FOREWORD INTRODUCTION

TRIETHYLENE TETRAMINE

CAS N°: 112-24-3

SIDS Initial Assessment Report for SIAM 8

(Paris, 28-30 October 1998)

Chemical Name : Triethylenetetramine

CAS No: 112-24-3

Sponsor Country: Germany

National SIDS Contact Point in Sponsor Country: Dr Jan Ahlers

HISTORY:

The SIDS Initial Assessment Report was discussed at SIAM 5 & 6 and adopted at SIAM 8.

COMMENTS:

Date of Circulation: July 1998

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-24-3
Chemical Name	Triethylene tetramine
Structural Formula	$H_2N\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH_2$

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is toxic to algae, but PEC/PNEC ratios are lower than 1. It is currently considered of low potential risk and low priority for further work.

Human Health

The chemical is genotoxic *in vitro*, a severe irritant to skin and eyes and a skin sensitiser, but exposure is low and well-controlled. Therefore, it is currently considered of low potential risk and low priority for further work. However due to its hazard character appropriate classification and labelling are recommended.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of triethylenetetramine (TETA) in 1990 is 1200-1500 t/a in Germany, ca. 6000 t/a in the Netherlands, >11000 t/a in the USA and ca. 1800 t/a in Japan. TETA is mostly used as intermediate in chemical synthesis. Ca. 160 t/a are directly used as curing agent for epoxy resins in Germany. For Sweden, a similar use pattern was described. TETA is stable in neutral solution and is classified as "non biodegradable". The most sensitive environmental species to TETA is the alga *Scenedesmus subspicatus* (72h-EC10 = 0.67 mg/l). A PNEC of 13.4 µg/l is determined.

TETA has a moderate acute toxicity: LD50 (oral, rat) > 2000 mg/kg bw, LD50 (dermal, rabbit) = 550-805 mg/kg bw. The NOAEL for repeated dose toxicity is 600 ppm (92 (male), 99 (female) mg/kg bw) for mice (oral, 90 days). In *in vitro* tests the substance showed genetic toxicity whereas in *in vivo* test negative results were found. There are no animal data on reproductive toxicity available. From experience with humans TETA reveals no effects on reproduction. TETA is a severe irritant to skin and eyes. TETA induces skin sensitisation in guinea pigs, mice and man.

The highest aquatic local PEC during processing as an intermediate was estimated to be 4.5 µg/l.

The estimated human exposure at the workplace is estimated at < 0.143 resp. < 0.0143 mg/kg bw. Data on consumer exposure are not available.

NATURE OF FURTHER WORK RECOMMENDED

Appropriate classification and labelling are recommended.

FULL SIDS SUMMARY

CAS-NO.: 112-24-3			PROTOCOL	RESULTS
PHYSICAL CHEMICAL				
2.1	Melting-Point		NA	12 °C
2.2	Boiling-Point		NA	ca. 280°C (at kPa)
2.3	Density		NA	ca. 980 kg/m^3
2.4	Vapour Pressure		NA	1.3 Pa at 20°C
2.5	Partition Coefficient (Log Pow)		(calc.)	- 1.4
2.6 A	Water solubility		NA	completely miscible
B	pH		NA	10.7. at 10 g/l
	pKa		20 °C	pKa1 = 3.32 pKa2 = 6.67 pKa3 =9.2 pKa4 = 9.92
2.12	Oxidation : Reduction potential		/	mV
ENVIRONMENTAL FATE / BIODEGRADATION				
3.1.1	Photodegradation		calc. (Atkinson)	In air $T_{1/2}$ = 1.7 hour
3.1.2	Stability in water		NA	no hydrolysis
3.2	Monitoring data			In air = / mg/m^3 In surface water= /µg/l In soil / sediment= /µg/g In biota= / µg/g
3.3	Transport and Distribution		calculated (fugacity level 1 type)	In air / % In water / % In sediment / % In soil / % In biota / %
3.5	Biodegradation		OECD 301 D	not readily biodegradable
			OECD 302 B	not inherently biodegradable

CAS-NO.:112-24-3		SPECIES	PROTOCOL	RESULTS
ECOTOXICOLOGY				
4.1	acute/prolonged toxicity to fish	Poecilia reticulata	84/449/EEC, C.1	LC_{50} (96 hr) =570mg/l
4.2	acute/prolonged toxicity to aquatic invertebrates (daphnia)	Daphnia magna	84/449/EEC, C.2	EC_{50} (24hr) =31.1mg/l
4.3	toxicity to aquatic plants e. g. algae	Scenedesmus subspicatus	DIN 38412 part 9	EC_{50} (72hr) =2.5mg/l EC_{10} (72hr) =0.67mg/l
4.4	toxicity to microorganisms	Pseudomonas fluorescens	DEV, L 8	EC_0 (24 hr) =500mg/l
4.5.2	chronic toxicity to aquatic invertebrates (daphnia)	Daphnia magna	OECD 202 part 2	NOEC (21d) =1mg/l
(4.6.3)	toxicity to other non mammalian terrestrial species (including birds)	Agelaius phoeniceus	NA	LD_{50} (18hr) => 101mg/kg
TOXICOLOGY				
5.1.1	acute oral toxicity	rat mouse rabbit	NA NA NA	LD_{50} =2500 mg/kg LD_{50} =1600 mg/kg LD_{50} =5500 mg/kg
5.1.2	acute inhalation toxicity			LC_{50} =mg/m^3
5.1.3	acute dermal toxicity	rabbit	NA	LD_{50} =550 mg/kg
5.4	repeated dose toxicity	mouse	NA	NOAEL =92mg/kg bw
5.5	genetic toxicity in vitro			
	bacterial test (gen mutation)	S. typhimurium	Ames test	positive (with and witout metabolic activation)
	non-bacterial in vitro test (chromosomal abberations)	CHO cells		positive (with and witout metabolic activation)
5.6	genetic toxicity in vivo	mouse	Micronucleus assay	negative
5.8	toxicity to reproduction			NOEL =mg/kg (general toxicity) NOEL =mg/Kg (rep. tox. parental) NOEL =mg/Kg (rep. tox. F1)
5.9	developmental toxicity / teratogenicity			NOEL =750mg/kg (general toxicity) NOEL =750mg/Kg (pregnancy/litter) NOEL =750mg/Kg (foetal data)
5.11	experience with human exposure			

SIDS Initial Assessment Report

1.Identity

Name: Triethylenetetramine (TETA)

CAS Nr.: 112-24-3

Empirical Formula: $C_6H_{18}N_4$

Structural Formula: $H_2N\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Purity of industrial product: 60 - 70 %

Major impurities:

N,N'-Bis-(2-aminoethyl)piperazine	11 - 13 %
N-[1-(2-Piperazin-1-yl-ethyl)]-ethane-1,2-diamine	10 - 13 %
Tris-(2-aminoethyl)-amine	4 - 6 %
Diethylenetriamine	<= 3 %
Water	<=0.5 %

2. Exposure

2.1 General discussion

Triethylenetetramine is produced by the reaction of aqueous ammonia with 1,2-dichloroethane. This process yields the entire family of ethyleneamines: ethylenediamine, piperazine, diethylenetriamine, triethylenetetramine, tetraethylenepentamine, pentaethylenehexamine and aminoethylpiperazine. These polyamines are produced as their hydrochloride salts, and must be neutralized, typically with aqueous caustic soda, to obtain the free amines. The by-product salt produced in the neutralisation step is separated and the individual products are isolated by fractional distillation (8).

