FOREWORD INTRODUCTION

TETRAETHYLENEPENTAMINE

CAS N°: 112-57-2

SIDS Initial Assessment Report For 13th SIAM

(Bern, Switzerland November 6-9, 2001)

Chemical Name: Tetraethylenepentamine

CAS No.: 112-57-2

Sponsor Country: USA

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History:

Tetraethylenepentamine was volunteered for the U.S. HPV program and subsequently the ICCA program by the Ethyleneamines Product Stewardship Discussion Group in the U.S. Use of data from the analog triethylenetetramine is proposed to reduce testing needs. The panel/consortia (Dow, UCC and Azko-Nobel) searched company files and publicly available databases to obtain data on TEPA. The "Environmental Risk Assessment of Complexing Agents" submitted by Germany was also included in this evaluation.

Testing: No testing (x)
Testing ( )

Comments:

Deadline for Circulation: September 14, 2001

Date of Circulation:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-57-2
Chemical Name	3,6,9-triazaundecamethylenediamine; tetraethylenepentamine (TEPA)
Structural Formula	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Use of Analog TETA to supplement TEPA data

Tetraethylenepentamine (TEPA) is similar toxicologically to triethylenetetramine (TETA) based on its structure and chelation properties. Therefore, data obtained using TETA have been used to address the endpoints for reproductive and developmental toxicity.

Human Health

Tetraethylenepentamine (TEPA) has a low acute toxicity when administered orally to rats (LD_{50} = 3250 mg/kg). In an acute inhalation toxicity study with saturated vapor and whole body exposure, the LC50 was calculated to be >9.9 ppm (highest dose tested). TEPA is corrosive to the skin and eyes of rabbits. TEPA is a skin sensitizer in the guinea pig. Dermal acute toxicity LD_{50} values in the rabbit range from 660 - 1260 mg/kg. The higher toxicity via the dermal route is most likely due to the corrosive nature of TEPA to the skin whereas TEPA would be neutralized by stomach acid.

The results of a 28-day repeated dose dermal toxicity study of TEPA indicated a systemic toxicity NOEL of 200 mg/kg/day and a dermal toxicity NOEL (local) of 50 mg/kg/day. The dermal LOAEL was 100 mg/kg/day. In addition, in a repeat dose study of TETA administered in drinking water to male and female rats for 90-92 days, the NOEL was 276 mg/kg/day in males and 352 mg/kg/day in females, the highest dose administered with the NIH-31 diet (several diets were used to study the effects of copper deficiency versus toxicity directly to TEPA). In this same study in mice the NOEL was 487 mg/kg/day in males and 551 mg/kg/day in females, the highest dose administered. A lifetime study was conducted via dermal administration in fifty male mice with a solution of 35% TEPA. There were 20 cases of hyperkeratosis, 13 cases of epidermal necrosis and no evidence of dermal hyperplasia.

There were no data available for TEPA for reproductive and developmental toxicity. As a result, data on TETA was used to address these endpoints. TETA data showed no effects on reproductive organs in rats up to 276 mg/kg/day (males) and 352 mg/kg/day (females) and in mice (up to 500 mg/kg/day) when administered in drinking water. TETA was not considered a developmental toxicant via dermal administration in rabbits at maternally toxic doses up to 125 mg/kg/day but showed developmental toxicity in rats at maternally toxic doses of 830 or 1660 mg/kg/day via drinking water. The maternal and fetal toxicity was most likely due to copper

deficiency and zinc toxicity at these levels. Subsequent studies where the diet was supplemented with copper resulted in a decrease of fetal abnormalities. There were no standard fertility studies available. However, there were no effects on the gonads observed in a 90-day drinking water study in rats and mice as described above.

In the Ames Salmonella assay, TEPA was found to be positive both with and without metabolic activation. TEPA was found to increase sister chromatid exchange in CHO cells and was considered positive in a UDS assay using rat hepatocytes. TEPA was not considered genotoxic in the mouse micronucleus assay and had equivocal results in the two dominant lethal assays in Drosophila melanogaster. Again, it is believed that the positive results are based upon TEPA's ability to chelate copper.

Environment

TEPA has the following physical chemical properties: melting point, -30 to −46 °C; boiling point, 320 °C, vapor pressure 1.07 x 10^{-6} hPa at 25 °C; partition coefficient −3.16 at pH 7; and it is completely miscible in water at 20 °C. The lowest acute EC/LC_{50} values of TEPA in fish (96-hr), invertebrates (48-hr) and algae (72-hr) are 310 mg/L, 14.6 mg/L and 2.1 mg/L, respectively. TEPA is not biodegradable (<10% after 28 days) and it should be noted that complexes of TEPA are expected to biodegrade even slower. However, TEPA is not expected to bioconcentrate due to its estimated low log K_{ow} of −3.16 and high water solubility. It should be noted that TEPA is protonated at environmental pH and the log K_{ow} is not a good indicator of the chemical's sorption behavior.

Exposure

TEPA, a synthetic, water soluble amine, is used primarily as a cbsed system intermediate in the synthesis of other products which are involved in the manufacturing of lubricating oil additives, fuel additives, paints and asphalt adhesives. As of 1998, US production of TETA, TEPA and higher molecular weight materials was 140 million pounds (63,636 tonnes). The source of release to the environment is primarily manufacturing sites. In the US, releases to the environment are anticipated to be small and limited to activities such as product transfer and maintenance operations. These activities could lead to TEPA being potentially released to surface water, air and soil. Based on well-controlled use and release from manufacturing sites, there is a low potential for exposure. In the US, there is no evidence to indicate that TEPA maybe present in consumer products. However, some other OECD member countries (Sweden, France and Denmark) records indicate that there is the possibility of TEPA being present in their consumer products. As a result, it is recommended that each OECD member country evaluate their own exposure scenarios to determine the chemical's priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

FULL SIDS SUMMARY: Tetraethylenepentamine

CAS NO: 112-57-2		SPECIES	PROTO COL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			-30 °C to 46 °C
2.2	Boiling Point			320 °C
2.3	Density			0.993 g/cm3
2.4	Vapour Pressure			$1.07x10^{-6}$ hPa at 20°C
2.5	Partition Coefficient (Log Pow)		Calculated	-3.16
2.6 A.	Water Solubility			100% at 20°C
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Calculated	Atmospheric half-life:1.2 hours
3.1.2	Stability in Water			No data
3.3	Transport and Distribution		Calculated (fugacity model level 3 – equal distribution to air, water, soil)	Air : <0.1% Water : 45% Soil : 55%
3.5	Biodegradation		Closed Bottle Test	not biodegradable
ECOTOXICOLOGY				
4.1	Acute Toxicity to Fish	*Poecilia reticulata*	OECD 203	96 h LC50 = 420 mg/l
		Pimephalas promelas		96 h LC50 = 310 - >1000 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia)*	*Daphnia magna*	OECD 202	48 h EC50 = 14.6-24.1 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	Green algae	OECD 201	72 h EC50 = 2.1-6.8 mg/l
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat		LD50 – 3250 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	8 hour exposure	LC50 - greater than 9.9 ppm (highest concentration tested)
5.1.3	Acute Dermal Toxicity	Rabbit		LD50 – 660-1260 mg/kg
5.2.1	Skin Irritation	Rabbit	4 hour exposure	Corrosive
		Rabbit	4 hour exposure (10% solution)	Not Irritating
5.2.2	Eye Irritation	Rabbit	Single exposure	Moderately Irritating
		Rabbit	Repeated Exposure	Corrosive

5.2.3	Skin Sensitization	Guinea Pig	Maximization Study	Sensitizing (50% challenge concentration)
5.4	RepeatedDose Toxicity	Rabbit	OECD 410 (dermal)	NOEL: skin – 50 mg/kg/day NOEL: systemic – 200 mg/kg/day (highest dose tested)
				Triethylenetetramine
		Rat	OECD 408 (diet)	NOEL – 276 mg/kg/day (males)
		Mouse	OECD 408 (diet)	NOEL – 487 mg/kg/day (males)
5.5	Genetic Toxicity *In Vitro*			
A.	Bacterial Test (Gene mutation)	*Salmonella typhimurium*	Strains TA98, TA100, TA1535, TA1537, TA 1538	Positive with and without metabolic activation
B.	Non-Bacterial *In Vitro* Test (Gene mutation)	Chinese Hamster Ovary Cells		Negative
C.	Non-Bacterial *In Vitro* Test (Sister Chromatid Exchange)	Chinese Hamster Ovary Cells		Positive
D.	Non-Bacterial *In Vitro* Test (Unscheduled DNA Synthesis)	Rat Hepatocytes		Positive
5.6	Genetic Toxicity *In Vivo*			
A.	Dominant Lethal Assay	Drosophila		Equivocal
B.	Micronucleus Assay	Mouse		Negative
5.8	Toxicity to Reproduction			No Data
				Triethylenetetramine
		Rat	OECD 408 (diet)	NOEL – 276 mg/kg/day (males)
		Mouse	OECD 408 (diet)	NOEL – 487 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			No Data
				Triethylenetetramine
		Rabbit	OECD 414 (dermal)	NOAEL – teratogenicity – 125 mg/kg/day (highest dose tested)
		Rat	OECD 414 (diet)	NOAEL – teratogenicity 830 mg/kg/day
5.10	Carcinogenicity	Mouse	Dermal – 3 d/w for lifetime 25% solution	Negative
HUMAN EXPOSURE				
6.1	Workers			No Data
6.2	Consumers			No Data
6.3	Indirect via the environment			No Data

SIDS Initial Assessment Report

1. IDENTITY

1.1 Chemical Identity

IUPAC name: 3,6,9-triazaundecamethylenediamine

CAS number: 112-57-2

Molecular formula: $C_8H_{23}N_5$

Molecular weight: 189

Structural formula: $NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$

Synonyms:

1,11-Diamino-3,6,9-triazaundecane;
1,2-Ethanediamine, N-(2aminoethyl)-N'-[2-[(2-aminoethyl)amino]ethyl]-;
1,4,7, 10,13-Pentaazatridecane;
3,6,9-Triazaundecane-1,11-diamine

1.2 Composition

Purity: >95%

1.3 Physical-Chemical Properties

ITEMS	RESULTS
Melting Point	-30 to -46°C
Boiling Point	320°C
Vapor Pressure	1.07 x 10^{-6} hPa at 25°C (8 x 10^{-7} mmHg at 25C)
Partition Coefficient (log Kow)	-3.16 (estimated and varies according to pH)
Soil stability (Log Koc) Water solubility	1098 (estimated) Completely miscible at 20°C
Density	0.993 g/cm^3 at 20 °C
Auto flammability	-321 °C at 1013 hPa
Flash point	150 – 160 °C (closed cup) 168.3 °C (open cup)

1.4 Use of Triethylenetetramine as an Analog

Tetraethylenepentamine (TEPA) is similar in structure to triethylenetetramine (TETA) containing an extra ethylamine. In addition to their structural similarity, TEPA and TETA have almost equally potent chelating properties and the same order of selectivity for various metals.

The strongest affinity for TEPA and TETA is for copper. Below is a table that summarizes the stability constants of TEPA and TETA.

Stability Constants for TETA and TEPA

	TETA	TEPA
Copper	20.4	23.1
Zinc	12.1	15.3
Cobalt	11.1	13.5
Iron ++	7.8	9.96
Manganese	4.9	6.6

Source: Smith, R.M. and Martell, A.E. (1975). Critical Stability Constants Vol. 2. Plenum Press.

2. GENERAL INFORMATION ON EXPOSURE

TEPA does not occur naturally. TEPA is produced only from the ethylene dichloride (EDC) process, which is a reaction of EDC and ammonia. The products of this reaction, ethylenediamine, diethylenetriamine, TETA, TEPA and highers are separated by distillation with the lighter components distilled first (Greiner et al., 1999). TEPA may also contain minor portions of the next higher- and lower-boiling ethyleneamines as a consequence of their relatively close vaporization properties.

Since many of the higher molecular weight products are used in the same applications, uses and production volumes for the higher molecular weight ethyleneamines, starting with DETA have been combined (Table 1) (Greiner et al., 1999). These materials are typically used as intermediates or scavengers in industrial situations. As of 1998, US production of DETA, TETA, TEPA and higher molecular weight materials was ~110 thousand tons. Of this, the major use in the US was in the production of polybutenylsuccinimides which used 43 thousand tons. These are ashless dispersant-detergent additives used in motor oil and are formed by reacting TEPA with polyisobutenylsuccinic anhydride. In Western Europe, the primary uses of TEPA include lube oil additives and surfactants. The other major uses, as defined in Table1, are for other ethyleneamines in this family.

Table 1: Consumption of Higher Ethyleneamines[a]

	1998 US Use	1998 Western Europe Use	1998 Japan Use
Lube oil additives	43[b]	11[c]	
Paper wet-strength resins	15.5	.6	4.0[c]
Epoxy curing agents	12.5	.9	2
Surfactants	7.5	.4	2
Oil field chemicals	6.5		
Reactive polyamide resins	3.3		
Chelating agents	3.5	5	0.2
Fabric Softeners		4	
Corrosion inhibitors		3	
Biocides and pesticides			0.2
Other	5	12.7	0.4
Total	97	48.8	8.3

[a] Greiner et al., 1999. Higher ethyleneamines includes diethylenetetramine, pentaethylenehexamine and highers and possibly cyclic amines, such as piperazine.
[b] Thousands of tons. Does not include cyclic amines.
[c] Thousands of tons including cyclic amines.

TEPA is a highly reactive molecule and will react with acids, oxides and other materials to make products sold into consumer and industrial applications. In the production of these materials, TEPA is the initial reactant and may undergo one, two or three subsequent reactions prior to the manufacture of the final product. Thus the concentration of TEPA in the final product is quite low. Exposure to high concentrations or pure TEPA is only expected to occur in manufacturing sites or during epoxy curing applications in industrial settings. Personal protective equipment is recommended whenever possibility of exposure may occur. The source of release to the environment is primarily manufacturing sites, which may occur during upset conditions. TEPA could potentially be released to surface water, air or soil.
Some OECD member countries (Sweden, France, Switzerland, Finland and Denmark) provided varied information from their respective product registries. In general, the product registries were

unable to provide additional information regarding other components (chemicals) that were present in the consumer products in which TEPA was reported to be present. These other components are believed to be acids, oxides and other materials, which react with TEPA. Reporting indicated that that less than 10% of products that contain TEPA are available for consumer use. Switzerland provided data indicating that TEPA was present in concentrations >10% in three hardner applications. Overall reporting indicated a total of six products containing TEPA in quantities between 1-10% (2 paints, varnishes and coatings; 2 hardners and 2 glue fillers.) One registry indicated that TEPA was present in paints, varnishes and coatings at <1%.

2.1. Environmental Exposure and Fate

2.1.1 Photodegradation

Based on a measured vapor pressure of 8 x 10^{-7}mm Hg, TEPA may exist in both the particulate and vapor phases in the ambient atmosphere (Delamine, 1993). The hydroxy radical atmospheric half-life is estimated to be 24 minutes (EPA 2000). Details of the model can be found in the IUCLID Dossier.

2.1.2 Sability in water

Hydrolysis of TEPA would not be expected under environmental conditions (pH 5 to 9) since the molecule does not contain functional groups susceptible to hydrolysis (Larson et al., 1994, Boethling et al., 2000). This assessment is supported by computerized estimations of hydrolysis rates based on structure activity relationships, which predict no reaction (EPA 2000). Details of the model can be found in the IUCLID Dossier.

2.1.3 Stability in soil

Based on an estimated Koc value of 1098, TEPA is highly mobile in soil and leaching may occur. However, TEPA will exist primarily as a cation under environmental conditions (pH 5–9) and no experimental data are available which suggest whether it will adsorb to soil more strongly than its estimated Koc value indicates. However, for polar or ionizable compounds such as TEPA, chemical sorption to soil/sediment can involve other mechanisms. For example, studies with the lower molecular weight ethyleneamine, EDA, have shown that interaction of protonated amines and negatively charged soil was possible. Volatilization from moist soils is not expected based upon a low Henry's Law constant. In addition, there is no data available to indicate that biodegradation is an important removal process in the terrestrial compartment.

2.1.4 Transport Between Environmental Compartments

The Level III Fugacity Model calculations were determined using four simulations: one with 1000 kg/hour emitted to air only, one with 1000 kg/hour emitted to water only, one with 1000 kg/hour emitted to soil only, and one using the default emissions of equal amount to soil, air and water (1000 kg/hour for each). Using the default emissions of equal amount to soil, air and water (1000 kg/hour for each) the percentages of TEPA in water, air and soil are estimated to be 45, <0.1 and 55%, respectively (EPA 2000).

The fugacity model predictions for partitioning of TEPA into the soil/sediment compartment is a function of the K_{ow} and water solubility, which is reasonable for most non-polar organic species. However, for polar or ionizable compounds such as TEPA, chemical sorption to soil/sediment can involve other mechanisms. For example, studies with the lower molecular weight ethyleneamine,

EDA, have shown that interaction of protonated amines and negatively charged soil was possible. Thus, the fugacity model predictions likely underestimate the adsorption capacity of EDA to soil and sediment.

LEVEL III Distribution of TEPA[a]

	Emissions to Air only - 1000 kg/hour	Emissions to Water only - 1000 kg/hour	Emissions to Soil only - 1000 kg/hour	Emissions to all compartments equally - 1000 kg/hour
	% Distribution	% Distribution	% Distribution	% Distribution
Air	<0.1	<0.1	<0.1	<0.1
Water	28	100	22	45
Soil	72	<0.1	78	55

[a] Data used in model: melting point –30 °C; boiling point 300 °C; Log Kow –3.16

2.1.5 Biodegradation

In a Closed Bottle Test , TEPA did not biodegrade after 28 days (Delamine, 1989a). In the Die-Away Test, TEPA biodegraded less than 10% after 28 days and did not biodegrade at 43 or 49 days (Davis and Goodwin, 1995). Since TEPA can chelate metals, biodegradation of complexes with metals would be expected to be slower than for the substance alone.

2.2 Human exposure

There are no exposure guidelines for TEPA. The higher molecular weight ethyleneamines (greater than pentaethylenehexamine) are used as binding agents in the road paving industry. The highest concentration of TEPA (which is present at low levels in these products) measured during road paving was 0.05 mg/m^3 (Levin et al., 1994). A search of the literature identified no studies on measurements of TEPA at U.S. production sites however, based on engineering design, exposures in the workplace would be expected to be very low. TEPA is approved by the FDA as an indirect food additive in adhesives and coatings (21CFR 175.105).

3. Human Health Hazards

3.1 Effects On Human Health

Studies have shown that TEPA and TETA have relatively the same toxicity for many endpoints. Where there are differences, TEPA appears to produce a less severe response than TETA which may be, in part, due to decreased absorption of TEPA due to its higher molecular weight. Examples include eye irritation, dermal sensitization and mutagenicity studies. The closely related structure and identical mechanism of toxicity of TETA and TEPA, that is, chelation of metals, is believed responsible for their similar toxicity profile. Therefore, data on TETA can be used for endpoints such as reproductive and developmental toxicity for which there are no data for TEPA. Located in Table 3 is a comparison of TEPA and TETA mammalian toxicity data.

Some studies were conducted with the hydrochloride salt of TEPA or TETA. As noted in the SIAR for ethylenediamine (EDA) (CAS#107-15-3), this was done for a number of reasons, which have been previously described for EDA and are applicable here. To briefly summarize, any ethyleneamine will be converted in the stomach to ethyleneamine-hydrochloride salt due to naturally occurring HCl in the stomach.

In the case of the lowest molecular weight ethyleneamine, little difference in toxicity was observed between EDA and EDA-2HCl when one corrects for molecular weight differences via the oral route.

3.1.1 Toxicokinetics And Metabolism

There is no information available on the toxicokinetics or metabolism of TEPA.

