Negative	OECD 474 (mouse); GLP; i.p.; cytoxicity at 250 mg/kg (doses 62.6, 125, 250 mg/kg)	1	Erexson, GL (2001)	Y

Reproductive Toxicity: Limited data are available on AEE to address the reproductive toxicity endpoint. An existing 90-day study is available following OECD test guideline 411 (dermal route) in which the male and female reproductive organs were evaluated; no data, however, are available for the developmental endpoint. As a result, consistent with OECD guidance, data from the existing 90-day study are not sufficient to address the endpoint. A study is proposed following OECD test guideline 422, combined repeated dose, reproductive and developmental toxicity study via the inhalation route. The inhalation route was selected based on the desire to obtain additional information applicable to AEE's use as a cutting fluid, which has the possibility of being aerosolized.

Table 7. Reproductive Toxicity

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
Reproductive Toxicity		**An OECD 422 is proposed via the inhalation route to address this endpoint.**			Awaiting results
	NOAEL = >175 mg/kg bw day	In a 90-day repeat dose study the reproductive organs were evaluated in which no effects were observed. OECD TG 411 under GLP	1	Zeiders, J.L. (2002) (rpt number 0470RH11.001)	

Developmental Toxicity: No existing data are available for AEE. A study is proposed following OECD test guideline 422, combined repeated dose, reproductive and developmental toxicity study via the inhalation route. The inhalation route was selected based on the desire to obtain additional information applicable to AEE's use as a cutting fluid, which has the possibility of being aerosolized.

Table 8. Developmental Toxicity

ENDPOINT	VALUE	METHOD/SPECIES	RL	REFERENCE	DATA MET
Developmental Toxicity		**An OECD 422 is proposed via the inhalation route to address this endpoint**			Awaiting results

Additional Data: Data on skin irritation, eye irritation, and sensitization are located in the submitted robust study summaries. AEE is considered a severe skin and eye irritant in several studies following acceptable guidelines. In most cases, results indicate irreversible necrosis. In OECD test guideline 406 under GLP conditions, the test article (AEE) induced, challenged, and rechallenged at a 10% concentration, did not cause delayed contact hypersensitivity in guinea pigs. As a result, AEE is not considered a sensitizer (Armondi, 1991). (Please refer to robust study summaries.)

References

American Health Foundation, 1982. The Hepatocyte Primary Culture/DNA Repair Assay on Compound 4236-45-25 Using Rat Hepatocytes in Culture. Unpublished report. Data owner: Hunstman Corporation. Report number: 030882 (Texaco Testing). Report date: 1982-06-25.

BASF AG, 1969. Industrial hygiene orientating investigation. Unpublished report. Report number: XIX/51. Report date: 1969-03-22.

BASF AG, 1990. Report on the Study of 2,2-Aminoethoxyethanol (ZST Test Substance No.: 89/230) in the AMES TEST (Standard Plate Test and Preincubation Test with Salmonella typhimurium). Unpublished report. Data owner: BASF SE. Report number: 40M0230/894476. Report date: 1990-11-26.

BASF AG., 1996a. Bestimmung des Siedeverlaufs von Aminodiglykol bei 1013 mbar. BASF AG, Technische Entwicklung Verfahrenstechnik. Report number: FE 96.355. BASF SE, D-67056 Ludwigshafen. Report Date: 1996-07-15.

BASF AG., 1996b. Prüfung der biologischen Abbaubarkeit von 2-Ethoxyethylamin im DOC-Abnahme (Die-Away) Test. Department of Ecology. Report number: 96/0079/21/1; Report date: 1996-04-15.

BASF SE, 1980. Test protocol "Standversuch". Unpublished report. Laboratory of Ecology. Report number: 79/318/I; Report date: 1980-12-09.

BASF SE, 1981. Report on the acute toxicity of 2,2' aminoethoxyethanol to Leuciscus idus L. Unpublished report. Report number: 80/438. Report date: 1981-03-11.

BASF SE, 1990a. Report on acute effect of 2,2'-aminoethoxyethanol to Daphnia magna Straus. Unpublished report. Report number: 1/0506/2/89. Report date: 1990-06-21.

BASF SE, 1990b. Algentest. Unpublished report. Report number: 2/w506/89t72. Report date: 1990-06-24.

Boethling R and Mackay D, 2000. Handbook of Property Estimation Methods for Chemicals. CRC Press, Boca Raton, FL, USA. cited in Neoacids C5 to C28 Category Analysis Report-IUCLID datasheet.

Chrysalis Preclinical Services Corporation, 2009. A 14-Day Dermal Toxicity Study in Rats (Dose-Range-Finding). Unpublished report. Data owner: Huntsman Corporation. Report number: 0437RH11.001. Report date: 2000- 09-20.

Daubert, T.E. and Danner, R.P., 1989 as cited in SRC PhysProp Database, 04 Jun 2007.

Erexson, G.L., 2001. *In vivo* mouse micronucleus assay with Diglycolamine (DGA). Unpublished report. Data owner: Huntsman Corporation. Report number: 2239-0455OECD. Report date: 2001-07-25.

Harris, J.C., 1990. Rate of hydrolysis. Lyman WJ et al., Handbook of chemical property estimation methods, 3rd edition, ACS Washington.

Hawley, G.G., 1981. The Condensed Chemical Dictionary. 10th ed.. New York: Van Nostrand Reinhold Co., 1981., p. 51. cited in HSDB 21 Sep 2006.

Kollig, HP et al., 1993. Environmental fate constants for organic chemicals under consideration for EPA's hazardous waste identification project. EPA/600/R-93/132.

Mallory VT, 1991a. Acute oral toxicity. PharmakonResearch International, Inc. Unpublished report. Data owner: Huntsman Corporation. Report number: PH 402-TX-012-90. Report date: 1991-01-18.

Mallory VT, 1991b. Acute exposure dermal toxicity. PharmakonResearch International, Inc. Unpublished report. Data owner: Huntsman Corporation. Report number: PH 402-TX-012-90. Report date: 1991-01-15.

Pharmakon Research International, Inc., 1982. Ames Salmonella/Microsome Plate Test. Unpublished report. Data owner: Huntsman Corporation. Report number: PH 301-TX-010-81. Report date: 1982-02-22.

Rundell, J.O., 1982. Evaluation of 4236-45-25 in the *in vitro* transformation of BALB/3T3 cells assay. Unpublished report. Data owner: Hunstman Corporation. Report number: 20992. Report date: 1982-02-28.

Smyth H.F. et al., 1951. Range-Finding Toxicity Data, List IV. Arch. Ind. Hyg. Occup. Med., 4, 119.

US EPA, 2009. Estimation Programs Interface Suite™ for Microsoft® Windows, Version 4.0 (EPIWEB v4.0)(EPISuite v4.0) Washington, DC, USA. Run date: December 12, 2009.

Zeiders, J.L., 2002. A 90-day dermal toxicity study in rats. Unpublished report. Calvert Preclinical Services Inc., PA 18447 USA. Data owner: Huntsman Corporation. Report number: 0470RH11.001. Report date: 2002-11-13.