TETA can be used as an intermediate in a number of production processes (10):

- The reaction with polyisobutenylsuccinic anhydride yields the corresponding polybutenylsuccinimides, which are ashless, dispersant-detergent additives for motor oil.
- Polyamide-epichlorohydrin resins are produced by the reaction of epichlorohydrin with a polyamide, such as those formed by polymerisation of adipic acid and TETA. These are used in the paper industry as wet-strength additives for liner board, toweling, tissue and sanitary applications.
- The ethoxylated products of TETA are curing agents for epoxy resins. The largest application is surface coatings (35%).
- Imidazolines from the condensation of TETA with two moles of fatty acid are cationic surfactants used as fabric softeners, asphalt emulsifiers, oil field corrosion inhibitors, ore flotation agents and epoxy curing agents.
- Reactive polyamides from the polymerisation of dimer acids with TETA are mostly used as curing agents for epoxy surface coatings.

In 1989 - 1991, 1200 - 1500 t/a were produced in Germany. Production capacities as of 1990 for other countries are available as well (8):

Netherlands	ca. 6000 t/a	(2 sites)
USA	> 11000 t/a	(3 sites)
Japan	ca. 1800 t/a	(1 site)

According to the German producer, ca. 40 to 50% are sold in Germany (> 10 clients) and ca. 40 - 50 % are exported; the rest is further processed by the same producer. Import volumes are estimated by the producer at ca. 1500 t/a. The total consumption in Germany amounts to ca. 2200 t/a.

In Germany, triethylenetetramine (TETA) is mainly used as

- intermediate for curing agents for epoxy resins (ca.1600 t/a)
- direct curing agent for epoxy resins (ca. 160 t/a)
- intermediary for auxiliary agents used in the paper industry, the textile industry and in glues (ca. 330 t/a)
- intermediate for asphalt emulsifiers (ca. 110 t/a)

Ca. 100 t/a are used by the producer as an intermediate. No information is available on the processing at other chemical manufacturers.

In Sweden, the use pattern of TETA is similar to the use pattern described for Germany:

- intermediate for transport, fertilizer and plastics industry (200 - 533 t/a)
- adhesive, binding agent (4 - 6 t/a)
- hardener for plastic (1 - 4 t/a)
- others (max 5 t/a)

The use pattern for other countries is not available.

2.2 Environmental exposure

2.2.1 General/Environmental fate

TETA is completely miscible with water forming an alkaline solution (pH 10 at 10 g/l). The technical product has a vapour pressure of ca. 1 Pa at 20 °C. The calculated Log Pow (unprotonated form) amounts to ca. -1.4 and indicates a low potential for bioaccumulation. There are no measured Koc-values available. For ethylenediamine (CAS Nr. 107-15-3) and diethylenetriamine (CAS Nr. 111-40-0), Koc-values of 4766 and 19111 were measured respectively (1). The high adsorption is most likely due to electrostatic interaction. A comparable Koc can be expected for TETA, which would suggest a high potential for geoaccumulation.

Based on the physical-chemical properties the target compartment of TETA in the environment is the hydrosphere (the estimation of the distribution with a Fugacity model is not opportune due to the protophile behaviour of TETA).

TETA is not readily biodegradable (0% after 20 days, OECD GL 301 D; same result with adapted inoculum). Also, in a test on inherent biodegradability with industrial sludge, TETA was not degraded (0 % DOC removal after 28 days, OECD GL 302 B). TETA has therefore to be regarded as **non biodegradable.** Adsorption onto sewage sludge was not observed.

In a test on hydrolysis, TETA was not found to have undergone hydrolysis after 36 days.

Direct photolysis of TETA in the hydrosphere is not to be expected (molar extinction coefficient < 10 l / (mol·cm) at > 240 nm). The half-life due to photooxidative degradation by OH-radicals in the atmosphere is estimated to be 1.7 hours. As TETA does have a low tendency to pass from water to air, this does not represent a significant removal process from the environment.

Based upon the physical-chemical and biodegradation properties of TETA, no elimination in waste water treatment plants is assumed.

2.2.2 Exposure assessment

a) Local concentrations

Considering the above described use pattern, point releases are to be expected during production and processing.

production

According to the German producer, no continuous releases occur during the production process to waste water. During cleaning operations of the production facility and the distillation column, the releases are estimated by the German producer at ca. 1 g/t related to the production capacity (8). For a production capacity of 5000 t/a (worst case assumption) a release of 5000 g TETA during one day (assuming one cleaning operation per year) can be estimated. Assuming no elimination in the WWTP, 5000 g are released into a river with a flow of 60 m^3/s, according to the generic release scenario for production in (3). A **PEC_{local} of 1 µg/l** is calculated.

processing

Many processes involving TETA as intermediate with different release rates are to be expected.
Specific data are available only from one German producer, using ca. 100 t TETA per year for processing with fatty acids: a maximum of 2.4 kg/a are released to the waste water (8).

For a generic estimation, the following worst case situation according to the release scenario for intermediates described in (3) is used.
For a processing site using 1000 t/a of TETA, a release factor of 0.7 % is assumed. Considering no elimination in the WWTP, 7 t/a are released into a river with a flow of 60 m^3/s. Assuming release over 300 days per year, a concentration of **PEC_{local} = 4.5 µg/l** is calculated.

b. Regional concentrations

Diffuse release into the environment would occur through the direct use of TETA as a curing agent. Also, the curing agents produced from TETA contain residual concentrations of TETA (approx. 7.9%).
The final extent of conversion of TETA during curing reactions is not known. On the other hand, the conversion of diethylenetriamine was determined to be 60 to 80 % (2) (related to the total NH-functions). As TETA presents 6 NH-functions, a molecular conversion rate of > 90% can be assumed.

About 160 t/a of TETA are used directly as curing agent. With a conversion factor of 90%, ca. 16 t are available as free molecules in the resins. On the worst case assumption , that 10% are released through migration from the matrix (3), a maximum of 1.6 t/a are released into the environment through this path.

About 1600 t/a are processed to yield curing agents containing an average of 7.9% free TETA. For a rough estimate, it is assumed that TETA reacts with the same amount of chemicals so that 3200 t of curing agents with ca. 250 t of free TETA result. Of these, max. 10% (see above) remain unreacted in the curing process and 10 % of these may be released through migration, i.e. a maximum of 2.5 t/a.