3.1.2 Acute Toxicity

Acute toxicity data is reported for rats and rabbits (Table 2). The pH of this material is alkaline, 11.8 at a 2% concentration, and the material can severely irritate the gastrointestinal tract following ingestion or burn the skin following dermal application. The oral LD50 in rats is 3250 mg/kg. The dermal LD50 in two studies was 660 and 1260 mg/kg. The higher toxicity via the dermal route is most likely due to the corrosive nature of TEPA to the skin whereas TEPA would be neutralized by stomach acid.

The acute LC50 for a saturated vapor, whole body exposure was >9.9 ppm at 22C (highest concentration tested) (Union Carbide, 1979). Aerosols are not expected to be relevant to occupational exposure.

Table 2: Acute toxicity of tetraethylenepentamine in experimental animals.

Route	Animals	Values	Type	Reference
Oral	Rat	3250 mg/kg	LD50	Union Carbide (1979)
Inhalation	Rat	>9.9 ppm (highest concentration tested)	LC50	Union Carbide (1979)
Dermal	Rabbit	660 mg/kg	LD50	J. Ind. Hyg. Tox. (1949) in RTECS
	Rabbit	1260 mg/kg	LD50	Union Carbide (1979)

Application to the skin caused necrosis in rabbits following a 4-hour exposure period (Union Carbide, 1982, Lockwood and Taylor, 1982). A 10% solution was non-irritating to rabbits following a 4-hour exposure period (Union Carbide Corp., 1979).

The results of eye irritation studies in rabbits ranged from moderately irritating (single application) to corrosive (multiple application) (Lefaux, 1968; Union Carbide Corp., 1979).

A 50% challenge concentration of TEPA was positive in the guinea pig maximization test (Union Carbide Corp., 1990). There was also evidence of cross-sensitization potential to triethylenetetramine, aminoethylpiperazine and aminoethylethanolamine. There was no evidence of cross-sensitization potential to ethylenediamine, diethylenetriamine and piperazine.

Conclusions:
The oral LD50 in rats for TEPA is 3250 mg/kg. TEPA was corrosive to the skin and eyes (multiple application) of rabbits and sensitizing to guinea pigs.

3.1.3 Repeated Dose Toxicity

Dermal: TEPA was administered to rabbits at doses of 50, 100 or 200 mg/kg/day for 6 hours/day, 5 days/week for 4 weeks. Skin irritation was seen at 100 or 200 mg/kg/day. By day 16, crusting and bleeding was seen in some animals. There were no systemic effects at any dose level. The results indicated a systemic toxicity NOEL of 200 mg/kg/day and a dermal toxicity NOEL (local) of 50 mg/kg/day. The dermal LOAEL was 100 mg/kg/day. (Szabo et al., 1986)

Drinking water: In a study to characterize the toxicity in animals fed diets containing nutritionally adequate levels of copper, to compare these to animals fed a low copper diet and to evaluate the relationship of possible adverse effects on TETA-2HCl on circulating copper levels, TETA was administered in drinking water to mice and rats for 92 days. As part of this study, rats and mice were fed a cereal-based (NIH-31) or a purified (AIN-76A) diet. As part of the low copper diet, an additional control group received a Cu-deficient AIN-76A diet. In rats fed the NIH-31 diet, a decrease in plasma ceruloplasmin levels was observed in males administered 276 mg/kg/day and a slight decrease in serum copper levels in females administered 352 mg/kg/day. The authors considered the decreased ceruloplasmin levels not biologically important. The decrease in serum copper levels was not statistically significant. Thus, these effects are considered of minimal concern. The NOAEL in rats was 276 mg/kg/day in males and 352 mg/kg/day in females. The NOEL in mice was 487 mg/kg/day for males and 551 mg/kg/day for females, the highest dose tested (Greenman et al. 1996).

Conclusions: In a 4 week repeated dose study in rabbits, the NOEL for systemic effects was 200 mg/kg/day (highest dose tested). Skin irritation was seen at doses of 100 and 200 mg/kg/day. In the case of TETA in the diet, the NOAEL was $\geq$276 mg/kg/day in rats and the NOEL was $\geq$487 mg/kg/day in mice.

3.1.4 Genotoxicity

In several Ames tests, the data showed that TEPA was positive in the presence and absence of metabolic activation. Although there were differences in strains of Salmonella in the various assays, which TEPA was positive, and whether or not metabolic activation was present, the weight of evidence suggests that TEPA tested positive in this assay (Union Carbide, 1979, 1987a; Leung, 1994; Mortelmans, 1986).

TEPA was tested in vitro in Chinese hamster ovary cells for induction of forward mutations and sister chromatid exchange in the presence and absence of metabolic activation. TEPA did not induce forward mutations but did cause an increase in sister chromatid exchange (Union Carbide, 1981; Leung, 1994; Union Carbide, 1987b). TEPA was positive in several assays when tested for unscheduled DNA synthesis in rat hepatocytes (Leung, 1994, Union Carbide, 1980).

In an in vivo study, TEPA was not genotoxic in a mouse micronucleus assay at intraperitoneal doses of 200 to 625 mg/kg (Leung, 1994). Equivocal results were seen in a dominant lethal assay in Drosophila melanogaster given a dose of 500 ppm of TEPA (Zimmering et al., 1989) and equivocal results were also reported in a second study (Mason et al., 1992).

The genotoxicity profile for TETA is very similar to that described for TEPA, positive in the Ames test, negative in CHO forward mutation, positive in SCE and negative in mouse micronucleus and fruitfly dominant lethal assay. In the case of TETA in the Ames test, copper sulfate modulated the mutagenicity of TETA when the molar concentration of TETA was equivalent to or lower than the molar concentration of copper sulfate (Lawlor, 2000). Both TETA and TEPA have been shown to inhibit hepatic Cu-SOD (superoxide dismutase) which prevents oxidative damage (Ishiyama et al., 1991). Others have suggested that a reduced expression of copper-dependent antioxidant enzymes may be associated with an increased likelihood of mutations and DNA damage. Specifically, they have shown that the activities of CU/Zn SOD and some other antioxidant enzymes in skin fibroblasts decreased with age, leading to an imbalance of enzymes resulting in an increase in reactive oxygen species 60 years of age (Lu et al., 1999). Hypocupremic cattle have been reported to increase DNA damage (Picco et al., 2001). Thus it would appear that the mutagenicity of TETA and TEPA in the in vitro mutagenicity assays may be due to chelation of copper.

Conclusions: TEPA was positive in the Ames test, caused an increase in sister chromatid exchange in Chinese hamster ovary cells and was positive in unscheduled DNA synthesis assays in rat hepatocytes. TEPA was not mutagenic in Chinese hamster ovary cells.
TEPA was not genotoxic in the in vivo mouse micronucleus assay. Based on the structural similarity and chelating activity of TETA and TEPA, it is probable that the positive results of TEPA in the Ames test, sister chromatid exchange and unscheduled DNA synthesis assay is due to chelation of necessary metals.

3.1.5 Carcinogenicity

TEPA (25 ul of a 25% solution in water) was applied to the skin of fifty male mice three times per week for a lifetime. There were 20 cases of hyperkeratosis and 13 cases of epidermal necrosis but no evidence of dermal hyperplasia. The mean survival time was 591 days. There were no abnormalities seen during necropsy. The test material used was 35% TEPA, 22% aminoethyldiaminoethylpiperazine and isoaminoethylpiperizinoethylenediamine, 12% aminoethyltriaminoethyamine and other minor components (DePass et al., 1987).

3.1.6 Reproduction/developmental Toxicity

There are no reproduction/developmental toxicity data available on TEPA. TETA, a structurally similar chemical to TEPA, has been tested in reproduction/developmental toxicity studies. TETA had no effects on reproductive organs in rats or mice when administered at concentrations of 120, 600 or 3000 ppm in the drinking water for 92 days water (in mice, corresponds to 22, 107 and 487 (males) or 551 (females) mg/kg and in rats, 10, 55 or 276 mg/kg in males and 14, 70 or 352 mg/kg in females, respectively) (Greenman et al, 1996).

TETA was not teratogenic to rabbits at dermal doses up to 125 mg/kg/day (Tyl, 1998). TETA was teratogenic to rats at concentrations of 0.83 and 1.67% (830 or 1660 mg/kg/day) in the drinking water but maternal and fetal copper deficiencies were also seen at these levels (Cohen et al., 1982; Keen et al., 1982a; Keen et al., 1982b; Keen, et al., 1983). A subsequent study with copper supplementation in the diet significantly decreased the fetal abnormalities (Cohen et al., 1983; Hurley et al., 1982; Keen et al., 1982c; Keen et al., 1983). Based on similar structure, toxicity at other endpoints and chelating activity (Smith and Martell, 1975), TEPA is expected to give the same results in reproduction/teratology studies as TETA. See table 3 for a detailed comparison of the toxicity of TETA and TEPA for other endpoints.
In a mouse teratology study, TETA was administered at 3000, 6000 or 12,000 ppm in the drinking water (approximately 500, 1000 or 2000 mg/kg/day, respectively) (Tanaka et al., 1992 and Tanaka et al., 1993). Maternal toxicity was noted at the highest concentration with decreased maternal body weight and increased number of litters totally resorbed. Fetal toxicity, demonstrated by decreased body weight, was noted at 6000 and 12,000 ppm. In addition, fetal liver and cerebrum copper levels were decreased at all three concentrations. Hemorrhages and delayed ossification were observed in the brain at doses of 3000 ppm and above, microcephaly and hydrocephaly were observed at doses of 6000 ppm and above and exencephaly was clearly observed at the dose of 12,000 ppm. While a No-Observable-Effect-Level was not determined in this study, there appears to be a good correlation between copper levels and brain effects.

Effects have been reported in the brain of mice and rats fed a copper-deficient diet (Carlton and Kelly, 1969 and Prohaska and Smith, 1982). Rats were fed a copper-deficient diet (1 ppm copper in diet) through pregnancy and the offspring were fed on the same diet for 6 weeks (Carlton and Kelly, 1969). Offspring had convulsive seizures with edematous, necrotic areas in the cerebral cortex. In mice, the brain weights of fetuses from copper-deprived dams were decreased 25% from control values and most fetuses from copper-deprived dams did not survive lactation (Prohaska and Smith, 1982).

In *in vitro* studies with rat embryos cultured on copper deficient diets, head malformations were observed (Mieden et al., 1986 and Hawk et al., 1998).
Both authors were able to reduce the incidence of effects by adding additional copper. Thus, it is very likely that copper supplementation would reduce the effects observed in the mouse.

Conclusions: Although there are no data available on the reproductive/developmental effects of TEPA, TEPA is expected to give the same results in reproduction/teratology studies as TETA based on similar structure, toxicity at other endpoints and chelating activity. Doses of TEPA that seriously reduce copper levels in the dam would be expected to produce a teratogenic response in the offspring. Levels that do not reduce the copper levels in the dam should not result in teratogenic response in the offspring.

Table 3: Brief review of Mammalian Tox Data for TETA and TEPA

	TETA	TEPA
Oral LD50	2500-4340 mg/kg	2140-3990 mg/kg
Dermal LD50	550-805 mg/kg	660-1260 mg/kg
Dermal irritation	Burns within 6 minutes	Burns within 20-30 minutes
Eye irritation Dermal Sensitization	Severe corneal injury Positive in Guinea Pigs and humans	Corneal injury Weak in Guinea Pigs
Cross Sensitization	Guinea Pigs and humans have reacted positive to TETA when sensitized to other amines, such as ethylenediamine	Guinea Pigs and humans have reacted positive to TEPA when sensitized to other amines, such

		as ethylenediamine
Subchronic tox	Male rats fed 500, 1230 or 2980 mg/kg and female rats fed 470, 1380 or 2630 mg/kg for 7 days High dose effects – decreased body weight gain, decreased absolute and relative liver weights and increased relative kidney weights. Middle dose, increased relative kidney weights, unknown whether histopathologic exam conducted. Rats and mice received 120, 600 or 3000 ppm TETA in the drinking water (In mice, corresponds to 22, 107 and ~500 mg/kg and in rats, 10, 55 or 276 mg/kg in males and 14, 70 or 352 mg/kg in females, respectively) for 92 days. Animals were fed several diets, including normal, NIH-31, and a copper-deficient diet. A complete histopathologic examination, including reproductive organs, was conducted. No effects were noted in mice fed the NIH-31 diet. Rats had lower plasma ceruloplasmin levels but no other effects were noted in animals fed the NIH-31 diet.	28 day dermal study conducted in rabbits at doses of 0, 50, 100 or 200 mg/kg/day, 6 hrs/day, 5 days/week for 4 weeks. Dermal irritation noted at the application site. No evidence of systemic toxicity was observed at any doses, based on general observations, body weights, clinical laboratory studies, organ weights and gross and histopathologic examination.
Chronic tox	A 2-year dermal application of TETA in mice was conducted at concentrations of 0, 0.2 or 2.0% in ethanol applied 3 times/week. In another skin painting study, TETA was applied three times a week at 1.25 mg/mouse for their lifetime. There was no evidence of carcinogenicity in either study.	In a mouse skin painting study, TEPA was applied three times a week at 6.25 mg/mouse for their lifetime. There was no evidence of carcinogenicity.
Teratology	Pregnant rabbits received 5, 50 or 125 mg/kg/day of TETA dermally on days 6-18 of gestation. Transient irritation was noted at 5 mg/kg/day and severe irritation was noted at 50 or 125 mg/kg/day. Maternal toxicity, exemplified by decreased body weight gain and mortality, was observed in dams receiving 125 mg/kg/day. Serum and urinary copper levels were comparable to control values at all dose levels. There was no developmental toxicity observed at 125 mg/kg/day. Pregnant mice received 3000, 6000 or 12000 ppm to TETA dihydrochloride in the drinking water on days 6-15 of gestation. At levels greater than 3000 ppm, fetal resorptions, reduced fetal and cerebral weight, brain malformations and decreased copper concentration in maternal liver were observed. Sample size was too small to determine whether maternal toxicity occurred. Pregnant rats received 0, 0.17, 0.83 or 1.67% (~170, 830 or 1660 mg/kg/day) in the diet on	No data.

	days 0-21 of gestation. Weight gain was lower at the two highest levels. Hemorrhages and edema were found in the fetuses from the 0.83 and 1.67% dams. In both fetuses and dams, copper levels were reduced. Authors concluded that TETA was teratogenic and caused copper deficiencies and zinc toxicity in rats. Subsequently, a study in pregnant rats receiving 0.83 or 1.67% in the diet combined with 0.05 or 0.5 mg Cu/kg/day was conducted. Decreased fetal abnormalities were observed in the high dose fetuses receiving 0.5 mg Cu/kg/day. This correlated with an increase in maternal or fetal tissue copper levels.	
Reproductive Tox	Rats and mice received 120, 600 or 3000 ppm TETA in the drinking water (In mice, corresponds to 22, 107 and ~500 mg/kg and in rats, 10, 55 or 276 mg/kg in males and 14, 70 or 352 mg/kg in females, respectively) for 92 days. Animals were fed several diets, including normal, NIH-31, and a copper-deficient diet. A complete histopathologic examination, including reproductive organs, was conducted. There was no effect noted in the reproductive organs of rats or mice.	No data.
Mutagenicity		
Ames test	Demonstrated to be positive in several Ames tests. Addition of Copper sulfate to the media in the Ames test resulted in no mutagenic response when the molar concentration of copper sulfate was greater than that of TETA.	Negative Positive Positive Positive
CHO gene mutation	Negative with and without S9	Negative with and without S9
SCE	Positive without S9; Questionable with S9	Positive with and without S9
UDS	Positive; and Negative	Positive
Mouse micronucleus	Negative	Negative
Recessive lethal (fruitfly)	Negative	Equivocal Equivocal

3.1.7 Human Exposure

There are no data currently available on the effects of TEPA on humans.

4. Hazard To The Environment

4.1 Aquatic Effects

4.1.1 Acute Toxicity

A summary of the LC/EC50 values of TEPA in fish, invertebrates and algae is presented in Table 4.

Table 4: Acute Toxicity of TEPA in Aquatic Organisms

Species*	Duration (hr.)	Parameter measured	Results (mg/L)	Reference
Fish				
Poecilia reticulata	96	LC50	420	Delamine (1989b)
Pimephales promelas *Pimephales promelas*	96 96	LC50 LC50	310 >1000	Union Carbide (1989) Alexander and Batchelder (1975)
Pimephales promelas	96	LC50	473	Bartlett (1978)
Salmo gairdneri	96	LC50	>100	Adema (1988)
Invertebrates				
Daphnia magna	24	EC50	179	Adema (1988)
Daphnia magna	48	EC50	24.1	Delamine (1989b)
Daphnia magna	48	LC50	14.6	Bartlett (1978)
Algae				
Selenastrum capricomutum	72	EC50	2.1, 6.8	Delamine (1990)

* *Poecilia reticulta* - guppy
Pimephales promelas – fathead minnow
Salmo gairdneri – rainbow trout
Daphnia magna – water flea
Selanstrum capricornutum – green algae

The lower EC50 values for algae compared to Daphnia and fish, may be due to a nutritional deficiency. Similar effects have been reported for other chelants (Schowanek, 1996). In studies conducted with ethylenediamine succinic acid, which appears to have similar stability constants to metals as TEPA, Schowanek demonstrated that supplementation with increased levels of cobalt, copper and zinc resulted in increased cell growth.
In bacteria respiration inhibition tests, the 2 and 17 hour EC10 values for TEPA were 97 and 186 mg/L. (Delamine ,1989a). The 1-hour EC50 was 1600 mg/L (Delamine, 1989c).

Conclusion: The acute EC50 value in algae, the most sensitive species, is between 1 and 10 mg/L.

4.1.2 Subchronic/chronic Aquatic Toxicity

4.1.3
There are no subchronic/chronic aquatic toxicity data currently available on TEPA.

4.2 Terrestrial Effects
There are no data currently available on the terrestrial effects of TEPA.

4.3 Other Environmental Effects
Based on an estimated log K_{ow} of -3.16, TEPA is not expected to bioconcentrate. (EPA 2000)

5. Conclusions And Recommendations

5.1 Conclusions

5.1.1 Physical/chemical property, production, use and distribution

TEPA, a synthetic, water soluble amine, is used primarily as an intermediate in the synthesis of other products which are involved in the manufacturing of lubricating oil additives, fuel additives, paints and asphalt adhesives. The production volume of TEPA in the U.S. was approximately 140 million pounds. TEPA is approved by the FDA for use as an indirect food additive in adhesives and coatings. TEPA is not readily biodegradable but is not expected to bioconcentrate.

5.1.2 Human Health

The oral LD50 in rats of 3250 mg/kg suggest that TEPA has slight acute toxicity. This chemical is corrosive to skin and repeated exposure might cause permanent eye damage. TEPA was weakly sensitizing to guinea pigs. Repeated dermal exposure to TEPA resulted in skin irritation but no systemic effects in mice or rabbits. TEPA was positive in some *in vitro* assays but not in an *in vivo* micronucleus study. Overall, TEPA is considered a low concern to human health from acute or chronic exposure.

5.1.3 Environment

The acute LC/EC50 values for TEPA in algae, Daphnia magna and fish are 2.1 mg/L, 14.6 mg/L, and 310 mg/L, respectively. Although TEPA is not readily biodegradable, it is not expected to bioconcentrate.

5.2 Recommendations

TEPA is currently of low priority for further work.

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I U C L I D Data Set

Existing Chemical	:	ID: 112-57-2
CAS No.	:	112-57-2
EINECS Name	:	3,6,9-triazaundecamethylenediamine
EINECS No.	:	203-986-2
TSCA Name	:	1,2-Ethanediamine, N-(2-aminoethyl)-N'-[2-[(2-aminoethyl)amino]ethyl]-
Molecular Formula	:	C8H23N5

Producer Related Part

Company	:	The Dow Chemical Company
Creation date	:	08.02.2001

Substance Related Part

Company	:	The Dow Chemical Company
Creation date	:	08.02.2001
Memo	:	
Printing date	:	14.03.2002
Revision date	:	
Date of last Update	:	14.03.2002
Number of Pages	:	282
Chapter (profile)	:	
Reliability (profile)	:	
Flags (profile)	:	???

