Pentaethylenehexamine

4067-16-7

OVERVIEW

Pentaethylenehexamine came to the attention of the National Cancer Institute (NCI) Division of Cancer Biology following a review of chemicals that do not meet the criteria for inclusion in the United States (U.S.) Environmental Protection Agency (EPA) HPV Challenge Program even though their 1998 production exceeded 1 million pounds. According to industry information, annual production or importation of pentaethylenehexamine in the European Union was 10 - 1,000 metric tons at some time between 1990 and 1994. Higher ethyleneamines are also used in Japan and other Asian markets.

Pentaethylenehexamine has important applications in a number of industries. It is a hardener used with epoxy resins that have both industrial and consumer applications. It is an intermediate in the synthesis of several substances, e.g. chemicals that are mixed with asphalt to pave roads. Pentaethylenehexamine has widespread use in the manufacture of lubricating oil and fuel additives. Although workers would be expected to be the population primarily exposed to pentaethylenehexamine, consumer exposure cannot be ruled out. Because pentaethylene-hexamine may produce long-term effects in aquatic ecosystems, its release in waste streams is also of concern.

Studies sufficient to evaluate the toxicity of pentaethylenehexamine are lacking. This chemical has been described as irritating, sensitizing, and corrosive in short-term tests in animals. However, there is no information on the subchronic or chronic effects of exposure to pentaethylenehexamine in either humans or animals. Although pentathylenehexamine was positive in multiple strains of *Salmonella typhimurium* in the Ames assay in the presence of metabolic activation, this chemical has not been evaluated in any mammalian genotoxicity assays. Structurally-related polyamines similar to pentaethylenehexamine have received limited testing for carcinogenic activity; in dermal studies in mice triethylenetetramine and tetraethylenepentamine did not produce tumors. The toxicity prediction program, DEREK considers that it is plausible that pentaethylenehexamine will be a carcinogen in rodents.

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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 pentaethylenehexamine. This chemical was added to Appendix B in the ITC's 56th Report (70 FR 61520, October 24, 2005) as one of 235 substances that were high production chemicals in the 1998 and 2002 Inventory Update Rules (IURs), but not in the 1990 or 1994 IURs. The ITC discussed a data-availability study of these 235 chemicals in its 56th Report and posted the results on its web site, http://www.epa.gov/opptintr/itc. 2',2'''-Dithiobisbenzanilide is also in the American Chemistry Council (ACC), Soap and Detergent Association (SDA), and Synthetic Organic Chemical Manufacturers Association (SOCMA) Extended HPV (EHPV) Program. The goal of the EHPV Program is to collect and publish health and environmental information on chemicals that did not qualify as HPV chemicals under the EPA's HPV Challenge program but have since reached the 1 million pound per year threshold. As a result of these activities, there are ongoing efforts to obtain and make available health effects and environmental data for this compound.

DATA GAPS IDENTIFIED BY NCI

The following studies would be needed to fully characterize the toxicity of pentaethylene-hexamine:

- Complete toxicological characterization, including histopathology, in a subchronic study, followed by a 2-year carcinogenesis bioassay, if needed.
- Evaluation of the genotoxicity of pentaethylenehexamine using mammalian-based assays.
- Developmental toxicity study.
- Due to its classification as an environmental hazard to aquatic systems, an assessment on this chemical's release into the environment should be conducted.

NOMINATION OF 2-NOMINATION OF PENTAETHYLENEHEXAMINE TO THE NTP

Based on a review of the available literature and the recommendations of the Chemical Selection Working Group (CSWG) on December 15, 2005, NCI nominates pentaethylenehexamine for testing by the National Toxicology Program (NTP) and forwards the following information:

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- The attached Summary of Data for Chemical Selection.
- Copies of references cited in the Summary of Data for Chemical Selection and Dr. Walker's post-meeting comments.
- CSWG recommendations to conduct short-term *in vitro* tests of pentaethylenehexamine to determine whether the corrosive nature of this compound would prevent humane testing in animal studies. Should testing be feasible, concerns expressed in the data gaps should be addressed, if possible.

The CSWG assigned the testing of pentaethylenehexamine moderate priority.