For the calculation of the regional PEC the use of a fugacity model is not opportune due to the ionic nature of TETA. The regional concentration can be estimated in a first approach with the following formula (9):

$$PEC_{regional} = \frac{EMIS}{FLOW + V \cdot k}$$

with: EMIS: emission into surface water = 1.6 + 2.5 = 4.1 t/a
FLOW: flow through the water compartment
V: Volume of water compartment
k: first order biodegradation rate constant

The default values described in (3) will be used for the calculation:
- a small but densely populated area is considered: 200x200 km with 20 million inhabitants;
- with an area fraction of water of 0.02 and a mixing depth of 3 m, V = $2.4 \cdot 10^9$ m^3
- with an average residence time of the water of 40 days, FLOW = $6 \cdot 10^7$ m^3/d
- TETA being non-biodegradable, k = 0

=> **$PEC_{regional}$ = 0.18 µg/l**

2.3 Consumer exposure

Where epoxy resins are cured in do-it-yourself applications (e.g. in coatings, adhesives, and epoxy-fiber composites), consumers may come into contact with TETA or TETA-derived curing agents, either when mixing the ingredients, or when grinding and polishing the solidified product whereby unreacted TETA may be set free.

2.4 Occupational exposure

The production unit simultaneously produces ethylenediamine, diethylenetriamine, triethylenetetramine and other substances from ammonia and 1,2-dichloroethane.

To date, exposure to triethylenetretamine (TETA) has not been measured directly. Instead, exposure is estimated on the basis of measurements of ethylenediamine (according to TRGS 402) - the end product with the lowest boiling point.

The MAK-value of 25 mg/m^3 for ethylenediamine is consistently met. All measurements indicate that exposure is below 1 mg/m^3.

Substance	Boiling Point	Vapour Pressure
Ethylenediamine	116.5 °C	12.1 hPa
TETA	approx. 280 °C	< 0.1 hPa

Due to ethylenediamine´s significantly lower boiling point and its greater vapour pressure (by a factor of 100) it can be concluded with certainty that the concentration of TETA in the air during synthesis and processing does not exceed 0.1 mg/m^3.

Exposure is, therefore, clearly below the actual occupational exposure limit of 6 mg/m^3 in Sweden.

3. Toxicity

3.1 Human Toxicity

a) Acute Toxicity

Triethylene tetramine is of low acute toxicity on oral administration (LD_{50} rat > 2000 mg/lkg bw) and moderate toxicity on dermal application (LD_{50} rabbit 550-805 mg/kg bw). Exposition to saturated vapour was tolerated without impairment whereas the exposition to aerosol leads to reversible irritations of the mucous membranes in the respiratory tract. According to EC Directive 67/584/EEC triethylene tetramine is labelled as harmful in contact with skin (R 21).

Conclusion:
Moderate acute toxicity
Priority setting: low priority or concern

b) Repeated Dose Toxicity

In a subacute study (rat, oral, up to 2980 mg/kg bw) retarded body weight gain and elevated liver and kidney weights were observed in the highest dose groups. From this study, a NOAEL of 500 mg/kg was derived.

In a subacute study, undiluted test substance was rubbed into the skin of pregnant and non-pregnant guinea pigs (4 mg/guinea pig and day = ca. 9 mg/kg bw) daily for 55 days. In the course of the experiment the death of test animals (2/9) as well as of the control animals (6/11) occurred (11). In another study, dermal application to pregnant and non-pregnant guinea pigs (4 mg/animal = ca. 9 mg/kg bw) daily for the first 10 days and every second day for next 45 days resulted in reduced weight gain, and from the 5th day of treatment in inflammatory alterations at the application site with subsequent erosions. In the course of the experiment 7/11 pregnant and 7/11 non-pregnant animals died (12). It is unclear whether the death of the animals is due to the strong irritant and/or the skin sensitization potential of the test substance.

In an additional study F344 rats and B6C3F1 mice received triethylenetetramine dihydrochloride in the drinking water at concentrations of 0, 120, 600, 3000 ppm (target concentration) for up to 92 days. Each dose group were fed either cereal based (NIH-31) or purified (AIN-76A) diet both containing nutritionally adequate levels of copper. An additional control group of rats and mice received a Cu-deficient AIN-76A diet. Sign of triethylenetetramine dihydrochloride toxicity were noted only in B6C3F1 mice fed AIN-76A diet given 3000 ppm triethylenetetramine dihydrochloride. These toxic signs included inflamation of the lung interstitium, hemapoetic cell proliferation of the spleen, liver periportal fatty infiltration, kidney weight reduction, reduced renal cytoplasmatic vacuolization and body weight gain reduction. From this study a NOAEL of 600 ppm for mice was derived. According to the authors, the signs observed in F344 rats appear to be related to copper deficiency (13).

Lifelong dermal application to mice (1.2 mg/mouse and application) caused no skin tumours or any tumours.

In a former inhalation study with rats, mice, guinea pig and rabbit (aerosol: 0.4 ml in 0.5 ml ethanol in a 400 l chamber, 10 d), no irritations or other toxic effects were observed.

Conclusion:
Signs of impairment only in mice following subchronic oral dosing of 3000 ppm triethylenetetramine dihydrochloride. NOAEL: 600 ppm [92 (male), 99 (female) mg/kg bw].
Priority setting low priority or concern

c) Reproductive/Developmental Toxicity

In rabbits, triethylene tetramine does not cause embryotoxic and teratogenic effects, even at maternally toxic dose levels (4).
In rats, there are several studies concerning developmental toxicity. The oral treatment of rats with 75, 375 and 750 mg/kg resulted in no effects on dams and fetuses, except slight increased fetal body weight (5). After oral treatment of rats with 830 or 1670 mg/kg bw only in the highest dose group increased fetal abnormalities in 27/44 fetus (69,2 %) were recorded, when simultanously the copper content of the feed was reduced. Copper-supplementation in the feed reduced significant the fetal abnormalities of the highest dose group to 3/51 (6,5 % fetus. These findings suggest that the developmental toxicity is produced as a secondary consequence of the chelating properties of triethylene tetramine (6).
In chapter 3.1.b) 2 studies on pregnant guinea pigs dermally treated with 4 mg/animal = ca. 9 mg/kg bw daily for 55 days or daily for 10 days and every second day for the next 45 days, respectively, were described (11, 12). Beside the clear mortality rate and the local effects, necrotic changes of the placenta and miscarriage or mortification of the fetuses and stillbirth of malformed fetuses were observed. Due to the clear maternal toxicity and due to the lack of dose-response relationship the reported studies are not suitable to evaluate developmental toxicity.