1.0.1 OECD and Company Information

Type	:	
Name	:	Akzo Nobel Surface Chemistry AB
Partner	:	
Date	:	
Street	:	
Town	:	44485 Stenungsund
Country	:	Sweden
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000		

Type	:	
Name	:	ANCHOR CHEMICAL(UK)LTD
Partner	:	
Date	:	
Street	:	CLAYTON LANE
Town	:	M114SR MANCHESTER
Country	:	United Kingdom
Phone	:	O61-223-2461
Telefax	:	061-223-5488
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000		

Type	:	
Name	:	Bayer AG
Partner	:	
Date	:	
Street	:	
Town	:	51368 Leverkusen
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000		

Type	:	
Name	:	DELAMINE BV
Partner	:	
Date	:	
Street	:	
Town	:	9930 AB Delfzijl
Country	:	Netherlands
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000		

Type	:	cooperating company
Name	:	
Partner	:	
Date	:	
Street	:	
Town	:	
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	

08.02.2001

1.0.2 Location of Production Site

1.0.3 Identity of Recipients

1.1 General Substance Information

Substance type	:	organic
Physical status	:	liquid
Purity	:	> 95 % w/w

27.08.2001

1.1.0 Details on Template

1.1.1 Spectra

1.2 Synonyms

1,11-Diamino-3,6,9-triazaundecane

Source	:	DELAMINE BV Delfzijl Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

01.06.1994

1,2-Ethanediamine, N-(2-aminoethyl)-N'-(2-((-2-aminoethyl)-amino)ethyl)-

Source	:	Bayer AG Leverkusen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

16.02.1998

1,2-Ethanediamine, N-(2-aminoethyl)-N'-[2-[(2-aminoethyl)amino]ethyl]-

Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

01.06.1994

1,4,7,10,13-Pentaazatridecane

Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

01.06.1994

3,6,9-Triaza-1,11-diaminoundecane

08.02.2001

3,6,9-Triazaundecane-1,11-diamine
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
01.06.1994

Pentamin
Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
16.02.1998

TEPA
Source : DELAMINE BV Delfzijl
Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
01.06.1994

TEPA-RG
08.02.2001

Tetraethylenepentamine
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
01.06.1994

Tetraethylennpentamin
Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
16.02.1998

Tetraethylpentylamine
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
01.06.1994

1.3 Impurities

1.4 Additives

1.5 Quantity

1.6.1 Labelling

Labelling : as in Directive 67/548/EEC
Symbols : CNXn
Nota : other RM: H
Specific limits : yes
R-Phrases : (21/22) Harmful in contact with skin and if swallowed
(34) Causes burns
(43) May cause sensitization by skin contact
(51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases : (1/2) Keep locked up and out of reach of children
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice

(36/37/39) Wear suitable protective clothing, gloves and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
06.03.2002

1.6.2 Classification

Classification : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (21/22) Harmful in contact with skin and if swallowed
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Classification : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (34) Causes burns
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Classification : as in Directive 67/548/EEC
Class of danger : dangerous for the environment
R-Phrases : (51) Toxic to aquatic organisms
(53) May cause long-term adverse effects in the aquatic environment
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Classification : as in Directive 67/548/EEC
Class of danger :
R-Phrases : (43) May cause sensitization by skin contact
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

1.7 Use Pattern

1.7.1 Technology Production/Use

1.8 Occupational Exposure Limit Values

Remark : No occupational exposure limits have been established.
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
01.06.1994

1.9 Source of Exposure

Memo : Information was supplied from Denmark, Finland, France, Sweden and France on products listed in their registries.
Remark : Switzerland identified 3 hardeners containing >10% TEPA. This number would appear to be suspect since TEPA is usually reacted with the epoxy to

form pre-polymers so that equal amounts of the hardener and epoxy adhesive can be used.

Result : Each country supplied some information. The number of products listed as containing TEPA varied from 53 (France) to 160 (Denmark).

While only Finland and Switzerland differentiated between consumer and industrial products, only 3 consumer products were listed as containing >10% TEPA.

A relatively small number of products are listed as sold into consumer markets. Finland had 0 and Switzerland listed 10.

The amount sold into Denmark was only 28 tons.

01.02.2002 (1)

1.10.1 Recommendations/Precautionary Measures

1.10.2 Emergency Measures

1.11 Packaging

1.12 Possib. of Rendering Subst. Harmless

1.13 Statements Concerning Waste

1.14.1 Water Pollution

Classified by : other: Bayer AG
Labelled by :
Class of danger : 2 (water polluting)
Source : Bayer AG Leverkusen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

14.08.1997

1.14.2 Major Accident Hazards

1.14.3 Air Pollution

1.15 Additional Remarks

Remark : Tetraethylenepentamine is an indirect food additive for use as a component of adhesives.
FDA 21 CRF 175.105 (4/1/91).
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

02.06.1994

Remark : Wassergefdhrdungsklasse (German water pollution classification): 1 (weak water polluting), Delamine own classification.

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

01.06.1994

Remark : The data in this dossier represent the technical product. Typically, technical product contains >95% tetraethylenepentamine and <3% triethylenetetramine and <4% pentaethylenehexamine.

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

27.08.2001

1.16 Last Literature Search

1.17 Reviews

1.18 Listings e.g. Chemical Inventories

2.1 Melting Point

Value	:	= -30 ° C
Decomposition	:	no at ° C
Sublimation	:	no
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions
27.08.2001		(2)

Value	:	= -46 ° C
Sublimation	:	
Method	:	other: ASTM D-1177
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions
27.08.2001		(3)

2.2 Boiling Point

Value	:	= 320 ° C at 1013 hPa
Decomposition	:	no
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions
27.08.2001		(2)

Value	:	= 320 ° C at 1013 hPa
Decomposition	:	no
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions
27.08.2001		(2)

2.3 Density

Type	:	density
Value	:	= 993 kg/m3 at 20° C
Method	:	
Year	:	

GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
27.08.2001 (4)

Type : relative density
Value : = 6.5 at ° C
Method :
Year :
GLP : no data
Test substance : no data
Remark : air = 1
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
27.08.2001 (2)

Type : density
Value : = .993 g/cm3 at ° C
Method : other: ASTM D-4052
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
27.08.2001 (3)

Type : bulk density
Value : at ° C
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4
Remark : Not applicable.
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
27.08.2001 (4)

2.3.1 Granulometry

2.4 Vapour Pressure

Value : < .01 hPa at 20° C
Decomposition :
Method other (measured): ASTM D-1719
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions
27.08.2001 (3)

Value : < .1 hPa at 20° C
Decomposition :
Method
Year :
GLP : no data
Test substance : no data
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (2) valid with restrictions
27.08.2001 (2)

Value : = .00000107 hPa at 25° C
Decomposition :
Method
Year : 1991
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
19.11.2001 (5)

2.5 Partition Coefficient

Log pow : = -3.16 at ° C
Method other (calculated): EPIWIN
Year : 2000
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions
27.02.2002 (6)

Method
Year : 2000
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : pH Predicted Log Kow
5 -8.30
7 -8.10
9 -4.54
>11 -2.25
Reliability : (2) valid with restrictions
27.02.2002 (7)

Log pow : < 1 at ° C
Method
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : In pH below 9 substance is protonated and therefore more hydrophylic than suggested by this value of log Pow. This would result in an extremely low bioaccumulation potential for this chemical.
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (2) valid with restrictions
27.08.2001 (8)

2.6.1 Water Solubility

Value : at ° C
Qualitative : miscible
Pka : at 25 ° C
PH : ca. 12 at 100 g/l and 20 ° C
Method :
Year :

GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Completely miscible with water. pKa1 = 9.68; pKa2= 9.10; pKa3= 8.08; pKa4= 4.72; pKa5= 2.98 Ref: Perrin D.D: Dissociation Constants of Organic Bases in Aqueous Solution: IUPAC Chemical Data Series no. 4014 (1965).
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions
27.08.2001		(8) (2)

Value	:	= 100 vol% at 20 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions
27.08.2001		(3)

2.6.2 Surface Tension

2.7 Flash Point

Value	:	= 150 ° C
Type	:	closed cup
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Pensky-Martens, closed cup.
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
27.08.2001		(4)

Value	:	= 160 ° C
Type	:	closed cup
Method	:	other: Pensky-Martens Closed Cup ASTM D-93
Year	:	
GLP	:	no
Test substance	:	no data
27.08.2001		(9)

Value	:	= 168.3 ° C
Type	:	open cup
Method	:	other: Cleveland Open Cup ASTM D-92
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
27.08.2001		(3)

2.8 Auto Flammability

Value	:	= 321 ° C at 1013 hPa
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

27.08.2001 (2)

2.9 Flammability

Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Not determined
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

27.08.2001 (10)

2.10 Explosive Properties

Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Not determined.
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

27.08.2001 (10)

2.11 Oxidizing Properties

Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Not applicable.
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

27.08.2001 (10)

2.12 Additional Remarks

3.1.1 Photodegradation

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Method	:	The following parameters were used in the model: melting point -30C, boiling point 300C and Log Kow-3.16.
Result	:	The half-life for atmospheric oxidation is 24.3 minutes.
Reliability	:	(2) valid with restrictions
05.09.2001		(11)
Remark	:	HSDB no.: 5171. ATMOSPHERIC FATE: Based on a measured vapor pressure of 8.0X10-7 mm Hg at 25 deg C(1), tetraethylenepentamine may exist in both the particulate and vapor phases in the ambient atmosphere(3). Vapor phase tetraethylenepentamine is degraded in the ambient atmosphere by reaction with photochemically formed hydroxyl radicals; the half-life for this reaction in air can be estimated to be about 1.2 hrs(2,SRC). Particulate phase tetraethylenepentamine may be susceptible to dry deposition. Also, based on its complete water solubility at 20 deg C(4), removal from air via wet deposition is likely to occur(SRC). [(1)Daubert TE, Danner RP; Physical & Thermodynamic Propertiesof Pure Chemicals Supplement 1 NY: Hemisphere Pub Corp (1991) (2) Atkinson R; Environ Toxicol Chem 7: 435-42 (1988) (3) Eisenreich SJ et al; Environ Sci Technol 15: 30-8 (1981) (4) Union Carbide; 1979-1980 Chemicals and Plastics Physical Properties Union Carbide Corp p. 16 (1979)]
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions
05.09.2001		

3.1.2 Stability in water

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	at degree C
t1/2 pH9	:	at degree C
Result	:	The model did not estimate hydrolysis based on the structure of TEPA.
Reliability	:	(2) valid with restrictions
05.09.2001		(11)
Remark	:	Expected to be stable for a minimum of 6 months in distilled water solution. Expectations based upon years of experience working with the product and general experimental organic amine chemistry. HSDB no.: 5171 AQUATIC FATE: Based on an estimated Henry's Law constant of 3.0X10-20 atm -cu m/mole at 25 deg C(2), tetraethylenepentamine is expected to be essentially nonvolatile from water(1). An estimated Koc of 1098 and BCF of 4.2 suggest that adsorption to sediment and bioconcentration in aquatic organisms may not be important

fate processes for tetraethylenepentamine in water systems(1,4). Based on pKa1, pKa2, pKa3, pKa4, and pKa5 values of 9.68, 9.10, 8.08, 4.72, and 2.98(3), respectively, tetraethylenepentamine will exist primarily as a cation under environmental conditions (pH 5-9). However, no experimental data are available which suggest whether it will adsorb to sediment more strongly than its estimated Koc value indicates. Amines are potentially susceptible to hydrolysis(4). Therefore, tetraethylenepentamine may hydrolyze in aquatic environments, but no rates were located (SRC). Furthermore, no data were located which suggest biodegradation is an important environmental fate process of tetraethylenepentamine in aquatic systems (SRC).

[(1) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington DC: Amer Chem Soc pp. 4-9, 5-10, 7-4, 15-15 to 15-32 (1990)
(2) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991)
(3) Perrin DD; Dissociation Constants of Organic Bases in Aqueous Solution Buttersworth London: IUPAC Chemical Data Series No. 4014 (1965)]
(4) Meylan, W., 1997. SRC - PCKOC for Microsoft Windows, v1.61, Soil organic carbon/water partition coefficient estimating software.

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (2) valid with restrictions
05.09.2001

3.1.3 Stability in soil

Remark : HSDB no.: 5171
TERRESTRIAL FATE: An estimated Koc value of 1098 (1, 4, SRC) for tetraethylenepentamine indicates high mobility in soil (2) and leaching may occur (SRC). However, tetraethylenepentamine will exist primarily as a cation under environmental conditions (pH 5-9) and no experimental data are available which suggest whether it will adsorb to soil more strongly than its estimated Koc value indicates. Volatilization from moist soils is not expected to be rapid based upon a low Henry's Law constant. Amines are potentially susceptible to hydrolysis(1). Therefore, tetraethylenepentamine is expected to hydrolyze in moist soils; however, no rates were located (SRC).
Furthermore, no data were located which suggest biodegradation is an important terrestrial fate process of tetraethylenepentamine(SRC).

[(1) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington DC: Amer Chem Soc pp. 4-9, 5-10, 7-4, 15-15 to 15-32 (1990)
(2) Swann RL et al; Res Rev 85: 17-28 (1983)
(3) Perrin DD; Dissociation Constants of Organic Bases in Aqueous Solution Buttersworth London: IUPAC Chemical Data Series No.4014 (1965)]
(4) Meylan, W., 1997. SRC - PCKOC for Microsoft Windows, v1.61, Soil organic carbon/water partition coefficient estimating software.

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (2) valid with restrictions
29.08.2001

3.2 Monitoring data

Remark : No scientifically determined information currently available.
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

02.06.1994

3.3.1 Transport between environmental compartments

Type : fugacity model level III
Media :
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method :
Year : 2001
Method : EPA and Syracuse Research Corporation 2000 EPIWIN v.3.10 Model was used. The following parameters were used in the model: melting point -30C, boiling point 300C and Log Kow -3.16.

The input values of melting point -30C, boiling point 300C resulted in the following default input values in EPIWIN: Log Kow -3.16, vapor pressure 0.00195 mmHg at 25C, and water solubility 1000000.

Result : Level III Distribution of TEPA

	% Distribution		
	Air	Water	Soil
Air only 1000 kg/hr	<0.1	28	72
Water only 1000 kg/hr	<0.1	100	<0.1
Soil only 1000 kg/hr	<0.1	22	78
Combined 1000 kg/hr	<0.1	45	55

06.03.2002

3.3.2 Distribution

Remark : TEPA is:
(i) Non-volatile
(ii) Highly water soluble
(iii) Expected to be completely protonated at neutral pH.
(iv) Pog Pow is low, therefore significant cobcentrations in Biota would be considered unlikely.

It is expected that main environmental compartment in which AEP is present will be water.
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

02.06.1994

3.4 Mode of degradation in actual use

3.5 Biodegradation

Type	:	aerobic
Inoculum	:	activated sludge, domestic
Concentration	:	2mg/l related to Test substance related to
Contact time	:	
Degradation	:	ca. 0 % after 28 day
Result	:	under test conditions no biodegradation observed
Deg. Product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1982
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Biodegradation of complexes with metals would be expected to be slower than for the substance alone.
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	Delamine, purity 95%.
Reliability	:	(1) valid without restriction
04.12.2001		(12)

Type	:	aerobic
Inoculum	:	other: Bay County, MI municipal wastewater treatment plant
Contact time	:	49 day
Degradation	:	% after
Result	:	
Deg. Product	:	
Method	:	OECD Guide-line 301 A (new version) "Ready Biodegradability: DOC Die Away Test"
Year	:	1995
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Inoculum was present at a final concentration of not greater than 30 mg suspended solids/L. This inoculum was from predominantly domestic sewage. Enough test material was added to provide a final concentration of chemical equivalent to 10-40 mg dissolved organic carbon (DOC)/L. Samples were incubated at 23C. Samples w ere analyzed for DOC and inorganic carbon (TIC) and CO2 caustic traps were analyzed for TIC using a Dohrmann Model 80 Carbon analyzer on days 0, 1, 3, 7, 14, 21, 28, 43 and 49. On days 0 and 28, the blanks, killed control and viable reactions mixtures were analyzed for the distribution of the four individual TEPA isomers by HPLC.
Result	:	Less than 10% degraded after 28 days. No biodegradation of the TEPA mixture was observed in the viable reaction flasks when the testing period was extended to 43 or 49 days. After 28 days, the distribution of TEPA isomers in the viable reaction flasks did not change and was essentially identical to the distribution observed on day 0.
Reliability	:	(1) valid without restriction
27.06.2001		(13)

Type	:	aerobic

Inoculum : other: Dow Michigan Division 437 wastewater treatment plant
Deg. Product :
Method : other: Clifford, D.A. (1968). Automatic measurement of total oxygen demand: "A New Instrumental Method", presented at 23rd Annual Purdue Industrial Waste Conference. Purdue University, Lafayette, Indiana.
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : BOD measured after 5, 10 and 20 days in industrial inoculum. Method of analysis was the Ionics Total Oxygen Demand Analyzer.
Result : Nil after 20 days in the industrial inoculum.

No additional information supplied.

19.11.2001 (14)

Type : aerobic
Inoculum : other: Dow Michigan Division 437 wastewater treatment plant
Contact time : 20 day
Degradation : % after
Result :
Deg. Product :
Method : other: Clifford, D.A. (1968). Automatic measurement of total oxygen demand: "A New Instrumental Method", presented at 23rd Annual Purdue Industrial Waste Conference. Purdue University, Lafayette, Indiana.
Year : 1978
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : BOD measured after 5, 10 and 20 days in industrial inoculum.
Result : It was 0.12 p/p after 5 days in the industrial inoculum and did not change after 10 or 20 days.

08.02.2001 (15)

Type : aerobic
Inoculum : other: Midland, MI wastewater treatment plant
Contact time : 20 day
Degradation : % after
Result :
Deg. Product :
Method : other: Clifford, D.A. (1968). Automatic measurement of total oxygen demand: "A New Instrumental Method", presented at 23rd Annual Purdue Industrial Waste Conference. Purdue University, Lafayette, Indiana.
Year : 1978
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : BOD measured after 5, 10 and 20 days in municipal inoculum.
Result : Nil after 20 days in the municipal inoculum.
08.02.2001 (16)
Kinetic of test substance : 5 day = 4 %

10 day = 7 %
20 day = 12 %
%
%

Deg. Product :
Method :
Year : 1990
GLP : no
Test substance : as prescribed by 1.1 - 1.4
08.02.2001 (17)

3.6 BOD5, COD or BOD5/COD ratio

3.7 Bioaccumulation

Remark : TEPA is:
- highly soluble
- expected to be completely protonated at neutral pH values
- Log Pow is low

Therefore significant Bioaccumulation would be considered unlikely.
Further support to this assessment is given by a recent study with Ethylenediamine, CAS No 107-15-3, a product of similar structure which shows that this has very low accumulation on algae.

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

02.06.1994 (18)

Remark : HSDB no.: 5171
Based on an estimated log Kow of -1.503(2), the BCF for tetraethylenepentamine can be estimated to be 4.2(SRC) using a recommended regression derived equation(1). This BCF value suggests thattetraethylenepentamine would not bioconcentrate in aquatic organisms(SRC).