Comments: Because the pentaethylenehexamine in commercial use is a technical grade mixture, the group had concerns about the identification of a suitable material for testing. The CSWG members also noted that the chelating properties of this chemical might influence its toxicity as a polyamine.

Because of the potential environmental hazards associated with pentaethylenehexamine, these materials are also being forwarded to the ITC for use in the data gathering activities described in their 56th Report.

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SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

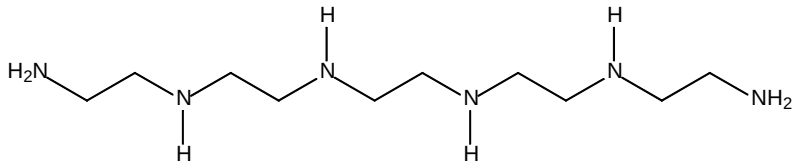
CAS Registry Numbers: 4067-16-7

Chemical Abstracts Service Name: ,6,9,12-Tetraazatetradecane-1,14-diamine (9CI)

Synonyms and Trade Name: Pentaethylenehexamine; EINECS 223-775-9; PEHA; 3,6,9,12-tetraazatetradecamethylenediamine (ChemFinder, 2005; ChemIDplus, 2005)

Structural Class: Polyamine

Structure, Molecular Formula, and Molecular Weight:



$C_{10}H_{28}N_6$ Mol. wt.: 232.37

Chemical and Physical Properties:

Description: Clear, yellow viscous liquid (Fisher Scientific MSDS, 2003)

Boiling Point: 380 °C (Fisher Scientific MSDS, 2003)

Melting Point: -35 °C (Fisher Scientific MSDS, 2003)
-26 °C (Eller & Henkes, 2002)

Flash Point: 175 °C (open cup) (Akzo-Nobel, 2004b)
186 °C (Eller & Henkes, 2002)

Density: 1 g/cm^3 (Sigma-Aldrich MSDS, 2004)
1.002 @ 20 °C/4 °C (Eller & Henkes, 2002)

Vapor Pressure: < 1 mbar at 20 °C (Fisher Scientific MSDS, 2003)

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Solubility:	Miscible with water, ethanol, acetone, ether, toluene, and benzene; slightly sol. in heptane; immiscible with hexane (Akzo Nobel, 2004b; Sridhar & Carter, 2001)
Reactivity:	Absorbs carbon dioxide from the air; hydrates may form with time creating a gel or it may solidify under ambient conditions. Reacts strongly with aldehydes, acids, chlorinated hydrocarbons, and oxidizing agents. Corrodes copper and copper alloys. Hazardous decomposition products include nitrogen oxides and carbon monoxide (Akzo Nobel, 2004b; Fisher Scientific MSDS, 2003; Sridhar & Carter, 2001)
Log Ko/w	-3.67 (calculated) (Merck Safety Data Sheet, 2004)

Technical Products and Impurities:

Technical pentaethylenehexamine (80-90%) is available from the Fluka Division of Sigma-Aldrich. Technical pentaethylenehexamine is available from the Acros Organics Division of Fisher Scientific; this product contains 30.5% nitrogen (Fisher Scientific, 2005; Sigma-Aldrich, 2005).

Technical grade pentaethylenehexamine is also available for commercial use as a distillation cut that contains branched isomers and cyclic compounds with the same number of nitrogen atoms. It is reported that commercial higher polyamine products can contain up to about 40% pentaethylenehexamine (Eller & Henkes, 2002; Sridhar & Carter, 2001).

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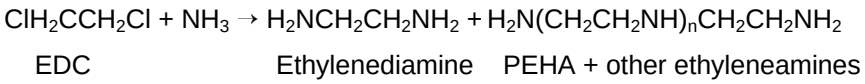
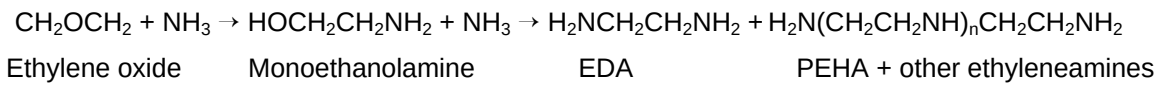
EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process. Pentaethylenehexamine and other ethyleneamines are produced via the ethylene dichloride (EDC) process. At high pressure and moderate temperature, EDC is reacted with an excess of ammonia. The resulting ethyleneamine hydrochloride solution is neutralized with caustic soda generating a mixture of ethyleneamines. Pentaethylene-hexamine is separated from the other ethyleneamines by distillation (Akzo Nobel, 2004a). The EDC process, shown below, accounts for approximately 65% of all ethyleneamine capacity in the United States (Malveda *et al*., 2003).