There are no data on effects on fertility with triethylene tetramine .In the subchronic toxicity studies with mice and rats, which were described in chapter 3.1.b, the reproductive organs are examined. In mice, there were no treatment related effects on the reproductive organs. According to the authors the only finding which may be attributable to trien-2HCl occured in AIN-76A-fed females rats. There was a significant dose-related trend toward an increased prevalence of uterine dilatation (13). There are no changes of the vagina and the ovaries. Therefore dilatation of uterus in isolation cannot be regarded as hormonal effects. Thus, this finding is not suitable to evaluate any reproductive toxicity. In addition, oral treatment of rats with the analogue diethylene triamine caused no adverse effects respective mating index, fertility index and number of live and dead pups.

Triethylene tetramine is used in the therapy of Wilsons' disease. While taking 400 to 800 mg triethylene tetramine 3 times a day for about 120 months, there have been six pregnancies in four female patients. There were no miscarriages and no fetal abnormalities. All six children developed normally (7).

Conclusion:
From experiences with humans (substance given as a drug) there is no reason to assume that the substance reveals effects on reproduction.

Priority setting: low priority or concern

d) Genetic Toxicity

The results of the genetic toxicity testing are not uniform. In vitro, triethylene tetramine has clear genotoxic activity in the Ames-test and in mammalian cytogenetic tests. Whereas in vivo, triethylene tetramine is not clastogenic in the mouse micronucleus test following intraperitonal injections of 130 to 600 mg/kg bw. The study was conducted in accordance with GLP standards. In addition, there is a further micronucleus test using oral application (14) which yielded a negative result as well. In this study, mice received once 1500, 3000 and 6000 mg/kg bw. These doses are within the range of and/or greater than the LD50 value for mice, which is cited in the basic data set: LD50(mice) = 1600 mg/kg bw (15). The test design and test performance was carried out according to W. Schmid and coworkers who developed the test (see references).
Following 1500 and 3000 mg/kg bw the percentage of erythrocytes containing micronuclei corresponds with the percentage of those in the concurrent solvent control. Following 6000 mg/kg bw a decrease in erythrocytes containing micronuclei was noted and was thus lower than those in the concurrent solvent control.
Triethylene tetramine revealed no mutagenic activity in the SLRL test in Drosophila melanogaster.

Conclusion:
As triethylene tetramine revealed no mutagenic activity in relevant in-vivo tests there is no reason to assume genotoxicity.
Priority setting: low priority or concern

e) Sensitizatio

The sensitization potency of triethylene tetramine was investigated in the Guinea Pig Maximization Test (GPMT) and in the Mouse Ear Swelling Test (MEST).
One of the GPMTs (16) used triethylene tetramine as a commercial product (no further information on purity of the substance). The method used was in accordance with the original description of the GPMT by Magnusson and Kligman (20, 21). Control animals received vehicle only. Induction concentration was 0.5 % in water and challenge concentration was 2 %. 12/15 animals (80 %) showed positive reactions 24 hours after removal af the patch. In the second GPM test, carried out according to OECD Guideline 406, purified TETA (purity: 99.5 %) was used and the applied concentrations were for induction 0.5 % and for challenge 2 % as well. As positive control served dinitrochlorobenzene. 9/10 animals (90 %) showed positive reactions (17). As additional test, the MEST was performed with 10 mice (17). The concentration of the purified TETA (purity: 99.5%) for the induction procedure was 10 % and the challenge concentration was 2.5 %. Oxazolone served as positive control. In 4/10 mice positive reactions were seen.
Cross reactions between triethylene tetramine, ethylenediamine and diethylenetriamine were also observed in guinea pigs (18).
Numerous reports concern the sensitizing potential of triethylene tetramine in humans (18).
In Poland, 20 - 51.2 % out of 20 - 447 examined workers exposed to epoxy resins reacted positive to triethylene tetramine (19). At another factory dermatitis was observed in 126 out of 422 workers. Skin tests were carried out on 99 patients. A positive reaction was observed in 55.1 % of these cases (18). In an examination of 20 workers exposed to casting resins and triethylene tetramine 5 showed positive reaction to triethylene tetramine whereas in another group of 23 epoxy resin-workers, suffering from dermatitis, none

reacted positive on a patch test with triethylene tetramine (18). In a control group of 112 persons 2 persons (1.5 %) gave positive patch test results (18).

Cross reactions between triethylene tetramine, diethylenetriamine and ethylenediamine were also reported (18).

Conclusion:
Triethylene tetramine induces skin sensitization in guinea pigs, mice and man. According to EC Directive 67/584/EEC triethelyene tetramine is labelled: R 43 = may cause sensitization by skin contact.

3.2 Ecotoxicity

3.2.1 Aquatic organisms

a) Toxicity to fish

Poecilia reticulata	96h-LC_{50}	570 mg/l

Other test results with *Leuciscus idus* and *Pimephales promelas*, which could not be validated, are in the same order of magnitude.

b) Toxicity to invertebrates

Daphnia magna	48h-EC_{50}	31.1 - 33.9 mg/l
(several tests)		
Effect: immobilisation	21d-EC_{50}	> 3.2 - < 10 mg/l
	21d-NOEC	1 mg/l

(immobilisation of parental organisms was the most sensitive effect parameter)

Furthermore, concentrations of 293 - 7313 mg/l had no teratogenic effects on sea-urchin (*Paracentrotus lividus*) eggs. The larvae were most sensitive and showed delay of development at 293 mg/l

c) Toxicity to algae

Scenedesmus subspicatus	72h-E_BC_{50}	2.5 mg/l
	72h-E_BC_{10}	0.67 mg/l
	72h-$E_\mu C_{50}$	>= 100 mg/l
	72h-$E_\mu C_{10}$	0.95 mg/l

Effect: growth inhibition (B = biomass; μ = growth rate)

Due to the intensive growth of the algae the pH in the control and in the concentrations up to 1 mg/l increased within 72 h to 10.2 - 10.3.

Selenastrum capricornutum	72h-EC_{50}	20 mg/l
Effect: growth inhibition (biomass)	72h-NOEC	< 2.5 mg/l

Selenastrum capricornutum	96h-EC_{50}	3,7 mg/l

Effect: growth inhibition (biomass)

A further test with *Chlorella pyrenoidosa* was considered to be non valid.

d) Toxicity to microorganisms

Pseudomonas fluorescens 24h-EC_0 500 mg/l
Effect: growth inhibition (biomass)

e) Derivation of PNEC

Algae are clearly the most sensitive species to TETA. According to the EU-Technical Guidance Document (3), the value of the safety factor is **F = 50** (long term tests have been performed for two trophic levels and with the organisms which were the most sensitive in the acute tests).
With the lowest aquatic effect concentration of 0.67 mg/l:

$$\textbf{PNEC} = \frac{670}{50} = \textbf{13.4 µg/l}$$

3.2.2 Terrestrial organisms

Acute oral toxicity to the redwinged blackbird (*Agelaius phoeniceus*) was determined to be 18h-LD_{50} > 101 mg/kg bw.