[(1) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington DC: Amer Chem Soc pp. 5-4, 5-10 (1990)
(2) GEMS; Graphical Exposure Modeling System. PCGEMS. (1987)]

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

02.06.1994

3.8 Additional remarks

Remark : HSDB no.: 5171
Tetraethylenepentamine is probably released to the environment in waste streams from its production and various uses as a solvent, oil additive and chemical intermediate.
If released to soil,tetraethylenepentamine is expected to leach (estimated Koc of 3.6); it will exist primarily as a cation under environmental conditions (pH 5-9) and no experimental data are available which suggest whether the cation will adsorb to soil more strongly than its estimated Koc value indicates. No data were located which suggest biodegradation is an important fate process of tetraethylenepentamine in soil or water. If released to water, tetraethylenepentamine may hydrolyze; however, no experimental data were located. Its complete water solubility suggests that it may be susceptible to long distance transport in aquatic environments.
Volatilization, adsorption to sediment and bioconcentration in aquatic organisms are not expected to be environmentally

important removal processes in aquatic systems. If released to the atmosphere, tetraethylenepentamine is expected to exist in both the vapor and particulate phases. Vapor-phase tetraethylenepentamine is expected to degrade rapidly by reaction with photochemically produced hydroxyl radicals (estimated half-life of 1.2 hrs). Particulate phase tetraethylenepentamine may be susceptible to dry deposition. Also, based on its complete water solubility, removal from air via wet deposition may occur. In occupational settings, exposure of tetraethylenepentamine may occur through eye and skincontact. (SRC)

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

02.06.1994

4.1 Acute/prolonged toxicity to fish

Type	:	other: static-renewal
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC0	:	m > 100
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Test solutions were renewed every day. Twenty fish used at each concentration. Five fish were used/20 liter test solution. Dose levels were 0 and 100 mg/L.
Result	:	All animals survived 96 hour exposure to 100 mg/L (nominal concentration). No adverse effects were observed during the study. Oxygen concentration for the spent solution was comparable between the two concentrations while the pH ranged from 7.6 to 8.0 in control to 8.8-9.5 in 100 mg/L solution
Reliability	:	(1) valid without restriction
27.06.2001		(19)

Type	:	semistatic
Species	:	Poecilia reticulata (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
LC50	:	= 420
Method	:	Directive 84/449/EEC, C.1 "Acute toxicity for fish"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Concentrations tested 100, 180, 320, 560 and 1000 mg/L. Guppies were 2 cm in length. Exposure was semistatic with renewal e very 48 hours. pH ranged 7.0 -7.7 from 0 to 96 hours. Temperature ranged from 21.7 -23.0C. Statistics - LC50 determined by Griffioen (RIZA) based on a model of Kooyman (1981). Reference Kooyman, S.A.L.M. (1981). Parametric analysis of mortality rates in bioassays. Water Research 15:107-119.
Result	:	No mortality at 100 and 180 mg/L through 96 hours.
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	Delamine, purity 97.3%
Reliability	:	(1) valid without restriction
14.03.2002		(20)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	

LC50	:	m = 310
Method	:	
Year	:	1989
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions
27.06.2001		(21)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	m = 473
Method	:	other: in general accordance with OECD guideline #203
Year	:	1978
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Nominal concentrations of 0, 210, 280, 370, 490, 650, 870, 1000, 1150 and 1550 mg/L only
Remark	:	Static study conducted using dechlorinated Lake Huron water. Water temperature was maintained at 12C.
Result	:	LC50 was 473 mg/L (95% confidence limits are 276-812 mg/L) at 96 hours. LC10 was 276 mg/L (166-367 mg/L) and LC90 was 812 mg/L (611-1336 mg/L).
Reliability	:	(2) valid with restrictions
27.06.2001		(15)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	m > 1000
Method	:	other: in general accordance with OECD guideline #203
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Static study conducted using dechlorinated Lake Huron water.
Reliability	:	(2) valid with restrictions
27.06.2001		(14)

4.2 Acute toxicity to aquatic invertebrates

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 24.1
Method	:	Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Daphnia were less than 24 hours old at the beginning of the test.

Concentrations tested - 10, 18, 32, 56, and 100 mg/L.

Statistics - LC50 determined by Griffioen (RIZA) based on a model of Kooyman (1981).

Reference Kooyman, S.A.L.M. (1981). Parametric analysis of mortality rates in bioassays. Water Research 15:107-119.

Result : EC50 - 24.1 mg/L (nominal); no mortality observed at 10 and 18 mg/L.

pH - 7.1-7.3 at the start of the study; 7.7-7.9 at 48 hours. Hardness - 73.1. Temperature - 19.7C-20.8C.

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Test substance : Purity 97.3%.

Reliability : (1) valid without restriction

14.03.2002 (20)

Type : Static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : No
LC50 : m = 14.6
Method : other: In general accordance with OECD Guideline #202
Year : 1978
GLP : No
Test substance : as prescribed by 1.1 - 1.4
Method : Static study conducted using dechlorinated Lake Huron water. Water temperature was maintained at 20C.

Nominal concentrations of 0, 5.6, 10, 18, 32, 56 and 100 mg/L only.

No further information provided.

Result : LC50 was 14.6 mg/L (95% confidence limits are 11.8-17.7 mg/L) at 48 hours.

LC10 was 5.2 mg/L (3.2-7.0 mg/L) and LC90 was 41.0 mg/L (31.3-62.5 mg/L).

Reliability : (2) valid with restrictions

19.11.2001 (15)

Type : Static
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
Analytical monitoring : No
EC0 : m = 32
EC50 : m = 179
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year : 1988
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Method : Twenty animals used at each concentration. Four beakers containing 5 Daphnia were used for each test or control solution. Each beaker contained 100 ml water. Stock solution of 1000 mg/L prepared and diluted to prepare test solutions. Test material was not renewed. Test temperature range was 19+1C. Animals were not fed.

0, 10, 18, 32, 56, 100, 180, 320, 560 and 1000 mg/L

Result : At 56-180 mg/L, swimming behavior of animals exposed to TEPA was irregular, was near the bottom of the vessel and was slower than control animals. At 32, 56, 100, 180, 320, 560 and 1000 mg/L, immobilization included 1,0, 3,7, 19, 20 and 20 animals, respectively. Oxygen concentration was 8.8-9.1 mg/L at the beginning of the study and 7.2-9.2 mg/L after 24 hours. The pH at the beginning of the study ranged from 8.0 in the control to 10.2 in the 1000 mg/L test solution. At the end of the study the pH ranged from 7.8 in the control to 9.5 in the 1000 mg/L test solution.

Reliability : (1) valid without restriction

28.06.2001 (22)

4.3 Toxicity to aquatic plants e.g. algae

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
NOEC	:	= .5
EC50	:	= 2.1
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1990
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Concentrations of 0, 0.5, 1, 2, 4 and 8 mg/L of TEPA in deionized water were tested. There were 3 replicates/concentration. Deionized water had conductivity of less than 5uS/cm and contained less than 0.01 mg/L Cu. The pH was 6.9 at beginning and 7.6 -7.8 after 72 hours. The temperature ranged between 22 and 24C and the illumination was 400 nm-700nm. No further information was supplied.
Test substance	:	Delamine, purity 97.3%.
Reliability	:	(1) valid without restriction
14.03.2002		23)

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
NOEC	:	= .5
EC50	:	= 6.8
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Concentrations of 0, 0.5, 1, 2, 4 and 8 mg/L of TEPA in deionized water were tested. There were 3 replicates/concentration. Deionized water had conductivity of less than 5uS/cm and contained less than 0.01 mg/L Cu. The pH was 6.9 at beginning and 7.6 -7.8 after 72 hours. The temperature ranged between 22 and 24C and the illumination was 400 nm-700nm. No further information was supplied.
Test substance	:	Delamine, purity 97.3%.
Reliability	:	(1) valid without restriction

14.03.2002 (24)

Species	:	Chlorella vulgaris (Algae)
Endpoint	:	
Exposure period	:	
Unit	:	
Analytical monitoring	:	
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1996
GLP	:	no data
Test substance	:	other TS: {S,S}-ethylenediamine disuccinate
Method	:	In a study of [S,S]-ethylenediamine disuccinate (EDDS) present at 1 mg/L, the total cell volume of Chlorella vulgaris was measured after 66 hours. Subsequently various levels of cobalt, copper and zinc, designated 1M, 2M or 3M, were added to the solution with and without EDDS to determine total cell volume after 66 hours.
Remark	:	Although this study was conducted with another chelant, it demonstrates the effect that chelation of metals can result in significant effects.
Result	:	Supplementation of growth medium with additional metals, specifically cobalt, copper and zinc at the 2M concentration, resulted in increased total cell volume.

Growth Inhibition Test Results

OECD	Concentration			EDDS	Total Cell
Medium	Co	Cu	Zn	mg/L	Vol. (106 um/ml)
Std	0.063	0.006	0.022	0	216
Std	0.063	0.006	0.022	1	29
1M	2.1	1.7	1.0	0	243
1M	2.1	1.7	1.0	1	45
2M	6.2	5.1	2.9	0	159
2M	6.2	5.1	2.9	1	223
3M	18.5	15.3	8.8	0	27
3M	18.5	15.3	8.8	1	155

Concentration of Cobalt is 10-7 M, Copper is 10-8 M and Zn is 10-6 M.

Reliability	:	(1) valid without restriction

04.12.2001 (25)

4.4 Toxicity to microorganisms e.g. bacteria

Type	:	aquatic
Species	:	activated sludge of a predominantly domestic sewage
Exposure period	:	1 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 1600
Method	:	Directive 87/302/EEC, part C, p. 118 "Biodegradation: Activated sludge respiration inhibition test"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Test substance	:	Delamine, purity 95%.
27.07.2001		(26)
Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	17 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC10	:	= 186
Method	:	other: ISO/TC 147/SC 5/WG 1
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	Delamine, purity 95%.
02.06.1994		(20)
Type	:	aquatic
Species	:	other bacteria: nitrifying bacteria
Exposure period	:	2 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC10	:	= 97
Method	:	other: Delamine respiration inhibition test
Year	:	
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	Delamine, purity 95%.
02.06.1994		(20)

4.5.1 Chronic toxicity to fish

4.5.2 Chronic toxicity to aquatic invertebrates

4.6.1 Toxicity to soil dwelling organisms

4.6.2 Toxicity to terrestrial plants

4.6.3 Toxicity to other Non-Mamm. terrestrial species

4.7 Biological effects monitoring

4.8 Biotransformation and kinetics

4.9 Additional remarks

5.1.1 Acute oral toxicity

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	
Value	:	= 3250 mg/kg bw
Method	:	
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The undiluted test material was administered via stomach intubation to male Wistar rats aged 3 to 4 weeks. These nonfasted animals were maintained on appropriate Wayne diets and water ad lib except during periods of manipulation or confinement.
Remark	:	In victims, lungs with petechiae; livers and spleens mottled; stomachs, liquid-filled, red; intestines distended, liquid-filled, red or lightly yellow; kidneys dark; bladders, fluid-filled. In survivors, livers mottled.
Reliability	:	(2) valid with restrictions
20.11.2001		(27)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 2100 mg/kg bw
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable
27.07.2001		(28)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 3990 mg/kg bw
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable
27.07.2001		(29) (30)

5.1.2 Acute inhalation toxicity

Type	:	LC50
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	
Exposure time	:	8 hour(s)
Value	:	> 9.9 ppm
Method	:	
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Substantially saturated vapor is prepared by spreading 50 to 100 grams of chemical over 200 cm^2 area on shallow tray placed near the top of a 120-liter plexiglass chamber which is then sealed for at least 16 hours while an intermittently operated fan agitates the internal chamber atmosphere. Rats are then introduced in a gasketed drawer type cage designed and operated to minimize vapor loss. Exposures were whole body. Exposure concentration appears to be based on nominal concentration.
Remark	:	Single inhalation, by rats, of substantially saturated vapor for 8 hours at room temperature resulted in neither mortality nor observed signs of toxicity. Static conditions at 22 ^oC; 8 hrs killed 0 of 6.
Reliability	:	(2) valid with restrictions

19.11.2001 **(27)**

5.1.3 Acute dermal toxicity

Type	:	LD50
Species	:	Rabbit
Strain	:	
Sex	:	Male
Number of animals	:	
Vehicle	:	
Value	:	= 1260 mg/kg bw
Method	:	
Year	:	1979
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Male New Zealand White rabbits, 3 to 5 months of age, are immobilized during the 24-hour contact period with the compound retained under impervious sheeting on the clipped intact skin of the trunk. Thereafter, excess fluid is removed to prevent ingestion. Maximum dosage that can be retained is 16 ml/kg.
Remark	:	In victims , lungs and kidneys reddened. In survivors, nothing remarkable. The dermal LD50 for TEPA is lower than the oral LD50 value. The most likely reason for this is that TEPA administered orally is neutralized in the stomach whereas TEPA applied to the skin is not neutralized.
Reliability	:	(2) valid with restrictions

19.11.2001 (27)

Type	:	LD50
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 660 mg/kg bw
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	The dermal LD50 for TEPA is lower than the oral LD50 value. The most likely reason for this is that TEPA administered orally is neutralized in the stomach whereas TEPA applied to the skin is not neutralized.
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions
19.11.2001		(31) (32)

5.1.4 Acute toxicity, other routes

5.2.1 Skin irritation

Species	:	Rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	4
PDII	:	
Result	:	corrosive
EC classification	:	
Method	:	Draize Test
Year	:	1982
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Male and female New Zealand White rabbits were dosed with 0.5 ml of the undiluted material. The dose was applied to the clipped, intact skin under a gauze patch and was loosely covered with impervious sheeting. The animals were restrained for the 4 hour contact period. Excess sample was removed after contact. Skin reaction was scored, by the method of Draize, at one hour, one day and 2 days after dosing. Any necrosis or other reaction was noted. Only 2 or 4 rabbits were dosed on the skin irritation test for each sample because of the severe reaction produced and because the U.S. Department of Transportation (DOT) interpretation requested by the sponsor could be made from results on 2 to 4 animals.
Remark	:	Two of 2, 2 of 2, and 3 of 4 rabbits had necrosis within 5 hours after the start of the contact period for TEPA, Taft HP TEPA and Dow TEPA respectively. Moderate to severe edema was also observed. At two days, scabs were present on the skin. Therefore, all 3 samples were DOT "corrosives" to the skin.
Test substance	:	Pure TEPA, Union Carbide HP TEPA and Dow TEPA were examined.
Reliability	:	(2) valid with restrictions
19.11.2001		

Species	:	Rabbit
Concentration	:	
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	
PDII	:	
Result	:	corrosive
EC classification	:	
Method	:	other: US CFR Title 49, Section 173.240, Appendix A
Year	:	1982
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Female New Zealand White rabbits received 0.5 ml/rabbit.
Remark	:	Three of six rabbits exhibited irreversible necrosis
Reliability	:	(2) valid with restrictions
28.06.2001		(33)

Species	:	Rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	Highly irritating
EC classification	:	irritating
Method	:	
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	DELAMINE BV Delfzijl EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	Dose: 495 mg, open application
Reliability	:	(2) valid with restrictions
27.07.2001		(31) (34)

Species	:	Rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	4 hour(s)
Number of animals	:	5
PDII	:	
Result	:	moderately irritating
EC classification	:	
Method	:	Draize Test
Year	:	1979
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Chemical is applied in 0.01 ml amounts to clipped, uncovered intact skin of 5 rabbit bellies either undiluted or in progressive dilutions of 10, 1, 0.1, or 0.01% in solvent. One of 10 grades are assigned based on appearance of moderate or marked capillary injection, erythema, edema or necrosis within 24 hours.
Remark	:	Moderate erythema on one rabbit, marked erythema on one, moderate necrosis on 3 from the undiluted material; no irritation on 5 rabbits from a 10% dilution in distilled water. Grade 6. No further information supplied.

Reliability : (2) valid with restrictions
19.11.2001 (27)

Species : Rabbit
Concentration :
Exposure :
Exposure time : 4 hour(s)
Number of animals :
PDII :
Result :
EC classification :
Method : other: US CFR Title 49, Secton 173.240, Appendix A
Year : 1980
GLP : No
Test substance : as prescribed by 1.1 - 1.4
Method : New Zealand White male rabbits received 0.5 ml/rabbit.
Remark : Slight redness and swelling but no irreversible necrosis. Two rabbits had a few small spots of very slight necrosis.
Result : Not corrosive.
Reliability : (2) valid with restrictions
28.06.2001 (35)

Remark : HSDB no.: 5171
Produces intense skin irritation and moderate eye injury in rabbits but not so severe as lower homologues.
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable
27.07.2001 (36)

5.2.2 Eye irritation

Species : Rabbit
Concentration : undiluted
Dose : .01 ml
Exposure Time : 24 hour(s)
Comment : not rinsed
Number of animals : 5
Result : moderately irritating
EC classification :
Method : Draize Test
Year : 1979
GLP : No
Test substance : as prescribed by 1.1 - 1.4
Method : Eyes not staining with 5%fluorescein in 20 seconds contact are accepted. Single instillation of 0.005, 0.02, 0.10, or 0.5 ml undiluted or of 0.5 ml of 40, 15, or 1% dilutions are made into conjunctival sac of 5 rabbits. Read immediately unstained and after fluorescein at 24 hours, with one of ten grades assigned.
Remark : Moderate corneal injury, with iritis on one, from 0.02 ml per eye; minor injury from 0.005 ml per eye. Grade 5.

No further information supplied.
Reliability : (2) valid with restrictions
19.11.2001 (27)
Remark : Highly irritating to the eye.
Delamine Safety Data Sheet
HSDB no.: 5171

FIVE DROPS OF LIQ IN EYES OF RABBITS CAUSES SEVERE BURNS. [Lefaux, R. Practical Toxicology of Plastics. Cleveland: CRC Press Inc., 1968. 166]

Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (2) valid with restrictions
28.06.2001
Species : rabbit
Concentration :
Dose :
Exposure Time :
Comment :
Number of animals :
Result : moderately irritating
EC classification : irritating
Method :
Year :
GLP : no data
Test substance : no data
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : Dose: 5 mg.
Reliability : (3) invalid
28.06.2001

(37)

5.3 Sensitization

Type : Guinea pig maximization test
Species : guinea pig
Concentration : Induction 5 % other: intradermal injection
Induction 60 % open epicutaneous
Challenge 50 % open epicutaneous
Number of animals : 20
Vehicle : water
Result : sensitizing
Classification :
Method :
Year : 1990
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Method : A group of 10 male and 10 female guinea pigs each received intradermal induction injections, as follows, into the clipped shoulder skin:

1) Two sites each with 0.1 ml of Freund's Complete Adjuvant (FCA) water emulsion.

2) Two sites each with 0.1 ml of 5% (v/v) TEPA in distilled water.

3) Two sites each with 0.1 ml of 5% TEPA in distilled water.

Epicutaneous inductions were given 7 days later to the clipped shoulder area skin. 60% TEPA was applied to saturation to 2 x 4 cm filter paper, which was then occlusively applied for 48 hours.

Epicutaneous challenge was undertaken by applying 2 x 2 cm filter paper squares soaked in 50% TEPA to the clipped shoulder region, 14 days after epicutaneous induction (i.e., 21 days from the start of the study). Patches

were left in place for 24 hours, and the sites inspected for signs of irritation 24 to 48 hours after removal of the occlusive dressings.

Irritation control animals, 5 male and 5 female guinea pigs, received the same challenge procedures as in the definitive sensitization study, but did not have preceding intradermal and/or epicutaneous induction procedures.

Observations for signs of dermal irritation (erythema, edema and eschar formation) were made approximately 24, and 48 hours after removal of the patches.

Seven days after the challenge exposure, the cross-challenge treatment was administered. Test materials were administered to the clipped skin in a similar manner as in the challenge phase but at a previously untreated site. Smaller patches were used (0.875 square inches) in order to allow all the material to fit on the test site. Materials were applied to saturation. Patches were left in place for 24 hr, and the sites inspected for signs of irritation 24 to 48 hr after removal of the occlusive dressings.

Remark : Two TEPA-treated animals, one male and one female, were found dead on days 20 and 22 of study, respectively. Gross postmortem observations, did not reveal a cause of death and were considered unremarkable except for the presence of tan patches on the surface of the liver of the female. Except for the presence of reddening and swelling in the ano-genital area of one test material-treated male on Days 21 and 28, no abnormalities were observed during weekly examinations.