Another process used to generate ethyleneamines, including pentaethylenehexamine, involves reacting ethylene oxide and ammonia to form monoethanolamine, which is added to ammonia to generate ethylenediamine (EDA) and higher ethyleneamines. The ethyene oxide route, illustrated below, is not widely used (Malveda *et al*., 2003).



Producers and Importers. Chemical Sources International (2005) lists 2 U.S. suppliers of pentaethylenehexamine. ChemACX lists two suppliers selling two products (ChemACX, 2005).

According to recent issues of chemical directories and the Chemical Economics Handbook, pentaethylenehexamine is manufactured or distributed in the U.S. by Ashley Polymers Inc.; Brook-Chem Inc.; Chemsyn Science Labs; EMS-Grivory America; Engelhard Corp.; Hilton Davis Co.; Honeywell, Engineered Applications & Solutions; Huntsman Ethyleneamines Limited; LANXESS; Peer Chemical Corp.; Sigma Aldrich Fine Chemicals; Strem

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Chemicals; TCI America; The Dow Chemical Company; Ticona; and Tomah Products, Inc. (Chemcyclopedia, 2005; DWCP, 2005; Malveda *et al*., 2003; OPD Search, 2005).

Pentaethylenehexamine is available to the industrial market in tankers, bulk containers, and steel drums (Akzo Nobel, 2004b).

Production/Import Levels:

Pentaethylenehexamine is listed in the EPA Toxic Substances Control Act (TSCA) Inventory (ChemIDplus, 2005).

The EPA's Inventory Update Rule reports nonconfidential production ranges of chemicals every four years. The production levels of pentaethylenehexamine during the years 1986-2002 are listed in Table 1.

Table 1. Production Levels of Pentaethylenehexamine

Year	Production Range (lbs.)
1986	10,000 - 500,000
1990	10,000 - 500,000
1994	10,000 - 500,000
1998	> 10,000,000 - 50,000,000
2002	> 1,000,000 - 10,000,000

Source: EPA (2005)

Pentaethylenehexamine is listed as an LPV chemical in the European Union, meaning that 10 to 1,000 metric tons a year were produced or imported into the European Union between 1990 and 1994. European producers of pentaethylenehexamine are Akzo Nobel Surface Chemistry AB, BASF Aktiengesellschaft; Bayer AG, Delamine BV, Dow Benelux NV, and Union Carbide Benelux. This compound is also produced in India, China, and Japan (Chemcyclopedia, 2005; European Chemical Bureau, 2005; Malveda *et al*., 2003).

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Tosoh is the sole producer of ethyleneamines, including pentaethylenehexamine, in Japan. Tosoh also has a joint subsidiary, Delamine BV, established with Akzo Nobel NV in the Netherlands. Japanese production of ethyleneamines in 2002 was 30 thousand metric tons. In 2003, production of higher ethyleneamines in Japan was 16 thousand metric tons, with imports of 5.0 metric tons and exports of 12.0 metric tons (Malveda *et al.*, 2003).

For the 10-month period from June 2004 to March 2005, the Port Import/Export Reporting Service (PIERS) database reported 5 U.S. imports of pentaethylenehexamine with a cargo weight of 260,821 pounds (Dialog Information Services, 2005).

Use Pattern:

Pentaethylenehexamine reportedly has applications in agricultural chemicals, fungicides, bactericides, wood preservatives, chelating agents, surfactants, mineral processing aids, and polymers (Akzo Nobel, 2005; Combined Chemical Dictionary, 2005; Delamine, 2005; Tosoh Corporation, 2005).