4. Initial Assessment

4.1 Human toxicity

4.1.1 Identification of critical toxic effects

Triethylene tetramine is a severe irritant to skin and eyes and induces skin sensitizations. Triethylene tetramine is of moderate acute toxicity: LD50(oral, rat) > 2000 mg/kg bw, LD50(dermal, rabbit) = 550 - 805 mg/kg bw. Acute exposure to saturated vapour via inhalation was tolerated without impairment.
Following repeated oral dosing via drinking water only in mice but not in rats at concentration of 3000 ppm there were signs of impairment. The NOAEL is 600 ppm [92 mg/kg bw (oral, 90 days)]. Lifelong dermal application to mice (1.2 mg/mouse) did not result in tumour formation.

There are differing results of the genetic toxicity for triethylene tetramine. The positive results of the in vitro tests may be the result of a direct genetic action as well as a result of an interference with essential metal ions. Due to this uncertainty of the in vitro tests, the genetic toxicity of triethylene tetramine has to be assessed on the basis of in vivo tests. The in vivo micronucleus tests (i.p. and oral) and the SLRL test showed negative results.

There are no data on reproductive toxicity (fertility assessment). The analogue diethylene triamine had no effects on reproduction. Triethylene tetramine shows developmental toxicity in animal studies if the chelating property of the substance is effective. The NOEL is 830 mg/kg bw (oral).
Experience with female patients suffering from Wilson´s disease demonstrated that no miscarriages and no fetal abnormalities occur during treatment with triethylene tetramine.

4.1.2 Comparison of Exposure and Critical effects

Workplace

There are no measurements of the concentration of triethylene tetramine in the air at the workplace. To estimate the exposition at the workplace adequately the results of the concentration measurements of the product with the lowest boiling point has to be applied: ethylene diamine (see chapter 4.2). All results of these measurements are below 1 mg/m^3 (TLV: 25 mg/m^3). Because of the higher boiling point and the lower vapour pressure of triethylene tetramine it can be assumed that the concentration in the air at the workplace is below or equal than 0.1 mg/m^3.

The EHE (Estimated Human Exposure) can be calculated according to the following equitation:

$$EHE = \frac{\text{respiratory rate (10 m}^3\text{) * exposition (mg/m}^3\text{)}}{\text{body weight (70 kg)}}$$

exposition < 1 mg/m^3 EHE < 0.143 mg/kg bw
exposition < 0.1 mg/m^3 EHE < 0.0143 mg/kg bw

Thus the estimated human exposure is far below the NOAEL described in animal experiments of 92 mg/kg bw for subacute toxicity and a NOAEL of 850 mg/kg bw for teratogenicity. The safety margin based on the lowest NOAEL is between:

$$\frac{92 \text{ mg/kg bw}}{< 0.143 \text{ mg/kg bw}} > 643.4 \quad \text{and} \quad \frac{92 \text{ mg/kg bw}}{< 0.0143 \text{ mg/kg bw}} > 6434$$

and thus does not suggest a particular risk.

Isolated cases of exposure through skin contact cannot be ruled out. However, the risk is to be assumed very low.

Consumer area

Data on consumer exposure are not available. However, it cannot be excluded that products containing triethylene tetramine give off small amounts of the substance. Due to the low toxicity in animal experiments it can be assumed that the probability of acute poisoning is very low. In addition, the application of triethylene tetramine as drug excluded high toxicity to humans. Also multiple administration of TETA to animals did cause neither significant systemic effects nor the formation of tumours.

Exposure via the environment

Data are not available on exposure of the general population. Exposure of the population via the hydrosphere is considered to be minimal, even assuming the concentration in drinking water to be equal to the regional predicted concentration in surface waters (0.18 µg/l). With 2 l drinking water/person/day, the daily dose would be 0.005 µg/kg bw/day. Compared to the exposure at the working place the exposure through the environment is negligible.

4.2 Assessment of environmental hazards

In the following table, the PEC/PNEC ratios for the different exposure scenarios are presented:

Scenario	$PEC_{local} + PEC_{regional}$ [µg/l]	PEC/PNEC
production (site)	1 + 0.18	0.08
processing (site)	4.5 + 0.18	0.35

A PEC/PNEC < 1 in all scenarios, a low potential risk to the aquatic compartment is at present to be expected.

A significant exposure to the **terrestrial** compartment could not be identified. Further work is presently not necessary for an assessment of risks to this compartment.

5. Conclusions and Recommendations

An environmental hazard assessment of triethylenetetramine was possible with the available data and showed that the compound was presently of low concern to the environment. No further work is recommended.

On the basis of the known facts and properties, triethylene tetramine may represent a hazard for human health. The chemical is a severe irritant to skin and eyes and induces skin sensitization. The substance is classified and labelled accordingly within the EU: R 34 = causes burns; R 43 = may cause sensitization by skin contact.

From experience with humans (substance given as a drug) there is no reason to assume that the substance reveals further toxic effects. Besides appropriate classification and labelling no further work is recommended.

References

1 OECD SIDS Diethylenetriamine (111-40-0), draft from April 1994

2. Kamon, T. and Saito, K., Kobunshi ronbunshu 41 (1984), H. 5, 293-299

3. Technical Guidance Documents in support of the Commissions Directive 93/67/EEC on Risk Assessment for New Notified Substances and the Commission Regulation (EC) 1488/94 on Risk Assessment for Existing Substances, 1996

4. Union Carbide Corporation, Bushy Run Research Center, Project Report 50-127 (1988) cited in: BG Chemie, Toxikologische Bewertung Nr. 181, 1991

5. Ciba Geigy Ltd, Report on TK10458, Report No. 830035 (1984) cited in BG Chemie, Toxikologische Bewertung Nr. 181, 1991

6. Cohen N. L. et al., DrugNutr. Interact. 2, 203-210 (1983)

7. Walshe J. M., The Lancet 1, 643-647 (1982)

8. BUA-Report 89: Triethylentetramin; Juni 1992; ISSN 0179-2601

9. van den Meent: Simplebox: a generic multimedia evaluation model; RIVM report no. 672720001; (1993)

10. Wm. K. Johnson: CEH Product Review "Ethyleneamines", SRI 1989

11. Dobryszycka W. et al., Archivum Immun. Therap. Exp. 23, 867-870 (1975)

12. Szacki J. et al., Archivum Immun. Therap. Exp. 22, 123-128 (1974)

13. Greenman D.L. et al., Fundam. Appl. Toxicol. 29, 185-193 (1996)

14. Heinz N., Schroeder H.F., Drug Res. 31, 950-953 (1981)

15.Stavreva M., Khig. Zdraveopaz. 22, 179-182 (1979)

