

Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene)

CAS No. 10595-60-5

U. S. EPA HPV Challenge Program Submission

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Submitted by

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REVISED TEST PLAN

Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) CAS No. 10595-60-5

HPV End Point	Information Available (Yes/No)	Acceptable (Yes/No)	Surrogate Data (Yes/No)	Testing Required (Yes/No)
Physical-chemical Data				
Melting Point	No			No
Boiling Point	No			No
Vapor Pressure	Yes	Yes		No
Water Solubility	No		Yes	No
Partition Coefficient	Yes	Yes		No
Environmental Fate and Pathway				
Photodegradation	Yes	Yes		No
Stability in Water	Yes	Yes		No
Transport/distribution (Fugacity)	Yes	Yes		No
Biodegradation	No		Yes	No
Ecotoxicity				
Acute toxicity to fish	No		Yes	No
Acute toxicity to <i>daphnia</i>	No		Yes	No
Acute toxicity to algae	No		Yes	No
Toxicity				
Acute Toxicity	Yes	Yes		No
Repeated Dose Toxicity	No		Yes	No
Toxicity to Reproduction/Developmental toxicity	No		Yes	No
Genetic toxicity <i>in vitro</i> (Gene Mutation)	No		Yes	No
Genetic toxicity <i>in vitro</i> (Chromosomal Aberration)	No		Yes	No

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1. Sponsoring Companies

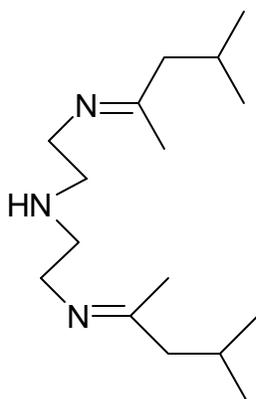
Air Products and Chemicals, Inc. and PPG Industries, Inc. are the manufacturers of Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) and are the joint sponsors of this substance for the U.S. Environmental Protection Agency's HPV Chemical Challenge Program. The technical contact is

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2. Test substance

Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) is an isolated intermediate and subsequently used to produce a resin that is the component of paint products. Since the test substance is an intermediate to be used for a production of resin and the vapor pressure is expected to be very low, the only reasonably anticipated potential exposure would be by skin contact and would occur in an occupational setting to a limited number of workers at Plants. There would be no reasonably anticipated exposure to the general public.

Its molecular structure is as follows:



The test substance is produced in the presence of excess Methyl Isobutyl Ketone (MIBK) (~30%). At this concentration, the material is a clear, light yellow, very fluid liquid. An attempt was made to drive off the MIBK by distillation when the test substance was prepared for HPV testing. However, this attempted removal of the excess MIBK solvent from the substance resulted in formation of polymeric by-products. Therefore, the production batch (70% test substance in 30% MIBK) was used for testing.

3. Criteria for Determining Adequacy of Data

All relevant studies were reviewed and assessed for adequacy according to the standards of Klimisch *et al.* (1977). Four reliability categories, 1-reliable without restriction, 2-reliable with restriction, 3-not reliable, and 4-not assignable, have been established and a rating of 1 and 2 were considered to be adequate.

4. Test Plan

4.1 Summary

The test substance, Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) is rapidly hydrolyzed to Diethylenetriamine (DETA, CAS Number 111-40-0) and MIBK (CAS Number 108-10-1) within minutes. Due to the rapid hydrolysis, some physical chemical properties, ecotoxicity, and toxicity are expected to result from the hydrolysis products, DETA and MIBK. Based on the structural characteristics, it is expected that data from separate studies of DETA and MIBK would be representative of the toxicity of the DETA/MIBK mixture that would result from hydrolysis of the test substance. There is no reason to suspect that synergistic effects or differences in mechanism of toxicity would result. There was no indication of synergistic effects when evaluating the existing oral LD₅₀ data. The oral LD₅₀ for Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) was 1.9 ml/kg. The oral LD₅₀ of DETA and MIBK is reported as 1080 mg/kg and 2090 mg/kg, respectively in RTECS (Registry of Toxic Effects of Chemical Substances). Therefore, most of the HPV end points will be referenced to the existing separate datasets on DETA and MIBK.