Pentaethylenehexamine has applications as an intermediate for the synthesis of the following products:

- Coatings and auxiliaries
- Coolants, lubricants, and antifreezes
- Plastics and auxiliaries
- Auxiliaries for the recovery and processing of oil, coal, and natural gas
- Auxiliaries for the construction industry
- Pharmaceuticals

The reaction of certain ethyleneamines, including pentaethylenehexamine, with fatty acids produces amidoamines and imidazolines used as corrosion inhibitors in petroleum production operations. Amidoamines from fatty acids and ethyleneamines, including pentaethylenehexamine, can also be used for the processing of minerals by the flotation process, and they are also used as anti-stripping agents to promote the adhesion between aggregates and bitumen (Akzo Nobel 2004b, 2005; Delamine, 2005).

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Ethyleneamines are reactive with a variety of other chemicals, making them unique intermediates for a broad range of applications. A major application area for ethylene-amines is the manufacturing of lube oil and fuel additives. The reaction of higher ethyleneamines, such as pentaethylenehexamine, with polyisobutenylsuccinic anhydride yields the corresponding polybutenyl-succinimides which are ashless dispersant-detergent additives for motor oil. Succinimides are expected to dominant the dispersant market. Estimated consumption of higher ethyleneamines in the production of polybutenyl-succinimides, especially tetraethylenepentamine and pentaethylenehexamine, was approximately 40 million pounds in 2002. Demand for ethyleneamines used in synthesizing lubricating oil additives is expected to grow moderately at about 1% annually through 2007 (Delamine, 2005; EPSDG, 2000; Malveda *et al*., 2003).

Ethyleneamines, including pentaethylenehexamine, are widely used as epoxy curing agents, both as a pure amine and in a modified form. The ethyleneamines react with epoxy resins to form cross-linked, infusible structures. Pentaethylenehexamine is listed as an ingredient in do-it yourself floor coatings used as sealants (Delamine, 2005; UcoatIt, 2003).

Pentaethylenehexamine is a cross-linking agent used in complex organic paint primers. These primers are applied to metal surfaces to promote the adhesion of paints to metal surfaces and to retard corrosion at the paint-metal interface (Jones *et al*., 1998).

In 2002, major end uses identified for pentaethylenehexamine in Japan included epoxy curing agents, ion exchange resins, and lubricating oil additives (Malveda *et al*., 2003). Due to the structural similarities and similarity in chemical properties between penta-ethylenehexamine and other ethylenediamines, pentaethylenehexamine may also have applications in fabric softeners, ore flotation agents, emulsifiers, binding agents, and bleach activators (ChemicalLand21.com, 2005).

Ethyleneamine E-100 is a mixture of ethyleneamines, including pentaethylenehexamine. This mixture has many of the same uses as pentaethylenehexamine such as applications in

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asphalt additives, corrosion inhibitors, epoxy curing agents, lube oil and fuel additives, and mineral processing aids (Huntsman Corporation, 2001).

A search for pentaethylenehexamine in the U.S. patent database from 1976 to September 28, 2005 indicated that 1,327 patents cited this compound. The patents that cited this chemical corresponded with the uses described above (US Patent and Trademark Office, 2005).

Human Exposure:

Occupational Exposure. Pentaethylenehexamine was not listed in the National Occupational Exposure Survey (NOES). This survey was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983 so that this information may not reflect present usage.

Handling ethyleneamine products is complicated by their tendency to react with other chemicals, such as carbon dioxide in the air, which results in the formation of solid carbamates. Because of their ability to produce chemical burns, skin rashes, and asthma-like symptoms, ethyleneamines also require substantial care in handling. The greatest potential for worker exposure to pentaethylenehexamine would be expected during the dispensing of this chemical from drums or other containers, from leaks occurring during transfer of bulk materials, and from improper use of personal protective equipment and the lack of adequate engineering controls. Activities that may lead to pentaethylenehexamine exposure are product sampling and cleaning and accidental spills that might occur during shipment. Higher molecular weight ethyleneamines are often handled at elevated temperatures further increasing the possibility of vapor exposure to these compounds (EPSDG, 2000).

Long chain fatty monoamines and diamines are often used in road construction as wetting agents to promote adhesion in bituminous pavements. The commercial fatty amines are crude technical products, contaminated by lower polyamines which can be released during hot paving. Exposure of road pavers to these low molecular weight polyamines was found

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to be in the range of <0.02-0.5 mg/m^3 (Levin *et al.*, 1994). Since pentaethylenehexamine is one of the polyamines used to produce bitumen emulsions, workers in the road paving industry would be expected to have exposure to pentaethylenehexamine. Likewise, individuals working with other paints and coatings containing pentaethylenehexamine would be expected to receive exposure to pentaethylenehexamine.

