OVERVIEW

4,7,10-Trioxatridecane-1,13-diamine (TTD) came to the attention of the National Cancer Institute (NCI) Division of Cancer Biology (DCB) following a review of chemicals that do not meet criteria for inclusion in the United States (U.S.) Environmental Protection Agency (EPA) HPV Challenge Program even though their production volume in 1998 exceeded 1 million pounds.

TTD is an amine curing agent with widespread use in several industries. Since this chemical is primarily an industrial intermediate, the main source of exposure would be anticipated to be workers.

Although there is very little information available on the toxicity of TTD, that information suggests that this chemical is severely acutely toxic. A TSCA 8(e) submission describes TTD as corrosive to rabbit skin, and an MSDS cautions that inhalation may result in spasm, inflammation and edema of the larynx and bronchi, pneumonitis, and pulmonary edema.

For this reason, the NCI recommends that a series of in vitro alternative test assays, including those that are being validated by ICCVAM, be run on this chemical to determine the indications of its acute effects and genotoxicity. Based on these results, it may be unnecessary to examine the effects of chronic exposure to TTD. This information was presented to the Chemical Selection Working Group (CSWG) on December 15, 2005. The group concurred with NCI’s position that interim data should be collected before a full evaluation of the testing needs for this chemical is performed.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

In comments provided on January 25, 2006, Dr. John Walker supplied the following post-meeting information on Interagency Testing Committee (ITC) activities regarding TTD. This chemical had production volumes greater than and less than a million pounds in 1998 and 2002, respectively. In its 56th Report (70 FR 61520, October 24, 2005), the ITC stated that it had not
determined whether to conduct a data-availability study on approximately 237 chemicals that were high production chemicals only in the 1998 Inventory Update Rule (IUR), but not in the 1990, 1994, or 2002 IURs. IUR data for 2006 will be available later this year.
SUMMARY OF RELEVANT DATA FOR NOMINATION

CHEMICAL IDENTIFICATION

CAS Registry No.: 4246-51-9

CAS Name: 3,3'-(Oxybis(2,1-ethanediyl))bis-1-propanamine (9CI)
1-Propylamine, 3,3'-(oxybis(ethylenedioxy)) bis- (6CI, 7CI, 8CI)

Synonyms: 4,7,10-trioxatridecane-1,13-diamine; TTD; diethylene glycol
diaminopropyl ether; diethylene glycol bis(3-
aminopropyl)ether; EINECS No. 224-207-2 (ChemID, 2005;
ChemSources, 2005; Sigma-Aldrich, 2004)

Structural Class: Etherdiamine

Structure, Molecular Formula, and Molecular Weight:

\[ \text{C}_{10} \text{H}_{24} \text{N}_{2} \text{O}_{3} \quad \text{Mol. wt. 220.3} \]

Chemical and Physical Properties:

Description: Colorless to pale yellow liquid (BASF, 1997)

Melting point: -32 deg C (BASF, 1997)

Boiling point: 147-148 deg C (BASF, 1997)

Solubility: Miscible in water and common organic solvents (BASF,
1997)

Density: 1.0 g/cm\(^3\) at 20 deg C (BASF, 1997)

Flash point: 110 deg C (closed cup) (Sigma-Aldrich, 2004)

Stability: Almost unlimited shelf life in unopened, original containers
when properly stored; must protect from moisture, air, light,
and heat; combustible but not explosive or spontaneously
flammable (BASF, 1997).

Prepared for NCI by Technical Resources International, Inc. to support chemical nomination under contract no. N02-CB-07-7 (10/05; 3/06)
Technical Products and Impurities:

TTD is available at 97% purity from the Aldrich Division and at Ξ98% from the Fluka Division of Sigma-Aldrich (Sigma-Aldrich, 2005). TTD, 95% pure, is available from Acros Organics, a division of Fisher Scientific (Fisher Scientific, 2005). TTD at a minimum of 96% purity is available from TCI (ChemACX, 2005).

EXPOSURE INFORMATION

Production and Producers:

TTD at 98% purity is available for the industrial market from BASF Corporation in tank trucks and 398 lb (net weight) drums (BASF, 1997).

Production/Import Level:

The EPA’s Inventory Update Rule reports non-confidential production ranges of chemicals every four years. The production levels of TTD during the years 1986-2002 are listed in Table 1.

<table>
<thead>
<tr>
<th>Year</th>
<th>Production Range (lbs.)</th>
</tr>
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<tbody>
<tr>
<td>1986</td>
<td>10,000 - 500,000</td>
</tr>
<tr>
<td>1990</td>
<td>10,000 - 500,000</td>
</tr>
<tr>
<td>1994</td>
<td>10,000 - 500,000</td>
</tr>
<tr>
<td>1998</td>
<td>&gt; 500,000,000 - 1,000,000,000</td>
</tr>
<tr>
<td>2002</td>
<td>&gt; 500,000 - 1,000,000</td>
</tr>
</tbody>
</table>

Source: EPA (2005)

TDD is listed as an LPV chemical in the European Union, meaning that annual production
was 10 - 1,000 metric tons and the chemical was produced or imported between 1990 and 1994. The European producer is BASF in Germany (European Chemicals Bureau, 2005).