Both MIBK and DETA are listed under the EPA HPV Challenge Program and these chemicals have been evaluated in the Organization for Economic Cooperation and Development (OECD) HPV Screening Information Data Set (SIDS) Program. In 1991, MIBK (sponsored by the United States) was determined to be of “low potential risk” with “low priority for further testing”. Also in 1991, DETA (sponsored by the Netherlands) was determined to be “currently of low priority”. Data contained in the dossiers prepared for DETA and MIBK for the OECD SIDS program can be found at <http://cs3-hq.oecd.org/scripts/hpv/>.

In addition, the Existing Chemicals Bureau of the European Commission has compiled dossiers for both DETA and MIBK in IUCLID format. . These dossiers are available in the public datasets on high volume chemicals (IUCLID CD-ROM, Year 2000 edition) and are attached below. Robust summaries of key studies for both materials are contained in these dossiers. Therefore, robust summaries for the HPV end points on DETA and MIBK will not be summarized again and should be referenced to the attached document. Only brief summaries of the results of test data for the HPV end points of MIBK and DETA included in the public dataset on high volume chemicals will be presented in this test plan.



IUCLID DETA.pdf

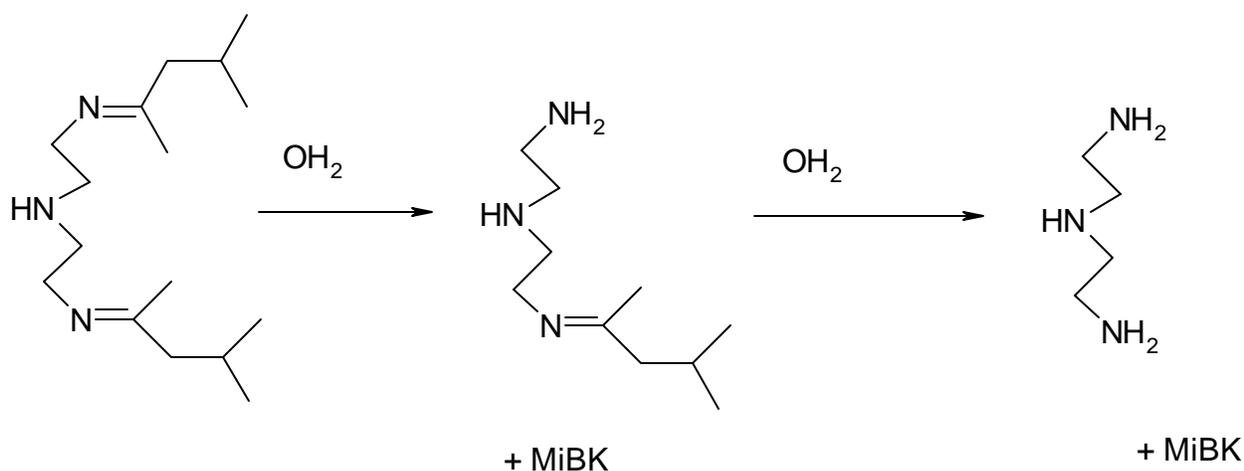


IUCLID MIBK.pdf

4.2 Physical/Chemical Properties

No data are available for melting point, boiling point, and water solubility. Because producing pure material (free of MIBK) for the purposes of determining a melting point and a boiling point is not possible, no meaningful data for melting and boiling points can be generated. In addition, the substance will probably begin to decompose before it boils, especially at atmospheric pressure. Therefore, no testing for these endpoints will be conducted.

The test substance, Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) is rapidly hydrolyzed to Diethylenetriamine (DETA) and MIBK within minutes (*see section below for the details*).



When the quantity of the test substance added to water reaches a certain point, the MIBK (hydrolysis product) that is produced will exceed the solubility of MIBK (1.9%) in water and a separate phase of MIBK will result. Therefore, the water solubility of this material is expected to be limited to the solubility of DETA and the water solubility of the test substance should be referenced to the DETA data. The water solubility of DETA is reported as miscible at 20°C. Data for vapor pressure and partition coefficient (K_{ow}) are estimated (calculated) using a modeled approach. No testing will be conducted.

4.3 Environmental Fate/Pathways

Results of the two hydrolysis studies indicate that the test substance is rapidly hydrolyzed to DETA and MIBK. The calculated half-life in the first study (Springborn report, 2002) ranges from 0.972 minutes to 51.2 minutes depending on the pH of the test solutions.