Consumer Exposure. Consumers may be exposed to pentaethylenehexamine when using do-it-yourself products that contain this chemical. The concentration of pentaethylene-hexamine reported in some epoxy hardeners ranges from 10-100% (Parchem MSDS, 2001; Sika Deutschland GmbH, 2004).

Environmental Exposure. Pentaethylenehexamine may be released into the environment through various wastestreams during the manufacture, transport, use, and disposal of this compound, which may result in human exposure.

Environmental Occurrence:

The aerobic biodegradability of pentaethylenehexamine in the closed bottle test was <60% after 28 days. Pentaethylenehexamine is extremely toxic to aquatic organisms and may cause long-term effects in the aquatic environment. The LC_0 in *Brachydanio rerio* (fresh water fish) was reported to be 100 mg/l at 96 hr in a static system. The EC_{50} in bacteria was >100 mg/l (Akzo Nobel Safety Data Sheet, 2004).

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 pentaethylenehexamine. Pentaethylenehexamine 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.

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Pentaethylenehexamine is not regulated under SARA Section 302 (Extremely Hazardous Substances), SARA Section 313 (Toxic Chemical Release Inventory), or CERCLA Section 103 (Hazardous Substances) (Fisher Scientific MSDS, 2003).

Pentaethylenehexamine is classified as corrosive and dangerous to the environment in the European Union. The proper shipping name is AMINES, LIQUID, CORROSIVE, N.O.S. (Pentaethylenehexamine) (Akzo Nobel Safety Data Sheet, 2004).

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TOXICOLOGICAL INFORMATION

Human Data:

No epidemiological studies or case reports investigating exposure to pentaethylene-hexamine with cancer risk in humans were identified in the available literature.

Pentaethylenehexamine is described as a potential skin sensitizer. It is also described as corrosive:

- A chemical that may cause eye, skin, gastrointestinal tract, and respiratory tract burns.
- Ingestion may cause severe and permanent damage to the digestive tract.
- Inhalation may be fatal as a result of spasm, inflammation, edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema (Fisher Scientific MSDS, 2003).

Animal Data:

Acute Toxicity. The oral LD_{50} for pentaethylenehexamine in rats was reported to be 1,600 mg/kg and 4,130 mg/kg (Akzo Nobel Safety Data Sheet, 2004; RTECS, 1997).

Pentaethylenehexamine is described as moderately irritating to rabbit skin and was corrosive to rabbit eyes (Akzo Nobel Safety Data Sheet, 2004).

Pentaethylenehexamine was sensitizing to the skin of Dunkin Hartley Haz:(DH)fBR albino guinea pigs in the guinea pig maximization test (Leung & Auletta, 1997).

Subchronic Toxicity. No subchronic toxicity studies were found for pentaethylenehexamine.

Chronic Toxicity. No chronic studies or 2-year carcinogenicity studies of pentaethylene-hexamine in animals were identified in the available literature.

Short-Term Tests:

Pentaethylenehexamine was tested for mutagenicity in *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 using the preincubation method at a concentration of 100-

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6,666 ug/plate in distilled water. Pentaethylenehexamine was negative without metabolic activation but produced mutations when incubated with S-9 from the liver of Aroclor 1254-induced rats (Mortelmans *et al*., 1986).

The genotoxicity of pentaethylenehexamine was assessed in *Drosophila melanogaster* using the sex-linked recessive lethal (SLRL) assay. The results of this experiment were described as equivocal using a feeding exposure of 25,000 ppm and negative using an injection exposure of 500 ppm (Foureman *et al*., 1994).

Metabolism:

Although no information was found on the metabolism of pentaethylenehexamine specifically, one possible pathway for pentaethylenehexamine metabolism may involve oxidative deamination by polyamine oxidase. Oxidative deamination of primary amines produces ammonia and an aldehyde, which is usually further oxidized to a carboxylic acid or is reduced to an alcohol (Parkinson, 1996).