Result : Of the 18 surviving animals only one challenged with TEPA showed a clear inflammatory response. No dermal responses occurred in any of the ten irritation control animals. Because of the questionable nature of the response in the treated animals, a second challenge was performed. Fourteen of the 18 animals exhibited clear responses. No significant response was observed in eight of the 10 control animals. Responses in treated animals clearly exceeded those in control animals.

A summary of dermal responses at cross-challenge is presented as follows.

Material	Concentration (%)	Test Animals	Irritation Controls
Ethylenediamine	5	0/18	0/10
Diethylenetriamine high purity	25	2/18	5/10
Aminoethylpiperazine	25	6/18	1/10
Aminoethylethanolamine	25	12/18	0/10
Triethylenetetramine	50	11/18	3/10
Piperazine	25	1/18	0/10

Under conditions of this test, TEPA exhibited a strong potential to produce dermal sensitization in the guinea pig. There was evidence of cross-sensitization to aminoethylpiperazine, triethylenetetramine and aminoethylethanolamine.

Reliability : (1) valid without restriction
19.12.2001 (38)
Remark : Causing skin sensitization (Human experience)
Source : DELAMINE BV Delfzijl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (2) valid with restrictions
05.09.2001 (31)

5.4 Repeated dose toxicity

Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	6 hrs/day, 5 days/wek for 4 weeks
Frequency of treatment	:	
Post obs. period	:	
Doses	:	0, 50, 100 or 200 mg/kg/day
Control group	:	yes, concurrent vehicle
Method	:	OECD Guide-line 410 "Repeated Dose Dermal Toxicity: 21/28-day Study"
Year	:	1986
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	One control rabbit was removed on study day 14 due to a broken back with spinal cord dysfunction.
Result	:	All rabbits treated with 100 or 200 mg/kg/day exhibited skin irritation. The degree of irritation was dose-related with more severe effects noted at 200 mg/kg/day. All rabbits receiving 200 mg/kg/day had very red and slightly swollen test material application sites by study day 6. On study day 16, the dermal test site of some female rabbits was severely irritated with some crusting and bleeding. Other animals at 200 mg/kg/day and those treated with 100 mg/kg/day had irritated skin where TEPA had been applied. Skin damage did not progress to any extent during the remainder of the study.
		NOEL for dermal test site 50 mg/kg
		LOEL for dermal test site 100 mg/kg
		NOEL for systemic effects 200 mg/kg
Reliability	:	(1) valid without restriction
28.06.2001		(39)

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	7 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	
Control group	:	
Method	:	
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Tetraethylene pentamine was added to ground Purina Chow and fed in the diet for 7 days. Groups of 5 male and 5 female Harlan-Wistar rats, 30 days of age at the start of the study, were randomly assigned to each dosage level and to a control level. This dietary inclusion study was completed in two parts. Three dosage levels, with one control level, were included on the first part. Actual dose levels were 0, 420, 1050 and 2800 mg/kg/day for males and 0, 470, 1260 and 3140 mg/kg/day for females. Because there were no observed effects from these levels, a higher dosage level and a control level were included on the second part of the study. Actual dose levels were 0 and 3990 mg/kg/day for males and 0 and 3630 mg/kg/day for females.

Animals were weighed on days 1, 4 and 7 with all animals necropsied on day 7. Absolute and relative liver and kidney weights were obtained.

No further information provided.

Remark : There did not appear to be any difference between males and females in the subacute toxicity of TEPA.

Result : There were no effects on body weight or organ weight from the highest dosage levels attained in the first part of the study These dosages were 2800 mg/kg/day for the males and 3140 mg/kg/day for females. During the second phase of the feeding study, dosages of 3990 mg/kg/day for males and 3630 mg/kg/day for females were achieved. The maximum no significant ill-effect level was an average of 2970 mg/kg/day based on body weight, liver weight and kidney weight. The minimum effect level (MiE) averaged 3810 mg/kg/day. 3810 mg/kg/day or 0.85 indicating a low degree of chronicity. Body weight loss was noted for both sexes throughout the 7 days. Liver weight, expressed as absolute weight, and as percentage of body weight, was significantly depressed. Kidney weight as percentage of body weight was significantly higher than that for controls. The absolute kidney weight was slightly, but not statistically, depressed. There were no deaths at any level.

Summary of 7 day dietary study of TEPA

Male Rats

Dosage goal, mg/kg	0	500	1250	3150
Dosage attained, mg/kg/day	0	420	1050	2800
Diet consumed gm/rat/day	16.8	15.3	15.5	16.5
Body weight changes, gm				
day 2	7.2	5.0	6.2	5.6
day 5	27.4	21.8	24.6	27.4
day 8	50.4	42.8	43.6	49.0
Liver weight, gms	8.11	7.86	7.07	8.15
Relative liver weight	4.76	4.85	4.36	4.67
Kidney weight, gms	1.59	1.54	1.54	1.57
Relative kidney weight	0.94	0.95	0.95	0.90
Mortality	0	0	0	0

Female Rats

Dosage goal, mg/kg	0	500	1250	3150
Dosage attained, mg/kg/day	0	470	1260	3140
Diet consumed gm/rat/day	13.8	12.9	13.8	13.8
Body weight changes, gm				
day 2	4.4	5.4	3.2	4.8
day 5	20.6	19.2	19.6	22.8
day 8	36.2	32.2	34.6	36.8
Liver weight, gms	6.39	5.96	6.49	6.26

Relative liver weight	5.14	4.93	5.06	4.82
Kidney weight, gms	1.16	1.17	1.19	1.21
Relative kidney weight	0.93	0.96	0.94	0.93
Mortality	0	0	0	0

Summary of 7 day dietary study of TEPA, 2nd phase

Male Rats		
Dosage goal, mg/kg	0	5000
Dosage attained, mg/kg/day	0	3990
Diet consumed gm/rat/day	17.0	9.3
Body weight changes, gm		
day 2	4.8	-3.0[c]
day 5	28.0	-7.6[c]
day 8	45.4	-14.8[c]
Liver weight, gms	7.32	3.57[c]
Relative liver weight	4.37	3.73[b]
Kidney weight, gms	1.46	1.22
Relative kidney weight	0.87	1.23[c]
Mortality	0	0

Female Rats		
Dosage goal, mg/kg	0	5000
Dosage attained, mg/kg/day	0	3630
Diet consumed gm/rat/day	16.0	8.2
Body weight changes, gm		
day 2	5.8	-2.8[c]
day 5	26.4	-3.6[c]
day 8	39.0	-3.8[c]
Liver weight, gms	6.85	4.10[c]
Relative liver weight	4.72	3.77[b]
Kidney weight, gms	1.42	1.27
Relative kidney weight	0.98	1.17[b]
Mortality	0	0

[b] Level of significance 0.01>P>0.001
[c] Level of significance P<0.001
No additional information provided.

Reliability : (2) valid with restrictions
04.12.2001 (27)

Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : drinking water
Exposure period : 92 days
Frequency of treatment : continuous

Post obs. period	:	
Doses	:	0, 120, 600 and 3000 ppm (0, 10, 55 and 276 mg/kg/day (males) or 0, 14, 70 and 352 mg/kg/day (females), respectively, for NIH-31 diet)
Control group	:	yes, concurrent no treatment
NOAEL	:	= 276 mg/kg bw
Method	:	other: generallyfollows OECD 408
Year	:	1996
GLP	:	no data
Test substance	:	other TS: triethylenetetramine dihydrochloride
Method	:	Rats were fed a cereal-based (NIH-31) or a purified (AIN-76A) diet. An additional control group received a Cu-deficient AIN-76A diet. Since interactions in the absorption and metabolism of Cu, Fe and Zn are known to exist, plasma levels of these three metals were determined in six rats/sex/dose group. Liver, aorta and spinal cord samples from six rats of each sex from control and high-dose groups were also analyzed for the metals. These tissues were analyzed in other dose groups if control and high-dose levels differed. Approximately 35 tissues, including reproductive organs, coagulating gland, epididymis, ovaries, seminal vesicles, testes, uterus and vagina, were examined histopathologically from the control and high dose animals. Tissues from other dose groups were examined also if lesions were clearly more prevalent in the high-dose group.
Remark	:	Effects observed in rats fed the AIN-76A diet are considered to be related to the purified diet and not directly due to triethylenetetramine hydrochloride. In animals ingesting the NIH-31 diet, the authors considered the decreased ceruloplasmin levels as not biologically important. Serum copper levels although decreased, most notably in females, were not statistically significantly decreased. Thus the effect is considered of minimal concern and the NOAEL is 276 mg/kg/day for males and 352 mg/kg/day for females.
Result	:	Cu-deficient AIN-76A diet - This low copper diet resulted in Cu-deficiency symptoms, such as anemia, liver periportal cytomegaly, pancreatic atrophy and multifocal necrosis, spleen hematopoietic cell proliferation and increasted heart weight, together with undetectable levels of plasma copper. AIN-76A diet - Triethylenetetramine hydrochloride lowered plasma copper levels somewhat at 600 and 3000 ppm in rats fed the AIN-76A diet but did not induce the usual signs of copper deficiency. In males receiving 3000 ppm triethylenetetramine hydrochloride coagulative necrosis of the liver was less frequent than in copper adequate controls and was absent from all low copper controls. NIH-31 - The only effect of triethylenetetramine hydrochloride in animals fed the NIH-31 diet was a reduced ceruloplasmin level (3000 ppm, 210+/-26; control 293+/-55 mg/dl) and reduced (not statistically) plasma copper levels in both rat sexes (males 3000 ppm, 0.70+/-0.09; control 0.73+/-0.04 ug/ml; females 3000 ppm, 1.00+/-0.11; control 1.40+/-0.15) at 3000 ppm.
Test substance	:	Test substance is >99% pure. This is the lower molecular weight analog in the ethylenediamine series.
Reliability	:	(2) valid with restrictions

04.12.2001 (40)

Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	drinking water
Exposure period	:	92 days
Frequency of treatment	:	continuous
Post obs. period	:	

Doses	:	0, 120, 600 and 3000 ppm (0, 22, 107, and 487 (males) or 551 (females) mg/kg/day, respectively, for NIH -31 diet)
Control group	:	yes, concurrent no treatment
NOAEL	:	=
Method	:	other: generally follows OECD 408
Year	:	1996
GLP	:	no data
Test substance	:	other TS: triethylenetetramine dihydrochloride
Method	:	Mice were fed a cereal-based (NIH -31) or a purified (AIN-76A) diet. An additional control group received a Cu-deficient AIN-76A diet. Since interactions in the absorption and metabolism of Cu, Fe and Zn are known to exist, plasma levels of these three metals were determined in five mice/sex/dose group. Approximately 35 tissues, including reproductive organs, coagulating gland, epididymis, ovaries, seminal vesicles, testes, uterus and vagina, were examined histopathologically from the control and high dose animals. Tissues from other dose groups were examined also if lesions were clearly more prevalent in the high-dose group.
Remark	:	The intent of this study was to characterize the toxicity in animals fed diets containing nutritionally adequate levels of copper, to compare these to animals fed a low copper diet, and to evaluate the relationship of possible adverse effects to the effect of trien-2HCl on circulating copper levels. The purified (AIN-76A) diet and copper-deficient AIN-76A diet was used by the authors as a means to provide a copper deficient diet. The two steps were necessary to define any possible differences between the cereal-based (NIH -31) and the artificial purified diet. There were no consistent effects noted in mice fed 3000 ppm triethylenetetramine hydrochloride in the drinking water for 92 days. Effects observed in mice fed the AIN -76A diet are considered to be related to the purified diet and not directly due to triethylenetetramine hydrochloride. The NOEL was 487 mg/kg/day for males and 551 mg/kg/day for female mice, the highest dose tested.
Result	:	Cu-deficient AIN-76A diet - There were no effects observed. AIN-76A diet - There were no clinical symptoms observed which were attributed to test material. A male mouse from the 3000 ppm group died on day 78. Body weight gains of the 3000 ppm males were decreased. High dose males gained 25% less than controls. The mean corpuscular volume of erythrocytes of high dose males was significantly lower than controls. In addition, the percentage of eosinophils in the high dose group was significantly lower than in the controls. The male kidney was the only absolute organ weight affected in mice fed AIN-76A diet. Multifocal chronic inflammation of the lung interstitium and lung alveolar histocytic infiltration were the most prevalent histologic findings associated with triethylenetetramine hydrochloride administration. These lesions occurred in high dose male and female mice fed the AIN-76A diet and were more severe but less frequent in males than in females. Spleen hematopoietic cell proliferation and liver periportal fatty change also were most prevalent in the high dose males fed AIN -76A fed animals. Furthermore, high dose males fed AIN-76A diet had a decreased prevalence of kidney cytoplasmic vacuolization (lipid content) when compared to controls. This cytoplasmic vacuolization is a normal feature of male B6C3F1 mice fed either NIH -31 or AIN-76A diet, but was suppressed by 3000 ppm triethylenetetramine hydrochloride only in those fed AIN-76AA diet. NIH-31 - Mice fed the NIH -31 diet drank more water than those fed either formulation of the purified diet. Female mice received somewhat higher daily doses than their male counterparts. There were no test material

related effects observed in mice receiving up to 3000 ppm triethylenetetramine hydrochloride in the drinking water for up to 92 days.

Test substance : Test substance is >99% pure. This is the lower molecular weight analog in the ethylenediamine series.

Reliability : (2) valid with restrictions

04.12.2001 (40)

5.5 Genetic toxicity 'in vitro'

Type	:	Ames test
System of testing	:	Salmonella/microsome bacterial mutagenicity assay
Concentration	:	0.001 to 0.1 mg/plate (in the absence of S9); 0.1 to 5 mg/plate (with S9)
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	Positive
Method	:	
Year	:	1984
GLP	:	Yes
Test substance	:	
Method	:	SOP #7.4.1A through 7.4.7A, 7.4.12A, and 7.4.13. For definitive testing, an initial stock solution of the test substance was prepared by mixing TEPA-Sample A in water to achieve a concentration of 50 mg/ml. All subsequent dilutions were made in the same solvent. Dilutions of the test substance were made fresh each day of testing. All dilutions for the mutagenicity tests were analyzed gravimetrically to determine actual concentrations. The test chemical was tested in triplicate at five doses chosen to span a range which included moderately toxic to relatively non-toxic concentrations. Testing was performed both with and without metabolic activtation in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538.
Remark	:	TEPA-Sample A did not produce a positive or dose-dependent mutagenic response in any of the Salmonella typhimurium strains that were tested without a metabolic activation system. However, in the presence of metabolic activation a weak positive and dose-related response was observed with strain TA1535 and marginal mutagenic activity was observed with TA100. Under the conditions of this assay, TEPA-Sample A was considered to be weakly mutagenic in the Salmonella/microsome mutagenicity assay
Result	:	In tests performed without S9, no indication of mutagenicity was observed with any of the strains, either by evidence of a dose-response relationship or a doubling of the average number of colonies over the average solvent control value. In the test performed with S9, all strains except TA 1538 showed signs of treatment-related inhibition of growth of the background lawn with the highest dole level of TEPA-Sample A tested (5 mg/plate). Weak mutagenic activity was evident in the test performed with S9 using strain TA1535. The highest dose level tested (5 mg/plate) produced a 2.8-fold increase in relative numbers of revertant colonies and the next lower dose of 3 mg/plate produced a 1.9-fold increase. A moderate increase in mutants was also observed with TA100 which showed a 1.5-fold increase in numbers of revertant colonies with the highest non-cytotoxic dose level tested of 3 mg/plate. Thus, TEPA was considered

		to be weakly mutagenic in the presence of S9 activation in this in vitro bacterial assay.
Test substance	:	TEPA-Sample A containing 89.7% TEPA.
Reliability	:	(1) valid without restriction
27.08.2001		(41)
Type	:	Ames test
System of testing	:	Salmonella/Microsome Bacterial Mutagenicity Assay
Concentration	:	0.001 to 1.0 mg/plate (in the absence of S9); 0.1 to 5 mg/plate (with S9)
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	positive
Method	:	
Year	:	1987
GLP	:	yes
Test substance	:	
Method	:	SOP #7.4.1A through 7.4.7A, 7.4.12A, and 7.4.13. For definitive testing, an initial stock solution of the test substance was prepared by mixing TEPA-Sample B in water to achieve a concentration of 50 mg/ml. All subsequent dilutions were made in the same solvent. Dilutions of the test substance were made fresh each day of testing. All dilutions for the mutagenicity tests were analyzed gravimetrically to determine actual concentrations. The test chemical was tested in triplicate at five doses chosen to span a range which included moderately toxic to relatively non-toxic concentrations. Testing was performed both with and without metabolic activation in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538.
Remark	:	TEPA-Sample B produced positive and dose-dependent mutagenic response with three of the five strains of Salmonella typhimurium that were tested without S9 (TA98, TA100, TA1537)and with all strains except TA1538 tested in the presence of a rat-liver metabolic activation system. Therefore, under the conditions of this in vitro assay, TEPA-Sample B was considered to be mutagenic in the Salmonella/microsome mutagenicity assay.
Result	:	In tests performed without S9, strains TA98, TA100, TA1537 showed positive and dose-related increase in numbers of revertant bacterial colonies. The highest dose level, 1 mg/plate, produced excessive cytotoxicity with all five strains tested. With strain TA98, the highest non-cytotoxic dose level of TEPA-Sample B tested, produced a positive increase that was 6.2 times higher than the concurrent control value. Moderately positive increases of 2.4-fold and 3.4-fold control values were observed for strains TA100 and TA1537 tested with the highest non-cytotoxic dose level of 0.3 mg/plate. In tests performed in the presence of a metabolic activation system, moderate dose-related cytotoxicity was evident as sparse growth of the with all strains except TA1538. Similar to the results without S9, TEPA-Sample B produced positive and dosage-related mutagenic effects in strains TA98, TA100 and TA1537 with maximum increases in excess of two times the concurrent control values. In the presence of S9, 1535 also showed positive and dose-related increases in numbers of revertant colonies which were not apparent in the test performed without S9.
Test substance	:	TEPA-Sample B This sample consisted of ~65% TEPA with the remainder of the identified components being other homologues.
Reliability	:	(1) valid without restriction

27.08.2001 (42)

Type	:	Ames test
System of testing	:	Salmonella/Microsome assay
Concentration	:	0.1, 0.3, 1.0, 3.0, 10 mg/plate
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	ambiguous
Method	:	
Year	:	1994
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538 were treated in triplicate with the vehicle control substance, and appropriate positive control substance, and 5 dose levels of TEPA both in the absence and in the presence of a rat liver S9 metabolic activation system using the plate incorporation method. Treated cultures were incubated at 37oC for 48-72 hours. Two independent repetitions of the complete assay were performed.
Remark	:	TEPA was weakly mutagenic in strains TA98, TA100, and TA 1535 in the absence of an S9 metabolic activation system. Although TEPA was not mutagenic in strains TA98 and TA100 in the presence of metabolic activation, it was weakly mutagenic in TA1535. No mutagenic activity was observed in strains TA1537 or TA1538, either in the absence or in the presence of metabolic activation. These results were observed in 2 independent tests. Under the conditions of this Salmonella/microsome mutagenicity assay, TEPA was considered to be a very weak mutagen with direct base substitution and frame shift activity.
Result	:	No mutagenic activity was observed in strains TA1537 or TA1538, either in the absence or in the presence of S9 activation. No mutagenic activity was observed in strain TA98 in the presence of S9 activation. Reproducible increases of approximately 2- to 4-fold were observed in the number of colonies/plate in strain TA1535 at the high dose, 10.0 mg/plate TEPA, both in the absence and in the presence of S9 activation. Increases in the mean number of colonies/plate of approximately 3-fold were observed in strain TA98 treated at 10.0 mg/plate TEPA in the absence of S9 in both tests. In strain TA100, consistent increases of approximately 2-fold were observed in the absence of S9 at 10.0 mg/plate TEPA, but were not reproducible in both independent tests in the presence of S9.
Reliability	:	(1) valid without restriction

05.09.2001 (43) (44)

Type	:	Mammalian cell gene mutation assay
System of testing	:	CHO cells
Concentration	:	80 x 10-2% to 2.5 x 10-2%
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	ambiguous
Method	:	
Year	:	1981
GLP	:	no
Test substance	:	other TS: TEPA-NaBH4
Method	:	SOP #7.2.4A; 7.2.5; 7.2.11. CHO cells were exposed for 5 hours to a minimum of five concentrations of TEPA-NaBH4 both with and without the addition of an S9 metabolic activation

system. Dilutions of TEPA-NaBH4 for testing were prepared by either direct addition of various aliquots of the test agent into the cell culture media or by making sequential one-half dilutions, in sterile H2O, from an initial stock solution. The surviving fraction was determined at 20 to 24 hours after treatment and the mutant fraction was determined after a 7 day period to allow "expression" of the mutant phenotype. Only the top five concentrations which allow sufficient cell survival are typically assessed for survival and induction of mutants. Sterile, distilled water (H2O) was used as the solvent and solvent control; glass-distilled dimethylsulfoxide (DMSO) was used as the negative control.