16. Thorgeirsson A., Acta Derm. (Stockholm) 58, 332-336 (1978)

17. Maisey J. et al., contact Dermatitis 18, 133-137 (1988)

18. BG: Berufsgenossenschaft der chemischen Industrie, Toxikologische Bewertung triethylene tetramine No. 18, 1991

19. Ruddzki E., contact dermatitis 6, 235-236 (1980)

20. Magnusson B., Kligman A.M., J. Invest. Dermatol. 52, 586 (1969)

21. Magnusson B., Kligman A.M., cited in: Identification of contact Allergens, Ch.C. thomas Publisher, Springfield, Ill., 1970

I U C L I D Data Set

Existing Chemical	ID: 112-24-3
CAS No.	112-24-3
EINECS Name	trientine
EC No.	203-950-6
TSCA Name	1,2-Ethanediamine, N,N'-bis(2-aminoethyl)-
Molecular Formula	C6H18N4
Producer Related Part	
Company:	Bayer AG
Creation date:	15-MAR-1993
Substance Related Part	
Company:	Bayer AG
Creation date:	15-MAR-1993
Memo:	AKTUELL OECD-SIDS
Printing date:	24-JUL-2002
Revision date:	17-MAY-1993
Date of last Update:	**27-JAN-1998**
Number of Pages:	**56**
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags:without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: cooperating company
Name: Bayer AG
Town: 51368 Leverkusen 1
Country: Germany

10-MAY-1994

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

1.1.1 General Substance Information

Substance type: organic
Physical status: liquid
Purity: 60 - 70 % w/w

Remark: technical mixture

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,2-Bis-(2-aminoethylamino)-ethan

1,2-Di-(aminoethylamino)-ethan

1,4,7,10-Tetraazadecan

1,8-Diamino-3,6-diaza-octan

2,2'-(1.2-Ethylenbis-amino-)bis-ethanamin

3,6-Diazaoctan-1,8-diamin

N,N'-Bis-(2-aminoethyl)-1,2-ethanediamine

N,N'-Bis-(2-aminoethyl)-ethylendiamin

N,N'-Di-(2-aminoethyl)-1.2-ethandiamin

N,N'-Di-(2-aminoethyl)-1.2-ethylendiamin

TETA

Tetramin

Trien

Triethylentetramin

1.3 Impurities

EINECS-Name: N,N¦-Bis-(2-aminoethyl)piperazin
Contents: 11 - 13 % w/w

EINECS-Name: N-(Piperazin-1-ethyl)-ethan-1,2-diamin
Contents: 10 - 13 % w/w

EINECS-Name: Tris-(2-aminoethyl)-amin
Contents: 4 - 6 % w/w

CAS-No: 111-40-0
EC-No: 203-865-4
EINECS-Name: 2,2'-iminodi(ethylamine)
Contents: <= 3 - % w/w

EINECS-Name: Water
Contents: <= ,5 - % w/w

1.4 Additives

1.5 Total Quantity

Quantity: 1000 - 5000 tonnes produced

Remark: in 1989-1991 (BRD)
29-NOV-1994 (1)

Remark: Netherland: ca. 6000 t/a
USA: ca. 1100 t/a
Japan: ca. 1800 t/a
29-NOV-1994 (1)

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (C) corrosive
R-Phrases: (21) Harmful in contact with skin
(34) Causes burns
(43) May cause sensitization by skin contact

S-Phrases: (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

Country: Germany

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: corrosive
R-Phrases: (21) Harmful in contact with skin
(34) Causes burns
(43) May cause sensitization by skin contact

Country: Germany

1.6.3 Packaging

1.7 Use Pattern

Type: industrial

Category: Chemical industry: used in synthesis

Remark: Intermediate for - hardeners for epoxy resins > 80 %
- agents used in glues, paper industry and textile industry > 15 %

Type: use

Remark: TETA can also be used directly as hardener in epoxy resins (approx. 8 % of total production)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: Bayer AG
Labelled by: other: Bayer AG
Class of danger: 2 (water polluting)
Country: Germany

1.8.4 Major Accident Hazards

Substance listed: no

1.8.5 Air Pollution

Classified by: TA-Luft (DE)
Labelled by: TA-Luft (DE)
Number: 3.1.7 (organic substances)
Class of danger: III

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Country: Germany

Remark: air: 6 kg/a at one processing site;
no release into the atmosphere at all other production and processing sites
water: 4,4 kg/a at all production and processing sites
waste treatment:
water: biological waste water treatment plant
air: incineration
There is no solid waste from production and processing.
Possible emissionof very small amounts through migration out of epoxy resins (residual concentration of TETA in hardeners: at max. approx. 7.9 %)

29-NOV-1994 (1)

1.11 Additional Remarks

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = 12 degree C
(2)

Remark: Solidification point: approx. -35 degree C (technical product)
26-APR-1994 (3)

2.2 Boiling Point

Value: 266 - 267 degree C
(4)

Value: = 277,5 degree C
Decomposition: yes

Remark: 93 - 96 % purity
(5)

Value: = 277,9 degree C
(6)

Value: = 278 degree C
Decomposition: yes
(7)

Value: ca. 280 degree C

Remark: technical product
26-APR-1994 (3)

2.3 Density

Type: density
Value: = ,9739 g/cm³ at 20 degree C
(8)

Type: density
Value: ca. ,98 g/cm³ at 20 degree C

Remark: technical product
26-APR-1994 (3)

Type: density
Value: = ,9818 g/cm³ at 20 degree C
(5)

Type: density
Value: = ,9839 g/cm³ at 20 degree C
(6)

Type: density
Value: = ,977 g/cm³ at 25 degree C
(9)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = ,013 hPa at 20 degree C

(6)

Value: < ,1 hPa at 20 degree C

Remark: technical product
26-APR-1994 (3)

2.5 Partition Coefficient

log Pow: = -1,66

Remark: calculated (no further information)

(10)

log Pow: = -1,41

Remark: calculated (no further information)

(11)

log Pow: = -1,4

Method: other (calculated): Leo, Hansch: A. Leo, CLOGP-3.63 (1991) Daylight, Chemical Information Systems, Inc. Irvine, CA, USA

Remark: undissociated form

(12)

2.6.1 Solubility in different media

Remark: completely miscible

(7)

2.6.2 Surface Tension

2.7 Flash Point

Value: = 118 degree C

(13)

Value: = 125 degree C

(6)

Value: ca. 129 degree C
Method: other: DIN 51758
Remark: technical product
26-APR-1994 (3)

Value: = 135 degree C

(5)

2.8 Auto Flammability

2.9 Flammability

Remark: LFL: 1.0 % v/v (180 deg. C)
UFL: 3.6 % v/v (180 deg. C)
Source: DOW Europe S.A., Switzerland
24-MAY-1994 (14)

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Remark: Henry-constant : 6.7x10E-11 Pa.m3/mol (at 25 degree C, calculated)
29-NOV-1994 (1)

Remark: Ignition-temperature : 335 Grad C (DIN 51794)
26-APR-1994 (3)