In addition to oxidative deamination, the metabolism prediction program, METEOR, suggests that another plausible metabolic pathway is oxidative N-dealkylation of pentaethylenehexamine (LHASA Ltd., 2004).

Other Biological Effects:

Pentaethylenehexamine and other polyamines have been investigated as potential chelating agents in the rat. In one study, eight male Sprague-Dawley rats received an ip injection of 1 ml of 0.9% saline solution and urine was collected for the next 24 hours. One day later, rats were given an ip injection of 1 mmol/kg pentaethylenehexamine hexahydrochloride (PENTAEN) in 0.9% saline and urine was collected for 24 hours. Analysis of the basal copper excretion versus the chelator-induced copper excretion showed that PENTAEN caused approximately a 7.8-fold increase in the daily urinary copper excretion in the rat. In a related study, PENTAEN increased the urinary excretion of cadmium in rats that had been loaded with cadmium at least 4 days prior to PENTAEN treatment (Jones *et al.*, 1995; Jones *et al*., 1996).

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It has been suggested that the chelating properties of the polyamines, tetraethylene-pentamine and triethylenetetramine, may be associated with their mutagenic activity because these compounds inhibit hepatic copper superoxide dismutase which prevents oxidative damage (Ishiyama *et al*., 1991, cited in OECD SIDS, 2001). Whether this mechanism applies to pentaethylenehexamine is yet to be determined.

Structure-Activity Relationships:

Compounds selected for structure-activity analysis for pentaethylenehexamine toxicity were polyamines with similar chain lengths and a potential metabolite of pentaethylenehexamine, 14-amino-3,6,9,12-tetraazatetradecan-1-ol. The polyamines, triethylenetetramine and tetraethylenepentamine, were tested in a dermal carcinogenicity study in mice and did not increase the incidence of skin tumors. These chemicals were also tested in a number of genotoxicity assays with mixed results. In general, the low-molecular weight polyamines have been positive in the Ames assay, increase sister chromatid exchange in Chinese hamster ovary (CHO) cells, and are positive for unscheduled DNA synthesis although they are negative in the mouse micronucleus assay. It is believed that the positive results are based on its ability to chelate copper (OECD SIDS, 2001).

Toxicity information on chemicals structurally related to pentaethylenehexamine is presented in Table 2.

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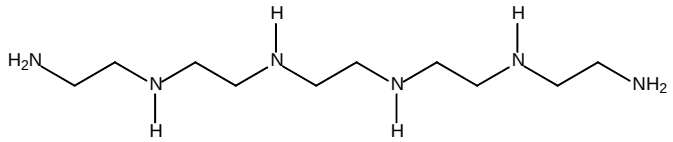
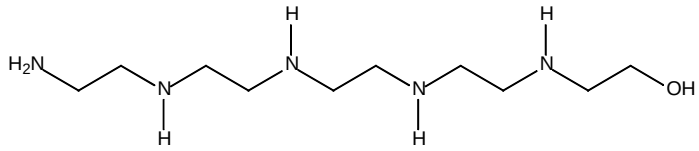
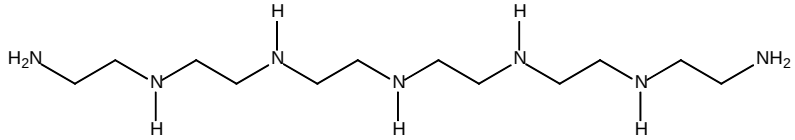
Table 2. Toxicological Information on Chemicals Structurally Related to Pentaethylenehexamine

Carcinogenicity Information	Genotoxicity Information
Pentaethylenehexamine [CAS No. 4067-16-7] 	
No data found	Negative in *S. typhimurium* TA98, TA100, TA1535 & TA1537 without S-9 (Mortelmans *et al*., 1986) Positive in *S. typhimurium* TA98, TA100, TA1535 & TA1537 with S-9 (Mortelmans *et al*., 1986) Equivocal results in the *Drosophila* SLRL test (Foureman *et al*., 1994)
14-Amino-3,6,9,12-tetraazatetradecan-1-ol [CAS No. 3403-79-0] 	
No data found	No data found
3,6,9,12,15-Pentaazaheptadecane-1,17-diamine [CAS No. 4403-32-1] 	
No data found	No data found