Remark : TEPA-NaBH4 was apparently inactive as a mutagenic agent for CHO cells when tested with and without the incorporation of an S9 metabolic activation system over a 16 fold range of concentrations. Only one statistically significant increase above the concurrent solvent control was produced at the 20 x 0-2% dose level in tests which included a metabolic activation system. However, the observation of unusually high spontaneous mutation frequencies for the solvent and negative controls, and the lack of dose-related cytotoxicity within the dose range tested, prevented an unequivocal classification of the test chemical as active or inactive as a potential mutagenic agent for CHO cells.

Result : TEPA-NaBH4 produced a statistically significant increase in the frequency of mutations of CHO cells at only one concentration (20 x 10-2) in test with the incorporation of a liver S9 metabolic activation system. The lack of a dose-related effect of treatment on the induction of mutations indicated that TEPA-NaBH4 was not highly active in producing gene mutations in CHO cells. However, the lack of adose-related cytotoxic response in this test and production of abnormally high numbers of mutants by the solvent and negarive controls prevented the use of these data to classify TEPA-NaBH4 as mutagenic or non-mutagenic.

Test substance : TEPA-NaBH4 was prepared by reacting TEPA with sodium borohydride. This was performed to minimize possible formation of nitrosamines.

TEPA was mixed with 1000 ppm NaBH4, contained at 200C for one hour at 600 mm Hg pressure, then distilled from the NaBH4 by increasing the vacuum. Distillate was then transferred into N2 purged bottles which had been acid treated and baked out at 500C. No further analytical information was provided.

Reliability : (2) valid with restrictions
27.08.2001 (45)

Type : Mammalian cell gene mutation assay
System of testing : CHO cells.
Concentration : 80 x 10-2% to 2.5 x 10-2%
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method :
Year : 1981
GLP : no
Test substance : other TS: TEPA-HC
Method : SOP #7.2.4A; 7.2.5; 7.2.11. CHO cells were exposed for 5 hours to a minimum of five concentrations of TEPA-HC both with and without the addition of an S9 metabolic activation system. Dilutions of TEPA-HC for testing were prepared by

either direct addition of various aliquots of the test agent into the cell culture media or by making sequential one-half dilutions, in sterile H2O, from an initial stock solution. The surviving fraction was determined at 20 to 24 hours after treatment and the mutant fraction was determined after a 7 day period to allow "expression" of the mutant phenotype. Only the top five concentrations which allow sufficient cell survival are typically assessed for survival and induction of mutants. Sterile, distilled water (H2O) was used as the solvent and solvent control; glass-distilled dimethylsulfoxide (DMSO) was used as the negative control.

Remark : TEPA-HC was consistently inactive as a mutagenic agent for CHO cells when tested with and without the incorporation of an S9 metabolic activation system over a 16- to 32-fold range of concentrations No statistically significant increase above the concurrent solvent control was produced at any dose level tested and TEPA-HC was considered to be non-mutagenic in the CHO test. These negative results indicated that TEPA-HC was not a potent mutagen when tested at near-cytotoxic dose levels, but additional tests within a narrow range of cytotoxic concentrations would be required to determine the validity of these conclusions.

Result : TEPA-HC did not produce a statistically significant increase in the frequency of mutations of CHO cells at any concentration between 80 x 10-2 to 2.5 x 10-2% in tests with and without the incorporation of a liver S9 metabolic activation system. The lack of a dose-related effect of treatment on the induction of mutations indicated that TEPA-HC was not highly active in producing gene mutations in CHO cells. However, additional testing over a narrow range of concentrations would be necessary to verify these results because the concentrations tested did not include the dose levels which produced a significant degree of cytotoxicity.

Test substance : TEPA-HC is Tetraethylenepentamine Hearts Cut and was 100% by GC analysis.

Reliability : (2) valid with restrictions

27.08.2001 (46)

Type : Mammalian cell gene mutation assay
System of testing : CHO cells
Concentration : 80 x 10-2% to 2.5 x 10-2%
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method :
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : SOP #7.2.4A; 7.2.5; 7.2.11. CHO cells were exposed for 5 hours to a minimum of five concentrations of TEPA both with and without the addition of an S9 metabolic activation system. Dilutions of TEPA for testing were prepared by either direct addition of various aliquots of the test agent into the cell culture media or by making sequential one-half dilutions, in sterile H2O, from an initial stock solution. The surviving fraction was determined at 20 to 24 hours after treatment and the mutant fraction was determined after a 7 to 9-day period to allow "expression" of the mutant phenotype. Only the top five concentrations which allow sufficient cell survival are typically assessed for survival

and induction of mutants. Sterile, distilled water (H2o) was used as the solvent and solvent control; glass-distilled dimethylsulfoxide (DMSO) was used as the negative control.

Remark : TEPA did not produce a statistically significant increase in the mutation frequency of CHO cells at any concentration between 80 x 10-2% to 2.5 x 10-2% tested with or without the presence of an S9 metabolic activation system. The lack of a dose-related effect on the mutation frequency indicated that TEPA was not active in producing gene mutations in CHO cells. The test in the presence of the S9 activation system evaluated one additional lower concentration than the test without S9 because the top dose-level (with S9) was highly cytotoxic and could not be evaluated for mutation induction.

Result : TEPA was consistently inactive as a mutagenic agent for CHO cells when tested with or without an S9 metabolic activation system over a 16-fold range of concentrations. Small increases in the numerical frequency of mutants, obtained at some concentrations of TEPA tested with or without S9 activation, were within the expected range of variations encountered with this test system and none of the mutation values produced by the test agent was statistically significant from the concurrent solvent control.

Reliability : (2) valid with restrictions

27.08.2001 (43) (47)

Type : Sister chromatid exchange assay
System of testing : CHO cells.
Concentration : 3.0 mg/ml (with S9); 0.8 mg/ml (without S9)
Cycotoxic conc. :
Metabolic activation : with and without
Result : Positive
Method :
Year : 1987
GLP : Yes
Test substance : other TS: TEPA-Sample A
Method : SOP #7.2.12E. For determination of direct mutagenic action, CHO cells were exposed to tetraethylenepentamine-Sample A and appropriate controls for 5 hours without S9 activation. Indirect mutagenic action, requiring metabolic activation by liver S9 homogenate, was studied with a 2-hour exposure period. Bromodeoxyuridine (BrdU), required to differentiate between the individual "sister" chromatids by SCE staining, was present at a concentration of 3 micrograms/ml in the growth medium during treatment and during the culture period following exposure. A total of twenty-five cells/concentrations was examined for SCE frequencies using duplicate cultures. At least 5 dose levels were tested both with and without metabolic activation. SCE production was determined for the highest 3 doses which did not produce excessive cytotoxic inhibition of cell division.

Remark : Tetraethylenepentamine-Sample A produced dose-related and statistically significant increases in the incidence of SCEs in the CHO cells exposed both in the presence and absence of an S9 metabolic activation system. Tetraethylenepentamine-Sample A was considered to produce a positive genotoxic effect in this in vitro screening test.

Result : TEPA-Sample A produced dose-related and statistically significant increases in SCEs in tests both with and without addition of a rat-liver S9 metabolic activation system. The highest increases in SCEs above control values were

approximately 1.8 fold without S9 and 1.6-fold with S9 activation. The test chemical was considered to be a positive genotoxic agent in the SCE test system.

Test substance : TEPA-Sample A containing 89.7% TEPA.
Reliability : (1) valid without restriction
27.08.2001 (48)

Type : Unscheduled DNA synthesis
System of testing : rat liver (hepatocyte) cells
Concentration : 100 x 10-2% to 0.1 x 10-2%.
Cycotoxic conc. :
Metabolic activation : with and without
Result : Positive
Method :
Year : 1980
GLP : No
Test substance : as prescribed by 1.1 - 1.4
Method : SOP #7.2.6; 7.2.7; 7.2.8A, 7.2.9A. Induction of primary DNA damage in rat liver cells (hepatocytes) was studied at a minimum of six dose levels which spanned a 1000-fold range of concentrations. Cells were treated with TEPA for 2 hours in culture medium containing 3H-Thymidine, hydroxyurea and appropriate dilutions of TEPA prepared in DMSO. Determination of UDS activity in treated and control cells was performed by analyses of 3H-thymidine incorporation into isolated hepatocyte nuclei and DNA (Precipitated from aliquots of the isolated nuclie) using a Searle Anaytic Model 81 or Packard Model 2650 scintillation spectrometer.
Remark : TEPA stimulated an elevated level of incorporation of radioactive thymidine in cells treated over a wide range of test concentrations in comparison to the solvent control data. The statistically significant stimulation of UDS in measurements with either nuclei or DNA from treated cells indicated that TEPA was an active mutagenic agent in the tests with hepatocytes. Highly significant incresases in UDS values produced by the positive control agents NQO and DMN indicated that the test system was responsive to mutagenic detection.
Result : Two separate experiments were performed to evaluate an overall range of TEPA concentrations between 100 x 10-2% to 0.01 x 10-2%. A statistically significant increase in the amount of UDS to the highest dose-level in experiment #1 prompted a repeat experiment at a 10-fold higher concentration rang in experiment #2 to determine whether this effect was repeatable. In experiment #2, TEPA produced a highly statistically significant increase in the amount of primary DNA damage at four of six test concentrations. Although the positive effects were observed consistently only at one concentration (10 x 10-2%), in comparisons between experiments #1 and #2, the reproducibility of the positive effect at a high degree of statistical significance indicated that TEPA was a probable, active agent in the hepatocyte test system.
Reliability : (2) valid with restrictions
28.06.2001 (43) (47)

Type : Unscheduled DNA synthesis
System of testing : rat liver (hepatocyte) cells
Concentration : 100 x 10-2% to 0.1 x 10-2%
Cycotoxic conc. :

Metabolic activation	:	with and without
Result	:	Positive
Method	:	
Year	:	1981
GLP	:	No
Test substance	:	other TS: TEPA-NaBH4
Method	:	SOP #7.2.6; 7.2.7; 7.2.8A, 7.2.9A. Induction of primary DNA damage in rat liver cells (hepatocytes) was studied at a minimum of six dose levels which spanned a 1000-fold range of concentrations. Cells were treated with TEPA-NaBH4 for 2 hours in culture medium containing 3H-Thymidine, hydroxyurea and appropriate dilutions of TEPA-NaBH4 prepared in DMSO. Determination of UDS activity in treated and control cells was performed by analyses of 3H-thymidine incorporation into isolated hepatocyte nuclei and DNA (Precipitated from aliquots of the isolated nuclei) using a Searle Anaytic Model 81 or Packard Model 2650 scintillation spectrometer.
Remark	:	TEPA-NaBH4 produced increases in the levels of UDS in hepatocytes which were significantly above values observed with historical controls. Although only a few of these increases were statistically significant from the concurrent solvent control, the test results were considered positive based upon similar weakly-positive effects in two separate tests.
Result	:	TEPA-NaBH4 did not produce consistent statistically significant or dose-related increases in the amount of UDS activity in evaluations of concentrations between 100 x 10-2% to 0.1 x 10-2%. However, in two separate tests, the quantitative levels of the numerical increases in UDS produced by the test agent were significantly greater than values included in the 95% confidence interval of the historical control data for this test. These increases were produced at similar test concentration in two separate tests and with two separate methods for measuring UDS. TEPA-NaBH4 was considered to be active in producing primary DNA damage in the present test with the hepatocyte test system.
Test substance	:	TEPA-NaBH4 was prepared by reacting TEPA with sodium borohydride. This was performed to minimize possible formation of nitrosamines. TEPA was mixed with 1000 ppm NaBH4, contained at 200C for one hour at 600 mm Hg pressure, then distilled from the NaBH4 by increasing the vacuum. Distillate was then transferred into N2 purged bottles which had been acid treated and baked out at 500C. No further analytical information was provided.
Reliability	:	(2) valid with restrictions

27.08.2001 (45)

Type	:	Sister chromatid exchange assay
System of testing	:	CHO cells.
Concentration	:	80 x 10-2% to 2.5 x 10-2%
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	Positive
Method	:	
Year	:	1980
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	SOP #7.2.12A. Selection of dose-levels which would permit survival of at least 50% of the treated cells was based on the pre-screening test for cytotoxicity performed as part of

the CHO mutation test. Dilutions of TEPA for testing were prepared either by direct addition of various aliquots of the test agent into the culture medium or by making sequential one-half dilutions in H2O from the stock solution for the maximum dose level. For determination of direct mutagenic action, CHO cells were exposed to TEPA and appropriate controls for 5 hours without S9 activation. Indirect mutagenic action, requiring metabolic activation by liver S9 homogenate, was studied with a 2-hour exposure period. Bromodeoxyuridine (BrdU) required to differentiate between the individual "sister" chromatids by SCE staining, was present at a concentration of 3 micrograms/ml in the growth medium during treatment and during the culture period following exposure. A total of 20 cells/dose level and cells treated at 5 dose levels, with or without metabolic activation, were examined.

Remark : TEPA produced a highly statistically significant increase in the frequency of SCE in CHO cells treated with a range of concentrations between 80 x 10-2% to 2.5 x 10-2 % in tests with and without the presence of an S9 metabolic activation system. The production of a dose-related increase in the frequency of SCE indicated that TEPA was an active agent in the production of primary DNA damage as measured by an increased frequency of chromatid exchanges. The highest concentration of TEPA tested (80 x 10-2) was cytotoxic to the CHO cells and prevented evaluation of SCE produced at that dose level.

Result : Treatments of CHO cells with TEPA over a 24 to 32-fold range of concentrations with and without S9 metabolic activation, respectively, indicated a significant effect of the test agent on the production of SCE. Highly statistically significant increases in the SCE values were observed with all of the dose levels of TEPA which could be evaluated. The highest concentration (60 x 10-2%) was cytotoxic to the cells and affected cell division necessary to visualize SCE. At lower, less cytotoxic dose levels, a dose-response effect was produced by treatment with increasing concentrations of TEPA. This result indicated that the test with S9 activation was a positive indication of mutagenicity and consistent with the findings in the test without addition of S9. TEPA was considered to be active as a mutagenic agent in the induction of SCE in vitro.

Reliability : (2) valid with restrictions

27.07.2001 (43) (47)

Type : Sister chromatid exchange assay
System of testing : CHO cells
Concentration : 80 x 10-2% to 2.5 x 10-2%
Cycotoxic conc. :
Metabolic activation : with and without
Result : Positive
Method :
Year : 1981
GLP : No
Test substance : other TS: TEPA-HC
Method : SOP #7.2.12A. Selection of a maximum dose-level which would permit survival of at least 50% of the treated cells was based on the pre-screening test for cytotoxicity performed as part of the CHO mutation test. Dilutions of TEPA-HC for testing, were prepared either by direct addition of various

aliquots of the test agent into the culture medium or by making sequential one-half dilutions in H2O from the stock solution for the maximum dose level. For determination of direct mutagenic action, CHO cells were exposed to TEPA-HC and appropriate controls for 5 hours without S9 activation. Indirect mutagenic action, requiring metabolic activation by liver S9 homogenate, was studied with a 2-hour exposure period. Bromodeoxyuridine (BrdU) required to differentiate between the individual "sister" chromatids by SCE staining, was present at a concentration of 3 micrograms/ml in the growth medium during treatment and during the culture period following exposure. A total of 20 cells/dose level and cells treated at 5 dose levels, with or without metabolic activation, were examined.

Remark : TEPA-HC produced highly significant increases effects on the frequency of SCE over the relatively wide range of concentrations tested with and without addition of an active S9 metabolic activation system. Dose-related effects of TEPA-HC exposure on the SCE frequency were evident and the test agent was considered to be active as mutagenic agent in the present in vitro assay.

Result : TEPA-HC produced statistically significant and dose-related effects on the frequency of SCE in CHO cells in tests both with and without the incorporation of an S9 metabolic activation system. An overall range of concentrations between 0 x 10-2% to 2.5 x 10-2% was used. Statistically significant ncreases in the frequency of SCE were obtained in the test both with and without metabolic activation and metabolic conversion did not appear to be a strict requirement for mutagenic activity. The results indicated that TEPA-HC was highly active in producing positive effects on the frequency of SCE in CHO cells and these effects were reproducibly in separate tests.

Test substance : TEPA-HC is Tetraethylenepentamine Hearts Cut and was 100% by GC analysis.

Reliability : (2) valid with restrictions

05.09.2001 (46)

Type : Sister chromatid exchange assay
System of testing : CHO cells
Concentration : 5 x 10-2% to 60 x 10-2%
Cycotoxic conc. :
Metabolic activation : with and without
Result : Positive
Method :
Year : 1981
GLP : No
Test substance : other TS: TEPA-RNT
Method : SOP #7.2.12A. Selection of a maximum dose-level which would permit survival of at least 50% of the treated cells was based on the pre-screening test for cytotoxicity performed as part of the CHO mutation test. Dilutions of TEPA-RNT for testing, were prepared either by direct addition of various aliquots of the test agent into the culture medium or by making sequential one-half dilutions in H2O from the stock solution for the maximum dose level. For determination of direct mutagenic action, CHO cells were exposed to TEPA-RNT and appropriate controls for 5 hours without S9 activation. Indirect mutagenic action, requiring metabolic activation by liver S9 homogenate, was studied with a 2-hour exposure

period. Bromodeoxyuridine (BrdU) required to differentiate between the individual "sister" chromatids by SCE staining, was present at a concentration of 3 micrograms/ml in the growth medium during treatment and during the culture period following exposure. A total of 20 cells/dose level and cells treated at 5 dose levels, with or without metabolic activation, were examined.

Remark : TEPA-RNT produced statistically significant effect upon the frequency of SCE over the 3- to 8-fold range of concentrations tested with or without addition of an active S9 metabolic activation system. A dose-related effect of TEPA-RNT exposure on the SCE frequency was also evident and the test agent was considered to be active in the present in vitro screening assay.

Result : TEPA-RNT produced statistically significant and dose-related effects on the frequency of SCE in CHO cells in tests both with and without the incorporation of an S9 metabolic activation system. An overall range of concentrations between 5 x 10-2% to 60 x 10-2% was used. The results indicated that TEPA-RNT was an active agent in this test and should be considered a probable positive mutagenic agent for production of DNA damage in animal cells in vitro.

Test substance : TEPA-RNT is produced by reacting TEPA with Raney Nickel. This was performed to minimize possible formation of nitrosamines.

TEPA-RNT was prepared by treating TEPA in an autoclave with Raney-Nickel for 1 hour at 100C after charging hydrogen to an initial 500 psig. Subsequently the sample was distilled under vacuum with a center cut saved for the mutagenicity studies. Subsequent analysis of the sample was not performed. All intervening transfers were handled under nitrogen. The treated material was stored under nitrogen until used.

Reliability : (3) invalid

05.09.2001 (49)

Type : Sister chromatid exchange assay

System of testing : CHO cells.