Remark: Ignition-temperature : 338 Grad C
(5)

Remark: UV-Spectrum in water : epsilon < 10 e/molxcm at lamda > 240 nm
(15)

3.1.1 Photodegradation

Type: other: photochemical degradation in atmosphere
INDIRECT PHOTOLYSIS
Sensitizer: OH
Rate constant: ,000000000225 cm³/(molecule * sec)
Degradation: 50 % after 1,7 hour(s)

Method: other (calculated): according to Atkinson

29-NOV-1994 (16) (1)

3.1.2 Stability in Water

Type: abiotic

Year: 1985
Test substance: other TS: technical grade (purity > 70 %)

Remark: No hydrolysis in water during the experiment of 36 days.
Tested concentrations: 1, 100 and 200 mg/l
(17)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Remark: Based on the physico-chemical properties transport from water to air is not to be expected (Henry-constant: H = 6.7 x 10E-11 Pa.m3/mol, 25 degree C, calculated)
29-NOV-1994 (1)

3.3.2 Distribution

Remark: Based on the physical-chemical data, the preferred environmental compartment of TETA is the hydrosphere

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, industrial
Concentration: 100 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 0 % after 28 day(s)
Result: under test conditions no biodegradation observed

Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"

Year: 1989
GLP: no data
Remark: technical product
(18)

Type: aerobic
Inoculum: predominantly domestic sewage, adapted
Concentration: related to Test substance
Degradation: 0 % after 20 day(s)
Result: under test conditions no biodegradation observed

Method: other: in accordance with OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1977
GLP: no data

Remark: technical product;
Substance concentrations: 2.6, 8.5, 25.5, 85 mg/l
(18)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Remark: Bioaccumulation is not to be expected (logPow = -1,4; -1.66 calculated)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: 180 -
LC50: 570 -
LC100: 1800 -

Method: Directive 84/449/EEC, C.1 "Acute toxicity for fish"
Year: 1989
GLP: yes
Test substance: other TS: Triethylenetetramine, purity: 97.5%

Remark: 48h-LC50 = 1140 mg/l
10-MAY-1994 (19)

Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC0: 200 -

Method: other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Arbeitskreis "Fischtest" im Hauptausschuss "Detergentien" (15.10.73)
GLP: no

Remark: open system;
at 500 mg/l, all test organisms had died after 27 h;
no further information on test conditions
(18)

Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 495 -

Remark: validation not possible
Source: DOW Europe S.A., Switzerland
26-APR-1995 (20)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: 18 -
EC50: 31,1 -
EC100: 56 -

Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1989
GLP: yes
Test substance: other TS: Triethylentetramine, purity: 97.5%

Remark: static test
24h-EC50: 75 mg/l
10-MAY-1994 (21)

Species: Daphnia magna (Crustacea)
Exposure period: 21 day(s)
Unit: mg/l **Analytical monitoring:**
NOEC: 1 -

Method: OECD Guide-line 202

Remark: EC50: > 3.2 - < 10 (Immobilization of parental organisms); a NOEC for the inhibition of the reproduction rate could not be determined
26-APR-1995 (18)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: 22 -
EC50: 92,4 -
EC100: 354 -

Method: other: Daphnien-Schwimmunfaehigkeits-Test, UBA-Verfahrensvorschlag Mai 1984, Bestimmung der Schwimmunfaehigkeit beim Wasserfloh Daphnia magna, EC0, EC50, EC100 24h, statisches System
Year: 1989
GLP: yes

Remark: Distillate of technical product
(18)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC50: 33,9 -

Method: other: EEC, 1989, Methods for the determination of ecotoxicity. C.2 Acute toxicitty for Daphnia (Updated Version 11/89). EEC Directive 79(831, Annex V, Part C. Brussels, Belgium (static)
Year: 1994
GLP: no data
Test substance: other TS: purity > 99 %

Remark: Arithmetic mean of 3 test results (standard deviation was 5.3 mg/l).
26-APR-1995 (22)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : 12 -

Remark: validation not possible
Source: DOW Europe S.A., Switzerland
26-APR-1995 (20)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Chlorella pyrenoidosa (Algae)
Endpoint: growth rate
Exposure period: 5 day(s)
Unit: mg/l **Analytical monitoring:**
EC100 : >= 146 -

Remark: Validity uncertain. Slow growth of the control culture.
Test condition: 25 degree C, pH 7

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: ,67 -
EC50: 2,5 -

Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
Year: 1989
GLP: yes
Test substance: other TS: purity 98.04 %

Remark: Due to the high growth rate, the pH rose to 10.2 - 10.3 after 72 hours in the control and for concentrations of TETA up to 1 mg/l
(18)

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: ,95 -
EC50: >= 100 -

Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
Year: 1989
GLP: yes
Test substance: other TS: purity 98.04 %

Remark: Due to the high growth rate, the pH rose to 10.2 - 10.3 after 72 hours in the control and for concentrations of TETA up to 1 mg/l
(18)

Species: Selenastrum capricornutum (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: < 2,5 -
EC50: 20 -

Method: Directive 87/302/EEC, part C, p. 89 "Algal inhibition test"
Year: 1990
GLP: yes

Test substance: other TS: Triethylenetetramine, purity 97.5%

Remark: For the enspoint ¦growth rate¦, the same results were obtained

10-MAY-1994 (24)

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC50: 3,7 -

Method: other: EEC, 1988, Methods for the determination of ecotoxicity. Algal inhibition test. Off J. Eur. Comm. L 133 1988-0530
Year: 1994
GLP: no data
Test substance: other TS: purity > 99 %

Remark: Arithmetic mean of 5 test results (standard deviation: 1.5 mg/l). The culture medium was modified by increasing the KH2PO4 conc. from 1.6 to 160 mg/l and the NaHCO3 conc. from 50 to 100 mg/l, to improve the growth of algae and the buffer capacity of the medium.