Hydrolytic rate constant and % Hydrolysis

<u>pH</u>	<u>Rate Constant (Kobs)</u>	<u>Calculate Half -Life (t_{1/2})</u>
1.2	0.813	51.2 minutes
4	1.22	34.0 minutes
7	8.25	5.04 minutes
9	0.713	0.972 minutes

In the second hydrolysis study (PPG Industries Analytical Report, 2002), greater than 90% of the test substance hydrolyzed within 5 minutes at all pH conditions.

Determination of Rate of Hydrolysis in different pH buffered conditions

<u>Time (minutes)</u>	<u>pH 1</u>	<u>pH 4</u>	<u>pH 7</u>	<u>pH 9</u>	<u>Distilled Water</u>
5	93.2%	94.5%	92.8%	87.9%	82.9%
15	94%	99%	98.9%	88.4%	90.8%
30	96.9%	99.7%	99.2%	92.7%	98.3%
60	98%	99.8%	100%	95.7%	100%

Since the test substance is produced in the presence of excess MIBK, which is used as a reflux solvent to assist in the removal of the product water via azeotropic distillation, only the presence of the one degradant DETA was confirmed in both studies.

Data for photodegradation and environmental transport are estimated using the EPIWIN/AOPWIN program. The estimated photodegradation hydroxyl radical rate constant is estimated to be $95.2679 \text{ E-}12 \text{ cm}^3/\text{molecule-sec}$ with a half-life calculated to be 0.112 days. Level III fugacity modeling indicates that the test substance should partition to water (3.59%), air (0.078%), soil (27.3%), and sediment (69%). No data on biodegradability is available. However, due to the rapid hydrolysis of the test substance into DETA and MIBK in water, the biodegradability of DETA and MIBK can be referenced for this end point. Several biodegradation tests have been conducted on both DETA and MIBK (IUCLID CD-ROM, 2000). The data indicated that MIBK is readily biodegradable. For DETA, conflicting results have been reported. In several studies, no biodegradation of DETA is noted after 14, 20 or 28 days. However, some other studies report DETA as biodegradable after 28 days or 30 days. No biodegradation testing will be conducted for the test substance.

4.4 Ecotoxicity

This end point is filled from DETA and MIBK data. Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) is rapidly hydrolyzed (in minutes) to DETA and MIBK. Due to the rapid hydrolysis, the ecotoxicity of this material is expected to result from the hydrolysis products, DETA and MIBK. The ecotoxicity of this test substance should be referenced to the ecotoxicity data from DETA and MIBK. Several aquatic toxicity studies in various species are available for

DETA and MIBK (IUCLID CD-ROM, 2000). Both DETA and MIBK show a low degree of toxicity for aquatic organisms. The 96 hr LC₅₀ values for fresh water fish (*Leuciscus idus* and *Poecilia reticulata*) ranged from 248 to 1014 mg/l for DETA. The 48 hr EC₅₀ values of 17 – 65 mg/l for *Daphnia magna* and the 96 hr EC₅₀ values of 346 – 592 mg/l for algae growth rate were determined for DETA. In chronic studies, no adverse effects were observed at DETA concentration of 5.6 mg/l for *Daphnia magna* and 10 mg/l for *Gasterosteus aculeatus*. The 96 hr LC₅₀ values for fresh water fish (*Pimephales promelas* and *Salmo gairdneri*) were reported as 505 – 780 mg/l for MIBK. The 48 hr EC₅₀ values for *Daphnia magna* ranged from 170 to >1000 mg/l. The 96 hr LC₅₀ values for algae was determined to be 400 mg/l. In chronic studies with MIBK, no observed effect concentration was determined to be 57 mg/l for *Pimephales promelas* and 78 mg/l for *Daphnia magna*. Based on these data, no aquatic studies will be conducted for the test substance.

4.5 Human Health Data

4.5.1 Acute Mammalian Toxicity

This endpoint is filled by one oral toxicity study in rats and one dermal toxicity study in rabbits utilizing the test substance (Carnegie Mellon Institute of Research Report, 1981). The oral LD₅₀ for Diethylenetriamine, 1,7-bis(1,3-dimethylbutylidene) was 1.9 ml/kg and the dermal LD₅₀ value was >2.0 ml/kg. In addition, due to the rapid changes of the test substance into DETA and MIBK in acidic conditions, the acute oral toxicity data from DETA and MIBK can be referenced for this end point. The oral LD₅₀ of DETA and MIBK in rats is reported as 1080 mg/kg and 2090 mg/kg, respectively in RTECS. In the public dataset (IUCLID CD-ROM, 2000), the oral LD₅₀ values for rats ranged from 2080 to 4600 mg/kg for MIBK and from 819 to 2600 mg/kg for DETA. The dermal LD₅₀ for rabbits was >16000 mg/kg for MIBK. The dermal LD₅₀ values for rabbits ranged from 950 to 1240 mg/kg for DETA. No testing will be conducted for the test substance.