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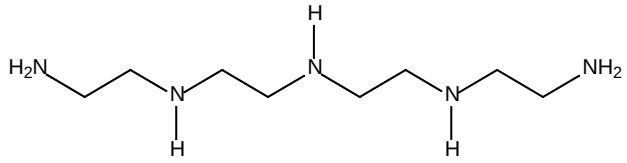
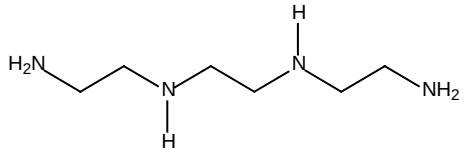
Tetraethylenepentamine [CAS No. 112-57-2]



Not carcinogenic in a dermal study in male C3HeJ mice administered 6.25 mg 3x/wk for their life span (DePass *et al*., 1987)	Positive in *S. typhimurium* TA1535 and TA100 with and without S-9; (-) in *S. typhimurium* TA1535, TA1537 & TA1538 w/wo S-9 (Mortelmans *et al*., 1986) Negative in an *in vivo* micronuclues assay in mice (Leung, 1994) Negative in the CHO gene mutation assay (Leung, 1994) Produced sister chromatid exchanges in CHO cells (Leung, 1994) Produced unscheduled DNA synthesis in rat hepatocytes (Leung, 1994) Equivocal results reported in the *Drosophila* SLRL test (Mason *et al*., 1992)

Triethylenetetramine [CAS No. 112-24-3]



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Not carcinogenic in a dermal study in male C3H/HeJ mice administered 1.25 mg 3x/wk for their life span (DePass *et al*., 1987) Not carcinogenic in a dermal study in male C3H/HeJ mice administered 0, 0.2, or 2.0% in ethanol 3x/wk for 2 years (Young *et al*., 1986, cited in IUCLID Data Set, 1998)	Positive in *S. typhimurium* TA98, TA100, TA1535 & TA1537 with and without S-9; positive in *S. typhimurium* TA1538 without S-9 but negative w/ S-9 (Mortelmans *et al*., 1986) Mutations in *E. coli* without S-9 (Warren *et al*., 1981, cited in IUCLID Data Set, 1998) Negative for micronuclei in an *in vivo* assay in mice (Leung, 1994) Negative in the CHO gene mutation assay (Leung, 1994) Produced sister chromatid exchanges in CHO cells (Leung, 1994) Produced unscheduled DNA synthesis in rat hepatocytes (Leung, 1994) Equivocal in the *Drosophila* SLRL test (Foureman *et al*., 1994)

Two SAR-based computer software programs were used as tools to assess the toxicity of pentaethylenehexamine. One program, named 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. The toxicity predictions made for pentaethylenehexamine by TOPKAT and DEREK are shown in Table 3.

Table 3. Toxicity Predictions for Pentaethylenehexamine Using SAR-based Programs

Prepared for NCI to support chemical nomination by Technical Resources International, Inc. under contract no. N02-CB-07007 (10/05; 3/06)

Toxicity Endpoint	Toxicity Prediction
TOPKAT	
Carcinogenicity (male rat, NTP model)	0.099 – Unlikely
Carcinogenicity (female rat, NTP model)	0.000 – Unlikely
Carcinogenicity (male mouse, NTP model)	0.000 – Unlikely
Carcinogenicity (female mouse, NTP model)	0.083 – Unlikely
Carcinogenicity (male rat, FDA model)	Prediction outside of confidence level
Carcinogenicity (female rat, FDA model)	Prediction outside of confidence level
Carcinogenicity (male mouse, FDA model)	0.993 – Probable
Carcinogenicity (female mouse, FDA model)	Prediction outside of confidence level
Weight of Evidence Carcinogenicity Call	Prediction outside of confidence level
Mutagenicity in the Ames assay	Prediction outside of confidence level
Developmental Toxicity	1.000 – Probable
Skin Irritation	0.958 – Probable
Skin Sensitization	0.985 – Probable
DEREK	
Carcinogenicity	Plausible for mammalian carcinogenicity
Respiratory Sensitization	Plausible as respiratory sensitizer
Skin Sensitization	Plausible as mammalian skin sensitizer

Source: Accelrys, Inc., 2004; LHASA Ltd., 2004

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