**Use Pattern:**

TTD is a commercially available low molecular weight polyetherdiamine used in the production of polycondensation products; polyaddition products; copolymers; textile, leather, and paper auxiliaries; emulsifying agents; and corrosion inhibitors. It is also used as a hardener and cross-linking agent for epoxy resins (BASF, 1997; Marrion, 1994).

TTD is suitable for reaction with tert-butyl(meth)acrylate to prepare epoxy resins with extremely long pot lives (Wolf & Schleimer, 1998). For example, the industrial adhesive 3M Scotch-Weld™ Epoxy Adhesive DP-460 ND is a two-part kit. Part A contains TTD at 50-60 percent by weight (3M, 2004).

Examples of various patented applications for TTD include:

- Reaction with unsaturated carbonyl or carboxy compounds used in the preparation of coating compositions resistant to impact and abrasion (Marrion, 1994).
- Amine-containing curing agent for the preparation of thermoplastic or thermoset reaction products suitable for use as golf ball covers (Wu et al., 2005).
- A preferred diamine for the preparation of breathable fluid impermeable barrier layers that find utility in durable goods such as tents, footwear, and rainwear, as well as for absorbent disposable articles such as disposable diapers, feminine napkins, and medical devices and dressings (Kroll & Van Lith, 2002).

A total of 69 patents citing 4,7,10-trioxatridecane-1,13-diamine and 7 patents citing 3,3’-(oxybis(2,1-ethanediyoxy))bis-1-propanamine were on file with the U.S. Patent and Trademark Office since 1976 as of October 2005 (USPTO, 2005).

**Human Exposure:**

The primary source of exposure to TTD would be expected to occur in the workplace, from its production, and to a greater extent, from its various uses.
The material is believed to be extremely destructive to tissues of the mucous membranes, upper respiratory tract, eyes, and skin. TTD is believed to be harmful if swallowed, inhaled, or absorbed through the skin (Sigma-Aldrich, 2004).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 13,486 workers, including 3,955 female workers, were potentially exposed to TTD in the workplace. Aircraft engine mechanics; assemblers, electrical and electronic equipment assemblers; janitors and cleaners; electrical and electronic technicians; aerospace engineers; insulation workers; miscellaneous machine operators; grinding, abrading, buffing, and polishing machine operators; and painting and paint spraying machine operators were the occupations identified as having exposure to this compound (NOES, 2005a). The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein.

**Environmental Occurrence:**

TTD is not a natural product. No information on its presence in the air or industrial effluents from its production or uses was found in the available literature.

**Regulatory Status:**

No standards or guidelines have been set by NIOSH or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of TTD. TTD was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

The proper shipping name under the Department of Transportation is Amines, liquid, corrosive, n.o.s., or Polyamines, liquid, corrosive, n.o.s (Sigma-Aldrich, 2004).
TOXICOLOGICAL INFORMATION

Human Data:
No epidemiological studies or case reports investigating the association of TTD and health effects in humans were identified in the available literature.

Animal Data:

Acute Studies. Based on range-finding toxicity data collected by Smyth and his colleagues, the LD$_{50}$ for oral administration in rats is 4.29 ml/kg and the LD$_{50}$ for dermal administration to rabbit skin is 2.50 ml/kg (Smyth et al., 1969).

A TSCA 8(e) submitted by Union Carbide Corporation in 1992 described TTD as corrosive to rabbit skin using Department of Transportation (DOT) standards. Application of 0.5 ml of the trade product polyglycoldiamine H-221 to rabbit skin resulted in severe erythema and moderate edema on all six animals. Ecchymosis and necrosis were also evident. Scabs developed by three days, and desquamation appeared on most animals after seven days. At 10-21 days, skin irritation slowly subsided but peeling scabs, desquamation, and two instances of scarring remained at 21 days.

The inhalation of TTD can reportedly result in spasm, inflammation and edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema (Sigma-Aldrich MSDS, 2004). The basis for this statement could not be determined.

Subchronic Studies. No information on the repeat-dose toxicity of TTD was found in the available literature.

Chronic Studies. No information on the effects of chronic administration of TTD was found in the available literature.
**Mutagenicity.** No information on the mutagenic or clastogenic activities of TTD were identified in the available literature.

**Metabolism.** The predictive program, METEOR, described metabolism through oxidative deamination and oxidative O-dealkylation to multiple products as plausible pathways (Lhasa Ltd., 2004).

**Other Biological Effects.** No information on any other biological effects was identified for TTD in the available literature.

**Structure-Activity Analysis:**

Two SAR-based computer software programs were used as tools to assess the toxicity of TTD. One program, TOPKAT uses robust, cross-validated models based on experimental data to calculate a probability value from 0.0-1.0 that a chemical will be positive for a certain endpoint. This program also incorporates a validity diagnostic that indicates if the predicted toxicity values may be accepted with confidence. Another SAR-based model, DEREK, uses structure alerts to predict the toxicity of a compound. TOPKAT, using the NTP-based model, predicts TTD will be a carcinogen in male rats and female mice, with probabilities of 0.977 and 0.916, respectively. TOPKAT predicted a probability of Ames mutagenicity of 0.179 (unlikely) with all validation criteria satisfied. DEREK found no structure alerts upon which to make a determination of the toxicity of TTD (Accelerys, 2004; Lhasa Ltd., 2004).
References