Concentration : 80 x 10-2% to 2.5 x 10-2%

Cycotoxic conc. :

Metabolic activation : with and without

Result : Positive

Method :

Year : 1981

GLP : No

Test substance : other TS: TEPA-NaBH4

Method : SOP #7.2.12A. Selection of a maximum dose-level which would permit survival of at least 50% of the treated cells was based on the pre-screening test for cytotoxicity performed as part of the CHO mutation test. Dilutions of TEPA-NaBH4 for testing, were prepared either by direct addition of various aliquots of the test agent into the culture medium or by making sequential one-half dilutions in H2O from the stock solution for the maximum dose level. For determination of direct mutagenic action, CHO cells were exposed to TEPA-NaBH4 and appropriate controls for 5 hours without S9 activation. Indirect mutagenic action, requiring metabolic activation by liver S9 homogenate, was studied with a 2-hour exposure period. Bromodeoxyuridine (BrdU) required to differentiate between the individual "sister" chromatids by SCE staining, was present at a concentration of 3 micrograms/ml in the growth medium during treatment and during the culture period following exposure. A total of 20

cells/dose level and cells treated at 5 dose levels, with or without metabolic activation, were examined.

Remark : TEPA-NaBH4 produced a highly significant increases in the frequency of SCE over the 12 to 16-fold range of concentrations tested with or without addition of an active S9 metabolic activation system. Although a linear, dose-related effect of TEPA-NaBH4 exposure on the SCE frequency was not produced, the test agent caused a highly significant increase in the frequency of SCE at almost every dose level employed. The results of these tests indicated that TEPA-NaBH4 was a positive agent in causing DNA damage observable as chromatid interchanges in the SCE test.

Result : TEPA-NaBH4 produced a highly significant effect on the frequency of SCE in CHO cells in tests both with and without the incorporation of an S9 metabolic activation system. An overall range of concentrations between 80 x 10-2% to 2.5 x 10-2% was used but the 80 x 10-2 % concentration produced excessive cytotoxicity and the SCE frequency could not be determined. Highly statistically significant increases in the frequency of SCE were obtained in the tests with and without metabolic activation at almost every concentration employed. These data indicated that TEPA-NaBH4 should be considered a positive mutagenic agent in the production of DAN damage discernable as increases in SCE production.

Test substance : TEPA-NaBH4 was prepared by reacting TEPA with sodium borohydride. This was performed to minimize possible formation of nitrosamines.

TEPA was mixed with 1000 ppm NaBH4, contained at 200C for one hour at 600 mm Hg pressure, then distilled from the NaBH4 by increasing the vacuum. Distillate was then transferred into N2 purged bottles which had been acid treated and baked out at 500C. No further analytical information was provided.

Reliability : (3) invalid

05.09.2001 (45)

Type : Unscheduled DNA synthesis

System of testing : rat liver (hepatocyte) cells

Concentration : 100 x 10-2% to 0.1 x 10-2%

Cycotoxic conc. :

Metabolic activation : with and without

Result : Positive

Method :

Year : 1981

GLP : No

Test substance : other TS: TEPA-HC

Method : SOP #7.2.6; 7.2.7; 7.2.8A, 7.2.9A. Induction of primary DNA damage in rat liver cells (hepatocytes) was studied at a minimum of six dose levels which spanned a 1000-fold range of concentrations. Cells were treated with TEPA-HC for 2 hours in culture medium containing 3H-Thymidine, hydroxyurea and appropriate dilutions of TEPA-HC prepared in DMSO. Determination of UDS activity in treated and control cells was performed by analyses of 3H-thymidine incorporation into isolated hepatocyte nuclei and DNA (Precipitated from aliquots of the isolated nuclie) using a Searle Anaytic Model 81 or Packard Model 2650 scintillation spectrometer.

Remark : TEPA-HC stimulated a significant increase in the incorporation of radioactive thymidine in hepatocytes treated over a wide range of test concentrations. TEPA-HC was considered active in producing primary DNA damage in the present test with the hepatocyte test system. Despite the

lack of dose-related effects, the consistent finding of increase values of UDS at similar concentrations in two separate test prompted the positive classification of TEPA-HC.

Result : TEPA-HC produced several statistically significant increases in the amount of UDS activity in evaluations of concentrations between 100 x 10-2% to 0.1 x 10-2%. TEPA-HC was considered to be active in the present test with the hepatocyte test system because essentially identical numerical increases were produced at similar concentrations in two independent tests.

Test substance : TEPA-HC is Tetraethylenepentamine Hearts Cut and was 100% by GC analysis.

Reliability : (2) valid with restrictions

05.09.2001 (46)

Type : Unscheduled DNA synthesis

System of testing : rat liver (hepatocyte) cells

Concentration : 100 x 10-2% to 0.1 x 10-2%

Cycotoxic conc. :

Metabolic activation : with and without

Result : negative

Method :

Year : 1981

GLP : No

Test substance : other TS: TEPA-RNT

Method : SOP #7.2.6; 7.2.7A; 7.2.8B, 7.2.9B. Production of primary DNA damage in rat liver cells (hepatocytes) was studied at a minimum of six dose levels which spanned a 1000-fold range of concentrations. Cells were treated with TEPA-HC for 2 hours in culture medium containing 3H-Thymidine, hydroxyurea and appropriate dilutions of TEPA-RNT prepared in DMSO. Determination of UDS activity was performed by analyses of 3H-thymidine incorporation into isolated hepatocyte nuclei or in DNA (recipitated from aliquots of the isolated nuclei) using a Searle Analytic Model 81 or Packard Model 2650 scintillation spectrometer.

Remark : TEPA-RNT stimulated a positive but very low level of incorporation of radioactive thymidine in cells treated over a 1000-fold range of test concentrations. TEPA-RNT was considered weakly active in the present test with the hepatocyte test system.

Result : TEPA-RNT produced a slight increase in the amount of UDS activity in evaluations of concentrations between 100 x 10-2% to 0.1 x 10-2%. TEPA-RNT was considered to be weakly active in the present test with the hepatocyte test system because a majority of the UDS levels for TEPA-RNT treated cells were significantly greater than historical negative control values for this test system.

Test substance : TEPA-RNT is produced by reacting TEPA with Raney Nickel. This was performed to minimize possible formation of nitrosamines.

TEPA-RNT was prepared by treating TEPA in an autoclave with Raney-Nickel for 1 hour at 100C after charging hydrogen to an initial 500 psig. Subsequently the sample was distilled under vacuum with a center cut saved for the mutagenicity studies. Subsequent analysis of the sample was not performed. All intervening transfers were handled under nitrogen. The treated material was stored under nitrogen until used.

Reliability : (3) invalid

05.09.2001 (49)

5.6 Genetic toxicity 'in vivo'

Type	:	Micronucleus assay
Species	:	Mouse
Sex	:	male/female
Strain	:	Swiss Webster
Route of admin.	:	i.p.
Exposure period	:	single injection
Doses	:	200 mg/kg to 625 mg/kg
Result	:	negative
Method	:	
Year	:	1987
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	SOP #7.2.18B, 7.2.19B and 7.2.20B. The definitive intraperitoneal toxicity study was conducted using 5 males and 5 females per dosage group. Animals were dosed with the test and control materials (concurrent positive triethylenemelamine, and negative water) by i.p. injection. Two or three additional animals were added to the highest dosage group because toxicity was expected to decrease survival. Blood samples were taken at 3 time periods at approximately 30, 48 and 72 hr after dosing.
Remark	:	TEPA was not an active agent in producing treatment-related increases in micronuclei in male or female Swiss-Webster mice. Dosage levels up to 80% of the LD50 dose for males and females did not produce treatment-related effects in this test. Tetraethylenepentamine was interpreted to be inactive as a clastogenic agent in vivo under the conditions of the micronucleus test system.
Result	:	No statistically significant or treatment-related increases in the numbers of micronuclei were observed at any of the harvest intervals. Past experiences with this test suggest that the greatest increases in micronuclei would be expected at the 30-hr or 48-hr harvest, but the data did not reveal any treatment-related increases for these sampling times. In addition, the incidence of micronuclei for the groups administered TEPA or the vehicle was within the expected range of variability for this test system noted in previous tests in our laboratory and there were no indications of dose-related increases in the incidences of micronuclei. According to the evaluation criteria in the protocol and accepted procedures to classify effects in this test system, TEPA was considered to be inactive in the production of chromosome damage in vivo under the conditions of this assay. The test evaluated reasonably high doses in males and females and no treatment-related increases were observed TEPA was considered to be non-clastogenic in the in vivo micronucleus test.
Reliability	:	(1) valid without restriction
28.06.2001		(43) (50)

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	male/female
Strain	:	other: Canton-S
Route of admin.	:	oral feed
Exposure period	:	

Doses	:	5000 ppm
Result	:	ambiguous
Method	:	
Year	:	1989
GLP	:	no
Test substance	:	other TS
Method	:	In order to obtain individuals for larval treatment, Canton-S females and males were mated and eggs exposed in vials with standard cornmeal containing the chemical plus sovent or solvent alone. Adult males emerging from the treatment were mated at approximately 24 hr of age with two successive harems of three to five Basc females to establish two single-day broods. Males were then discarded, and the conventional SLRL assay carried out. Concentration finding experiments preceded definitive runs, and efforts were made to select a concentration inducing approximately 30% mortality during treament without excessive sterility. Distilled water, Tween-60, and/or EtOH were employed as solvents.
Remark	:	For the test substance, there was an 18% mortality rate. Percent mortality is the percent of chemically treated males that died minus the percent of solvent-treated males that died during treatment. TEPA was determined to be equivocal for the mutagenicity of the chemical.
Reliability	:	(2) valid with restrictions
04.12.2001		(51)

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	male/female
Strain	:	other: Canton S
Route of admin.	:	oral feed
Exposure period	:	throughout the larval stage
Doses	:	5000 ppm
Result	:	ambiguous
Method	:	other: Valencia et al., 1988 Env Mol Mutagen 14:238-244
Year	:	1989
GLP	:	no data
Test substance	:	other TS: Aldrich technical analyzed purity 10.8%
Method	:	Male and female Drosophila flies were mated and eggs exposed in vials with standard cornmeal food containing the chemical plus solvent or solvent alone. Adult males emerging from the treatment were mated at approximately 24 hours of age with two successive harems of 3-5 Basc females to establish two single-day broods. Males were then discarded and the conventional SLRL assay carried out.
Result	:	At 5000 ppm, 18% mortality was observed in the males with 2% of the males sterile. There were 7 lethals observed in fruitflies at 5000 ppm compared to 2 lethals in the controls. The percent lethals was 0.03 and 0.11 in the control and 5000 ppm groups respectively.
Reliability	:	(2) valid with restrictions
05.09.2001		(52)

5.7 Carcinogenity

Species	:	mouse
Sex	:	male
Strain	:	C3H

Route of admin.	:	dermal
Exposure period	:	lifespan
Frequency of treatment	:	three times a week
Post. obs. period	:	lifespan
Doses	:	25 microliters of 25% (v/v) solution in deionized water
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	C3H mice were used in this study. They were used because of their low incidence of spontaneous skin tumors. Deionized water was selected for use as the negative control substance. On Tuesday or Thursday of each week, the fur was clipped from the back of each mouser. Mice were treated three times weekly, following a Monday, Wednesday, Friday treatment schedule (holidays excepted). A 25 microliter dose was applied using an Eppendorf automatic pipette, by spreading the aliquot up the back of each mouse with a clean disposable tip. Mice were observed daily for mortality and were carefully examined monthly for les ions of the skin. Necropsies were performed on all mice shortly after death or after sacrifice of culled and moribund animals. Necropsy included the careful examination of the skin and body cavities, and the recording of observations.
Remark	:	The results of the present study indicated that TEPA was not carcinogenic to the skin of male C3H/HeJ mice when applied as a 25% (v/v) solution in deionized water until the death of the animals.
Result	:	One skin nodule was found among the nine negative control mice treated with deionized water. Various lesions were encountered in both the TEPA-treated and the deionized water-treated mice in these sacrifice groups. A dermal mastocytoma was diagnosed in a TEPA-treated mouse. These occasionally occur spontaneously and therefore this tumor was not considered biologically important. The skin nodule found grossly in the deionized water-treated negative control group was diagnosed as a sebaceous adenoma. No skin neoplasms or nodules were found in the TEPA-treated group or in the negative control group. The TEPA-treated mice had skin lesions indicative of mild irritation, namely hyperkeratosis and necrotic debris present in the keratin. However, there was no evidence of notable epidermal hyperplasia.
Reliability	:	(2) valid with restrictions

28.06.2001 (53) (54)

5.8 Toxicity to reproduction

Type	:	other: 92-day drinking water study
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	drinking water
Exposure period	:	92 days
Frequency of treatment	:	continuous

Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
Doses	:	0, 120, 600 and 3000 ppm (0, 10, 55 and 276 mg/kg/day (males) or 0, 14, 70 and 352 mg/kg/day (females), respectively, for NIH-31 diet)
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	1996
GLP	:	no data
Test substance	:	other TS: triethylenetetramine dihydrochloride
Method	:	Rats were fed a cereal-based (NIH-31) or a purified (AIN-76A) diet. An additional control group received a Cu-deficient AIN-76A diet. Since interactions in the absorption and metabolism of Cu, Fe and Zn are known to exist, plasma levels of these three metals were determined in six rats/sex/dose group. Liver, aorta and spinal cord samples from six rats of each sex from control and high-dose groups were also analyzed for the metals. These tissues were analyzed in other dose groups if control and high-dose levels differed. Approximately 35 tissues, including reproductive organs, coagulating gland, epididymis, ovaries, seminal vesicles, testes, uterus and vagina, were examined histopathologically from the control and high dose animals. Tissues from other dose groups were examined also if lesions were clearly more prevalent in the high-dose group.
Remark	:	In animals ingesting the NIH-31 diet, the authors considered the decreased ceruloplasmin levels as not biologically important. Serum copper levels although decreased, most notably in females, were not statistically significantly decreased. Thus the effect is considered of minimal concern. Effects observed in rats fed the AIN-76A diet are considered to be related to the purified diet and not directly due to triethylenetetramine hydrochloride.
Result	:	Cu-deficient AIN-76A diet - This low copper diet resulted in Cu-deficiency symptoms, such as anemia, liver periportal cytomegaly, pancreatic atrophy and multifocal necrosis, spleen hematopoietic cell proliferation and increasted heart weight, together with undetectable levels of plasma copper. AIN-76A diet - Triethylenetetramine hydrochloride lowered plasma copper levels somewhat at 600 and 3000 ppm in rats fed the AIN-76A diet but did not induce the usual signs of copper deficiency. In males receiving 3000 ppm triethylenetetramine hydrochloride coagulative necrosis of the liver was less frequent than in copper adequate controls and was absent from all low copper controls. NIH-31 - The only effect of triethylenetetramine hydrochloride in animals fed the NIH-31 diet was a reduced ceruloplasmin level (3000 ppm, 210+26; control 293+55 mg/dl) and reduced (not statistically) liver copper levels in both rat sexes (males 3000 ppm, 0.70+0.09; control 0.73+0.04 ug/ml; females 3000 ppm, 1.00+0.11; control 1.40+0.15) at 3000 ppm. + = plus or minus
Test substance	:	Test substance is >99% pure. This is the lower molecular weight analog in the ethylenediamine series.
Reliability	:	(2) valid with restrictions
05.09.2001		(40)
Type	:	other: 92 day drinking water study
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1

Route of admin.	:	drinking water
Exposure period	:	92 days
Frequency of treatment	:	continuous
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
Doses	:	0, 120, 600 and 3000 ppm (0, 22, 107, and 487 (males) or 551 (females) mg/kg/day, respectively, for NIH -31 diet)
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	1996
GLP	:	no data
Test substance	:	other TS: triethylenetetramine dihydrochloride
Method	:	Mice were fed a cereal-based (NIH-31) or a purified (AIN-76A) diet. An additional control group received a Cu-deficient AIN-76A diet. Since interactions in the absorption and metabolism of Cu, Fe and Zn are known to exist, plasma levels of these three metals were determined in five mice/sex/dose group. Approximately 35 tissues, including reproductive organs, coagulating gland, epididymis, ovaries, seminal vesicles, testes, uterus and vagina, were examined histopathologically from the control and high dose animals. Tissues from other dose groups were examined also if lesions were clearly more prevalent in the high-dose group.
Remark	:	There were no consistent effects noted in mice fed 3000 ppm triethylenetetramine hydrochloride in the drinking water for 92 days. Effects observed in mice fed the AIN -76A diet are considered to be related to the purified diet and not directly due to triethylenetetramine hydrochloride.
Result	:	Cu-deficient AIN-76A diet - There were no effects observed. AIN-76A diet - There were no clinical symptoms observed which were attributed to test material. A male mouse from the 3000 ppm group died on day 78. Body weight gains of the 3000 ppm males were decreased. High dose males gained 25% less than controls. The mean corpuscular volume of erythrocytes of high dose males was significantly lower than controls. In addition, the percentage of eosinophils in the high dose group was significantly lower than in the controls. The male kidney was the only absolute organ weight affected in mice fed AIN -76A diet. Multifocal chronic inflammation of the lung interstitium and lung alveolar histocytic infiltration were the most prevalent histologic findings associated with triethylenetetramine hydrochloride administration. These lesions occurred in high dose male and female mice fed the AIN-76A diet and were more severe but less frequent in males than in females. Spleen hematopoietic cell proliferation and liver periportal fatty change also were most prevalent in the high dose males fed AIN-76A fed animals. Furthermore, high dose mlaes fed AIN -76A diet had a decreased prevalence of kidney cytoplasmic vacuolization (lipid content) when compared to controls. This cytoplasmic vacuolization is a normal feature of male B6C3F1 mice fed either NIH -31 or AIN-76A diet, but was suppressed by 3000 ppm triethylenetetramine hydrochloride only in those fed AIN -76AA diet. NIH-31 - Mice fed the NIH -31 diet drank more water than those fed either formulation of the purified diet. Female mice received somewhat higher daily doses than their male counterparts. There were no test material related effects observed in mice receiving up to 3000 ppm triethylenetetramine hydrochloride in the drinking water for up to 92 days.
Test substance	:	Test substance is >99% pure. This is the lower molecular weight analog in the ethylenediamine series.
Reliability	:	(2) valid with restrictions
05.09.2001		**(40)**

5.9 Developmental toxicity/teratogenicity

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	6 hrs/day on days 6 -18 of gestation.
Frequency of treatment	:	daily
Duration of test	:	6 hrs/day occlusive dermal wrap
Doses	:	0.0, 5.0, 50 or 125 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	< 5 mg/kg bw
NOAEL Teratogen	:	= 125 mg/kg bw
Method	:	other: essentially follows OECD 414
Year	:	1988
GLP	:	yes
Test substance	:	other TS: triethylenete tramine purity 95%
Method	:	Four groups of 22 mated rabbits each were administered TETA in vehicle or vehicle (distilled water) alone by occluded cutaneous application for 6 hours/day on gestation days 6-18. A 5 x 5 inch area on the middorsum between the scapulae of each rabbit was clipped and shaved 1 -2 days prior to initiation of dosing and as needed throughout the dosing period. A 2 ml aliqot of the appropriate dosing solution was drawn up into a syringe and applied to the dosing site under a 4 x 4 inch sterile gauze square. A Lycra-Spandex jacket with Velcro closures with a 5 x 5 inch polyethylene film attached (corresponding to the dosing site) was used for occlusion (jackets custom designed and sown). The rabbit's forelimbs were placed through the jacket's "armholes" and the jacket was fastened in the back by the Velcro closures. After the daily 6 hour exposure, the gauze and jacket were removed and the application site was wiped gently with sterile gauze moistened with warm water. Does were weighed on gestation days 0, 6, 12, 15, 18 and 29. Does were examined daily for clinical signs and the dosing site was examined once daily during the postdosing (gd 19-29) period and twice daily during the dosing period for any skin irritation, erythema, edema or eschar formation. Grading scheme was the Draize score of grades 0-4. On gestation day 29, approximately 3 ml of blood was drawn for subsequent analysis of serum copper content.
Remark	:	Systemic LOAEL = 125 mg/kg/day based on reduced body weight gain and mortality. Application site LOAEL = 5 mg/kg/day.
Result	:	No embryotoxic or teratogenic test material related effects at any dose. There was no effect of treatment on pre-or post-implantation loss, percentage of live fetuses or on fetal body weights/litter. There were no significant treatment- or dose-related increases in the incidence of individual or pooled fetal external, visceral, skeletal or total malformations or variations. Maternal toxicity: 125 mg/kg induced delayed weight gain (weight gain during the treatment period was 35, 11, -28 and -171g for 0, 5, 50 and 125 mg/kg/day groups, respectively) and death of 2 out of 22 rabbits. Strong local irritations of the skin at 50 and 125 mg/kg (scores of 3 for erythema and edema during GD6-18) and slight reversible irritations at 5 mg/kg (scores typically <1 during GD6-18). There were no effects on maternal organ weights, gravid uterine weight or on maternal serum or urinary copper

concentrations.