4.5.2 Repeated Dose Mammalian Toxicity

Due to the rapid hydrolysis of this test substance into DETA and MIBK under acidic conditions, the mammalian oral toxicity is expected to result from the hydrolysis products, DETA and MIBK. In a 90 day feeding study with Dihydrochloride salt of DETA, rats were exposed to 70-80, 530-620, and 1060-1210 mg /kg/day in the diet (Bushy Run Research Center Report 51-45). Some decreases in body weight and food consumption were noted at the two highest dose levels as well as some changes in hematology parameters, kidney weights, liver weights and/or adrenal weights. The NOAEL (no observed adverse effect level) was 70-80 mg/kg in that study. A NOAEL of 50 mg/kg was reported in a 13-week oral gavage study with MIBK in rats at concentrations of 50, 250, and 1000 mg/kg (Microbiological Associates Report 5221.04). Increased liver and kidney weights were observed at the highest concentration; however, there were no corresponding histopathological lesions present in the liver. A general nephropathy was seen for both male and female rats. The effects seen at the high dose group were present to a significantly lesser extent in the mid dose group. Several additional repeated dose studies in various species and different routes conducted on MIBK and DETA can be referenced to the public data on high volume chemicals (see attached document). Based on these available data, no repeated dose mammalian toxicity testing will be conducted for the test substance.

4.5.3 Genetic Toxicity

Due to the rapid hydrolysis of this test substance into DETA and MIBK, the genetic toxicity is expected to result from the hydrolysis products, DETA and MIBK. Both MIBK and DETA are not considered to be mutagens in various genotoxicity studies (IUCLID CD-ROM, 2000). No genetic toxicity testing will be conducted on the test substance.

4.5.4 Reproductive/Developmental Toxicity

Due to the rapid hydrolysis of the test substance into DETA and MIBK, the mammalian oral reproductive/developmental toxicity is expected to result from the hydrolysis products, DETA and MIBK. No references on oral reproduction/developmental toxicity studies are included in the public dataset on high volume chemicals. However, two developmental toxicity studies by inhalation conducted on MIBK, one in the rats and the other in the mouse are included in the dataset (Tyl, R.W. et. al., 1987). Rats and mice were exposed by inhalation at concentrations of 300, 1000, or 3000 ppm during gestation days 6 through 15. Exposure to 3000 ppm resulted in maternal toxicity and fetotoxicity. No increase in fetal malformations was observed in any exposure groups. The NOAEL was 1000 ppm for the maternal effects and was determined to be >3000 ppm for the teratogenic effects. In one generation reproduction study with DETA where a dose of 30, 100, or 300 mg/kg was administered by gavage to rats, increased duration of gestation, increased post-implantation loss, and reduced mean litter size were noted, resulting in a NOAEL of 30 mg/kg for reproduction and developmental effects. No effects other than reduced body weight and food consumption at the highest concentration was observed for the parents and it was determined to be 100 mg/kg as a NOAEL. No testing will be conducted for the test substance.

5. References

- (1) Springborn Smithers Laboratories. Report 511.6215, Dated 10-29-02.
- (2) PPG Industries Analytical Report No. CR10040, Dated 9-18-02.
- (3) Carnegie-Mellon Institute of Research report No. 81-21S, Dated 3-13-81.
- (4) Public data on High Volume Chemicals, IUCLID CD-ROM, Year 2000 Edition, European Commission, European Chemicals Bureau.
- (5) Bushy Run Research Center Report 51-45 (1988) cited in Public data on High Volume Chemicals, IUCLID CD-ROM, Year 2000 Edition.
- (6) Microbiological Associates (1986) Report No 5221.04 cited in Public data on High Volume Chemicals, IUCLID CD-ROM, Year 2000 Edition
- (7) Tyl, R.W. et. al. (1987), Fundam. Appl. Toxicol. 8, 310-327 cited in Public data on High Volume Chemicals, IUCLID CD-ROM, Year 2000 Edition