Reliability : (1) valid without restriction
04.12.2001 (55) (56)

Species	:	Rat
Sex	:	Female
Strain	:	Sprague-Dawley
Route of admin.	:	oral feed
Exposure period	:	day 0-21 of gestation
Frequency of treatment	:	daily ad libitum
Duration of test	:	
Doses	:	0, 0.17, 0.83 and 1.66% in the diet (0, 170, 830 and 1660 mg/kg/day, respectively)
Control group	:	yes, concurrent no treatment
NOAEL Maternalt.	:	= 170 mg/kg bw
NOAEL Teratogen	:	= 170 mg/kg bw
LOAEL Maternal Toxicity	:	= 830 mg/kg bw
LOAEL Teratogenicity	:	= 830 mg/kg bw
Method	:	other: essentially follows OECD 414
Year	:	1982
GLP	:	no data
Test substance	:	other TS: triethylenetetramine tetrahydrochloride
Method	:	Rats were fed throughout gestation a completely purified diet containing 0, 0.17, 0.83 or 1.67% TETA. At term, fetuses were removed, examined for visible malformations, resorptions counted, and Cu, Zn, Fe and Mn analyzed in fetal and maternal tissues.
Remark	:	Litter size unchanged. All described effects significant and dose-related. Authors comment: teratogenicity of the drun in part due to induced Cu deficiency and Zn toxicity.
Result	:	Controls (N = 7 dams): No resorbed or abnormal fetuses.

0.17% (N = 5 dams): No effects except reduced liver copper and increased kidney zinc concentration. Fetuses: 5.8% resorbed (3/52), whole fetus and liver Zn concentration elevated, Cu liver concentration reduced.

0.83% (N = 9 dams): Reduced weight gain, decreased copper concentration in liver and plasma, Zn concentration increased in kidney and muscle. Fetuses: 8.7% resorbed (7/93), 25.6% abnormalities (22/86) like hemorrhage and edema, Cu decreased in whole body, liver and placenta, Zn concentration elevated in whole body and liver.

1.66% (N = 5 dams): Reduced food consumption; highly significant reduced weight gain and copper concentration in liver and plasma. Zn concentration in kidney and muscle, manganese concentration in muscle and iron concentration in liver increased. Fetuses: 18.8% resorbed (9/48); 100% abnormalities (39/39) like hemorrages, edema, reduced ossification of caudal vertebrae and phalanges; fetal weight and length reduced. Trace elements same results as in medium dose.

Maternal Weight gain

Conc. (%)	Weight Gain (g)
0	130+/-8
0.17	131+/-10
0.83	107+/-4b
1.66	90+/-7c

Maternal Plasma Levels

Conc.(%)	copper (ug/ml)	zinc (ug/ml)
0	1.27+/-0.11	0.86+/-0.13
0.17	0.91+/-0.22	0.82+/-0.08
0.83	0.45+/-0.07[c]	0.64+/-0.06
1.66	0.06+/-0.03[c]	0.67+/-0.08

Maternal Liver Levels

Conc.(%)	copper (ug/g)	zinc (ug/g)
0	4.57+/-0.29	24.1+/-0.9
0.17	3.62+/-0.16[b]	23.1+/-0.8
0.83	3.35+/-0.23[b]	26.5+/-0.7
1.66	1.75+/-0.10[c]	26.5+/-0.4

Fetal Levels

Conc.(%)	copper (ug/g)	zinc (ug/g)
0	1.40+/-0.07	15.5+/-0.6
0.17	1.50+/-0.20	23.7+/-1.4[c]
0.83	0.60+/-0.08	33.3+/-1.4[c]
1.66	0.21+/-0.04	37.2+/-1.2[c]

[b] P<0.01 compared to control
[c] P<0.001 compared to control

Reliability : (2) valid with restrictions
04.12.2001 (57) (58) (59)

Species : Rat
Sex : Female
Strain : Sprague-Dawley
Route of admin. : oral feed
Exposure period : day 0-21 of gestation
Frequency of treatment : daily ad libitum
Duration of test :
Doses : 0, 0.83 and 1.67% in diet combined with 0.05 or 0.5 mg Cu/kg diet.
Control group : Yes
Method : other: essentially follows OECD 414 except 4 rats/group
Year : 1983
GLP : no data
Test substance : other TS: triethylenetetramine purity >99%
Remark : Litter size not altered by test substance of Cu administration.

Authors comment: teratogenicity of the test substance in part due to induced Cu deficiency. Doses used here correspond to 830 or 1670 mg/kg/day.

Result : Maternal weight gain and fetal weight and length were significantly decreased at 1.67% without improvement by copper supplement.

Frequency of resorption not different in any group. Significant incidence of fetal abnormalities (69%, 27 out of 39 fetuses) due to 1.67% in combination with the low Cu concentration was lowered to 6.5% (3/46) by high Cu concentration. Types of abnormalities: hemorrhage, edema, hydronephrotic kidneys, micrognathia and domed skulls. The lowered teratogenic effect of 1.67% was correlated with an increase in maternal and fetal tissue copper levels by Cu supplement. Increased maternal and fetal zinc levels due to the test substance were not altered by Cu coadministration.

Reliability : (2) valid with restrictions
28.06.2001 (60) (61) (62)

Species : Rat
Sex : Female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : day 6-15 of gestation
Frequency of treatment : once daily
Duration of test :
Doses : 0, 75, 325 and 750 mg/kg/day
Control group : yes, concurrent vehicle
Method : other: essentially follows OECD 414
Year : 1984
GLP : no data
Test substance : other TS: triethylenetetramine purity >98%
Method : Test substance was diluted in water.
Remark : No further information available.
Result : No substance related effects on dams or fetuses, except increased fetal body weight at 750 mg/kg (no data about significance).
Reliability : (4) not assignable
27.07.2001 (63)

Species : Mouse
Sex : Female
Strain : C3H
Route of admin. : drinking water
Exposure period : Gestation day 0-19.
Frequency of treatment : daily ad libitum
Duration of test :
Doses : 0, 3000, 6000 or 12,000 ppm in drinking water.
Control group : yes, concurrent vehicle
Method :
Year : 1993
GLP : no data
Test substance : other TS: triethylenetetramine-HCl 98.6% pure
Method : Pregnant mice were divided into four treatment groups with 6-14 dams/group. Pregnant dams received 0, 3000, 6000 or 12,000 ppm (correspond to 0, 500, 1000 or 2000 mg/kg/day, respectively, according to Tanaka et al., 1992)) triethylenetetramine in the drinking water. Pregnancies were terminated on gestational day 19 at 10:00 by cesarean section after chloroform anesthesia. The uterus was examined intact and then cut open. The number of resorbed sites, live and dead fetuses was counted. Live fetuses were examined for body weight and gross external abnormalities especially in head. One hour after cesarean section the live fetus was subjected to tissue removing and weighing. Stillborn fetus and dead fetus after birth were immersed in buffered neutral formalin solution. Statistical analysis used Student's t-test and chi-square test.
Remark : In the Tanaka et al., 1992 study, 7 of 15 mice in the 12,000 ppm group were pregnant. This effect was not observed in this study but does suggest the dose level is at or near a maternally toxic dose.

The authors suggest that these effects which are similar to ones observed in brindled mutant mice are due to a copper deficiency.

Result : Litter size was comparable between control and high dose groups with 7.3 (SD=1.2) and 7.3 (SD=1.7) pups/litter, respectively. A slight decrease in the number of live fetuses was observed at 12,000 ppm (0, 3000, 6000 and 12,000 ppm had 5.6 (SD=2.2), 5.3 (SD=2.1), 5.4 (SD=2.2) and 5.1 (SD=2.2), respectively).

The percentage of fetuses with grossly visible abnormal brains was 2.5, 12.5, 27.1 and 48.8% in the 0, 3000, 6000 or 12,000 ppm groups, respectively. Grossly visible effects included hemorhages, delayed ossification in cranium, hydrocephaly, exencephaly and microcephaly. As hemorrhages increased dose-dependently, massive or multiple hemorrhages in external and internal brain were defined. The ossification of cranium appeared to be reduced in a dose-dependent manner, and at the 12,000 ppm soft and very thin cranial bone was observed. As microcephaly, clearly small to almost no cerebral mass was defined. On these criteria of abnormalities, hydrocephaly was observed at the dose of 6000 ppm and above, and then exencephaly and microcephaly were clearly observed at the dose of 12,000 ppm. Thus, the number of live fetuses with these abnormal brain characteristics and the number of brain abnormalities per live fetus increased dose-dependently in the three treated groups as compared with controls.

Reliability : (2) valid with restrictions
10.01.2002 (64)

Species : Mouse
Sex : Female
Strain : C3H
Route of admin. : drinking water
Exposure period : Gestation day 0-19.
Frequency of treatment : daily ad libitum
Duration of test :
Doses : 0, 6000 or 12,000 ppm in drinking water.
Control group : yes, concurrent vehicle
Method :
Year : 1993
GLP : no data
Test substance : other TS: triethylenetetramine-HCl 98.6% pure
Method : Based on data presented in this report, the pregnant mice were divided into three treatment groups of 0, 6000 or 12000 ppm (corresponds to 0, 1000 or 2000 mg/kg/day, respectively, according to Tanaka et al., 1992) for purposes of microscopic observation. The experimental procedures for pregnant dams and offspring were the same as presented previously in this report, except for the following point; 1 hour after cesarean section two or three live fetuses per dam were randomly selected and removed heads or brains were immersed in the above phosphate-buffered formalin.

All fetal brains were fixed in the same fixative for at least 2 weeks. After the brain was immersed in fresh fixative, it was sectioned and stained with hematoxylin and eosin or double stained with luxol fast flue and cresyl violet.

Result : When compared to controls, spongiform changes increased dose-dependently, in regard to extent and severity. Microscopic findings revealed an increase in spongiform changes, structural dysorganization of neuronal cell layers and reduced development of myelination in a dose-related manner.

Reliability : (2) valid with restrictions
10.01.2002 (64)

Species	:	Mouse
Sex	:	Female
Strain	:	C3H
Route of admin.	:	drinking water
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	0, 3000, 6000 or 12,000 ppm in drinking water
Control group	:	
Method	:	Pregnant mice were given tap water containing 0, 3000, 6000 or 12,000 ppm TETA-2HCl (corresponds to 0, 500, 1000 or 2000 mg/kg/day) on days 0-19 of gestation. Body weights were recorded on gestation 19. Maternal blood samples were collected by cardiac puncture. Offspring were examined for body weight, litter size, gross abnormalities and fetal viability. One hour after cesarean section the live fetus was subjected to tissue weight determination and biochemical or morphological analysis. Cerebral weight was obtained by weighing brain excluding the cerebellum and the lower brain stem. Copper, zinc and magnesium were measured by atomic absorption spectrometry.
Remark	:	This study did not follow current guidelines with respect to sample size and current morphology practices. Maternal toxicity was noted at the highest concentration with decreased maternal body weight and increased number of litters totally resorbed. Fetal toxicity, demonstrated by decreased body weight, was noted at 6000 and 12,000 ppm. In addition, fetal liver and cerebrum copper levels were decreased at all three concentrations. At the lowest concentration, brain effects were less severe than observed at higher concentrations. While a No-Observable-Effect-Level was not determined in this study, there appears to be a good correlation between copper levels and brain effects. Thus, it is very likely as Keen and Hawk have demonstrated in the rat and Tanaka suggests in this report, that copper supplementation would reduce the effects observed in the mouse.
Result	:	The percentage of dams with fetus/pregnant dams and the fetal viability were decreased at 12,000 ppm (Table 1). Dam body weights were significantly decreased at 12,000 ppm (Table 2). Fetal body weights were significantly decreased at 6000 and 12,000 ppm (Table 3). Copper concentration in fetal liver and cerebrum tissue b ut not maternal serum was decreased (Table 4). Zinc concentrations followed a similar tendency as copper, however, zinc cerebrum levels were unaffected (Table 5). Magnesium levels were reportedly unaffected. Brain abnormalities in live fetuses were as follows (number of fetuses with abnormality/number of fetuses observed): 1.3% (1.79) in the 0 ppm group, 6.3% (2/32) in the 3000 ppm group, 8.5% (5/59) in the 6000 ppm group and 39.0% (16/41) in the 12,000 ppm group. Hemorrhages and delayed ossification were observed at the dose of 3000 ppm and above, microcephaly and hydrocephaly were observed at the dose of 6000 ppm and above and exencephaly was clearly observed at the dose of 12,000 ppm. The authors conclude that the effects observed in the cerebrum may be explained in part by copper depletion alone.

Table 1
Total resorption, litter size and fetal viability

Repro parameter	Triethylenetetramine-2HCL (ppm) 0	3000	6000	12000
# dams with fetus/pregnant dams	13/13	6/6	10/11	7/15
Total offspring/dam	6.4+/-1.3	6.0+/-1.5	6.1+/-1.9	5.7+/-1.6
Fetal viability (%)	94+/-10	94+/-9	92+/-13	76+/-24

Table 2
Maternal body, liver and placenta weights

parameter	Triethylenetetramine-2HCL (ppm) 0	3000	6000	12000
Number dams	13	6	10	7
Body (g)	35.5+/-3.4	34.4+/-2.6	34.6+/-2.6	31.3+/-2.9a
Liver (g)	1.73+/-0.23	1.66+/-0.10	1.65+/-0.15	1.61+/-0.16
Placenta (mg)	87+/-6	97+/-9	89+/-9	82+/-4

Table 3
Fetal body, liver and cererbrum weights

parameter	Triethylenetetramine-2HCL (ppm) 0	3000	6000	12000
Number dams	13	6	10	7
Body (g)	1.28+/-0.10	1.24+/-0.10	1.17+/-0.07[a]	1.08+/-0.07[a]
Liver (mg)	70+/-10	70+/-8	67+/-7	61+/-7
Cerebrum (mg)	56+/-3	53+/-3	52+/-2	48+/-2[a]

Table 4
Copper concentrations in maternal and fetal tissues

parameter	Triethylenetetramine-2HCL (ppm) 0	3000	6000	12000
Number dams	5	6	6	3
Mat serum	0.92+/-0.18	0.96+/-0.11	1.01+/-0.07	1.08+/-0.15
Number dams	10	5	6	7
Fet liver	89.0+/-17.6	54.0+/-7.7[a]	50.3+/-7.5[a]	33.5+/-9.4
Fet cerebrum	5.27+/-0.47	4.44+/-0.42[a]	4.03+/-0.47[a]	3.30+/-0.30[a]

[a] - Significantly different from control value, alpha =0.05.

Table 5
Copper and zinc levels in maternal and fetal tissues

parameter	Triethylenetetramine-2HCL (ppm) 0	12000
Copper levels (ug/g)		
Maternal liver	14.0+/-0.9	13.1+/-1.1
Placenta	11.9+/-3.2	7.2+/-0.8[a]
Fetal liver	88.1+/-18.1	31.5+/-14.1[a]
Fetal cerebrum	5.08+/-0.38	3.29+/-0.53[a]
Zinc levels (ug/g)		
Maternal liver	123+/-5	125+/-4
Placenta	122+/-8	107+/-4[a]
Fetal liver	140+/-20	265+/-62[a]
Fetal cerebrum	104+/-3	104+/-5

[a]- Significantly different from control value, P<0.01.

Reliability : (2) valid with restrictions
10.01.2002 (65)

Species : other: chicken
Sex :
Strain : other: White Leghorn
Route of admin. : other
Exposure period : once in 3 day old embryos
Frequency of treatment :
Duration of test :
Doses : 0.051, 0.102, 0.204 or 0.408 mg/egg
Control group : yes, concurrent vehicle
Method : other: injection on the inner shell membrane
Year : 1983
GLP : no data
Test substance : other TS: technical grade triethylenetetramine
Remark : This test is considered to be not relevant for purposes of assessing developmental toxicity.
Result :

Dose	Embryo deaths	Malformed survivors
0.051 mg	1/30	2/29
0.102 mg	3/30	3/27
0.204	10/30	4/20
0.408	20/20	----
acetone	1/100	0/100

Malformations occurred in the eyes, wings and abdominal wall. Edema, enlarged lymph sacs and stunting and twisting of the backbone. ED50 for embryotoxicity: 0.155 mg/egg.

Reliability : (3) invalid
27.07.2001 (66)

Species : rat
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Method : Rat embryos (gestation days 9.0 and 10.0) obtained from dams that were

fed a Cu-adequate (8 ug Cu/g) or Cu-deficient (<0.5 ug Cu/g) diet were cultured for 48 hr in Cu-adequate (16.2 uM or Cu-deficient (1.0 uM) rat serum.

To test the idea that abnormalities were due in part to free radical induced damage occurring secondary to an impaired oxidant defense system, a chemiluminescence assay was used to detect superoxide dismutase activity in the cultured embryos.

Remark : While this copper deficient in-vitro study demonstrated effects that were not observed in the in vivo study with TEPA, the limited data available suggests that under copper deficient conditions in the rat effects similar to that reported by Tanaka et al., in the mouse can be observed.

Result : Control embryos cultured in control serum were morphologically normal. Embryos from Cu-deficient dams developed abnormally when culturedin Cu-deficient serum; The abnormalities distended hindbrains, blisters, blood pooling and cardiac defects. Control embryos cultured in Cu-deficient serum and Cu-deficient embryos cultured in control serum also showed abnormal development, but to a lesser degree than that of the Cu-defficient embryos cultured in Cu-deficient serum.

To test the idea that the above abnormalities were due in part to free radical-induced damage occurring secondary to an impaired oxidant defense system, superoxide dismutase (SOD) activity was measured in the cultured embryos. SOD activity was lowest in embryos cultured in CU-deficient serum. When the Cu-deficient serum was supplemented with antioxidants (CuZnSOD or glutathione peroxidase), its teratogenicity was reduced. These data support the idea that an impaired oxidant defense system contributes to the dysmorphology associated with Cu deficiency. However, the Cu-deficient embryos also had low cytochrome c oxidase activity compared to control values - thus, multiple factors are likely contributing to Cu deficiency-induced abnormalities.

Reliability : (2) valid with restrictions
06.12.2001 (67)

5.10 Other relevant information

Type : other: developmental toxicity
01.02.2002 (68) (69)

Type : other: developmental toxicity
05.02.2002 (70) (71)

5.11 Experience with human exposure

Memo : Human Patch Test

Remark : The test substance was applied via patch test in a concentration (we think) of 1%. The patient was patch tested with a series of epoxy resin compounds.

Result : On day three, it was noticed as a weak sensitizer. By day four, it gave a + reaction on a +++ grade basis. Brominated DGEBA epoxy resin, which contains DGEBA-ER, and several epoxy resing hardeners gave positive reactions. It was concluded that the patient had become sensitized to DGEBA-ER, several amine hardeners (possibly cross-reacting) and Cl+Me-isothiazolinone, which had probably been used in

water-based pints as a preservative. Among the rubber additives, IPPD, but no other amines or other chemicals, gave a + reaction.

Reliability : (3) invalid
28.06.2001 (72)

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