26-APR-1995 (22)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas fluorescens (Bacteria)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: 500 -

Method: other: Bestimmung der biologischen Schadwirkung toxischer Abwaesser gegen Bakterien. DEV, L 8 (1968) modifiziert

Remark: technical product;
no further information on test conditions

(18)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Remark: no validated information

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: other avian: Agelaius Phoenicus (redwinged blackbird)
Endpoint: mortality
Unit: mg/kg bw
LD50 : > 101 -

Method: other: no data
GLP: no data
Test substance: other TS: TETA (no information about purity)

Remark: Estimated LD50 based on food consumption data over a 18 h period
29-NOV-1994 (25)

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

Remark: Sea-urchin: Inhibition of development
Eggs of the species Paracentrotus lividus were incubated in sea-water 30 min after impregnation (concentration TETA: 293 - 7313 mg/l). No teratogenic effects observed.
Depending on the developmental stage there was an effect on larvae (293 mg/l), gastrula (731 mg/l), blastula (2925 mg/l), cleavage stage (7313 mg/l).
(26)

Remark: Application of 1460 mg/l TETA (alcoholic solution) to 1-2 days old larval stages and 2 days old egg-stages of the species Dysdercus koenigii F. had no acute toxic effects and no effects on the eggs as well as no sterilizing effects.
(27)

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Value: = 2780 mg/kg bw

Method: other: male rats, undiluted testsubstance (no further information)
GLP: no data
Test substance: no data

29-JUL-1996 (28)

Type: LD50
Species: rat
Value: ca. 3750 mg/kg bw

Method: other: 3 animals per group; doses: 1000, 2500, 3750, 5000 mg/kg; test substance diluted in water
GLP: no data
Test substance: no data

17-OCT-1994 (29)

Type: LD50
Species: rat
Value: = 4340 mg/kg bw

Method: other: 5 animals per group, test substance diluted in water
GLP: no data
Test substance: no data

(30)

Type: LD50
Species: rat
Value: = 2500 mg/kg bw

GLP: no data
Test substance: no data

Remark: method: no data

(13)

Type: LD50
Species: rat
Value: = 4300 mg/kg bw

GLP: no data
Test substance: no data

Remark: method: no data
17-OCT-1994 (31)

Type: LD50
Species: mouse
Value: = 1600 mg/kg bw

GLP: no data
Test substance: no data

Remark: method: no data
17-OCT-1994 (31)

Type: LD50
Species: rabbit
Value: = 5500 mg/kg bw

GLP: no data
Test substance: no data

Remark: method: no data
17-OCT-1994 (31)

5.1.2 Acute Inhalation Toxicity

Type: other: see method
Species: rat

Method: other: saturated vapor at 21 degree C, 8 h exposure, 6 animals
GLP: no data
Test substance: no data

Remark: no symptoms
17-OCT-1994 (28)

Type: other: see method
Species: rat

Method: other: saturated vapor inhalation up to 8 h
GLP: no data
Test substance: no data

Remark: maximal time for no deaths 4 h
(30)

Type: other: see method
Species: other: see method

Method: other: 2 rats, 1 rabbit, 1 guinea pig, and 4 mice were exposed together to aerosol (10 ml of 40 % (v/v) ethanol solution, 400 l chamber) for 1 h
GLP: no data
Test substance: no data

Remark: effects: slight irratation of the mucous membranes and impeded respiration, effects reversible
17-OCT-1994 (29)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Value: = 550 mg/kg bw

Method: other: 4 animals per dose, undiluted test substance
GLP: no data
Test substance: no data

Remark: no further information available
17-OCT-1994 (28)

Type: LD50
Species: rabbit
Value: = 805 mg/kg bw

Method: other: occlusive application of undiluted test substance
GLP: no data
Test substance: no data

Remark: no further information available
(30)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 200 mg/kg bw

Method: 3-5 animals per group, test substance as aqueous solution
GLP: no data
Test substance: no data

Remark: impeded respiration
17-OCT-1994 (29)

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 78,4 mg/kg bw

Method: no data
GLP: no data
Test substance: no data

Remark: symptoms like hyperemia, extravasations; regressive changes in liver and kidneys; abstract
(32)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 604 mg/kg bw

Method: test substance neutralized with HCl, 10 mice per group
GLP: no data
Test substance: no data

Remark: convulsions for max. 20 min, hyperemia of inner organs in the dead animals

(33)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit

Method: other: non occlusive appl.;
a) 0.01 ml undiluted
b) 10% in water
GLP: no data
Test substance: no data

Remark: effects: a) 2 out of 2 animals with necrosis
b) no effects
no further information available
17-OCT-1994 (28)

Species: rabbit

Method: other: 20 mg applied to skin
GLP: no data
Test substance: no data

Remark: effects: necrotic foci and extravasations
no further information available, abstract

(32)

Species: rabbit

Method: other: undiluted drug applied to the skin of 5 animals; no further information available
GLP: no data
Test substance: no data

Remark: effects: erythema, edema, necrosis

(30)

Species: guinea pig

Method: other: intracutaneous injection of 0.1 ml 0.5-1% solution in water (non neutralized) or 2-3% solution in neutralized form
GLP: no data
Test substance: no data

Remark: effects: slight necrosis
no further information available

(34)

Species: rat

Method: other: a) 1000 mg/kg undiluted; b) 50 mg/kg (25% in water); application on the shaved ventral skin; exposure time: 2 h
GLP: no data
Test substance: no data

Remark: effects: strong irritations in both cases
17-OCT-1994 (29)

5.2.2 Eye Irritation

Species: rabbit

Method: other: instillation of a) 0.005 ml undiluted or b) 0.5 ml of a 40% watery solution
GLP: no data
Test substance: no data

Remark: effects: a) severe damage of the cornea b) 15% of the cornea damaged
17-OCT-1994 (28)

Species: rabbit

Method: other: 20 mg applied to the conjunctival sac
GLP: no data
Test substance: no data

Remark: effects: inflammation and lymphatic exudation
no further information available, abstract
(32)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Method: other: 10 animals tested; induction concentration 0.5% intradermal and topical, challenge 2%
GLP: no data
Test substance: other TS: purity 99.5 %

Remark: 90% positive
(35)

Type: Guinea pig maximization test
Species: guinea pig
Result: sensitizing

Method: other: 15 animals tested; induction concentration 0.5% intradermal and topical, challenge 2% (in water)
GLP: no data
Test substance: other TS: technical grade (no specification)

Remark: 80% of guinea pigs with positive reaction
(36)

Type: Mouse ear swelling test
Species: mouse
Result: sensitizing

GLP: no data
Test substance: other TS: purity 99.5 %

Remark: 4/10 positive (significant), induction conc. 10%, challenge 2.5%.
(35)

Type: Open epicutaneous test
Species: human

Remark: 10 out of 22 workers exposed to araldite D and hardener TETA showed slight dermatosis, one worker serious allergic eczema. One of the 11 (the one with serious allergic eczema) showed allergic hypersensitivity in epicutaneous testing to TETA.
(37)

Type: Patch-Test
Species: guinea pig
Result: not sensitizing

Method: other: no data
GLP: no data
Test substance: no data

Remark: no further information available, abstract
(32)

Type: Patch-Test
Species: human

Test substance: no data

Remark: 4 out of 10 patients with dermatitis due to oil-based, amine containing drilling mud, showed allergic response to a 0.5% solution in the patch test.
(38)

Type: Patch-Test
Species: human

Remark: In 23 out of 135 (18%) workers exposed to epoxy resins, a work-related dermatosis on the hands and/or forearms had been presented during the past 3 years. In all workers patch tests were performed and in 2 positive reactions to TETA were observed (2 out of 112 without dermatosis).
(39)

Type: Patch-Test
Species: human

Remark: 422 employees of 8 factories had contact to epoxy resins and hardener TETA. In the course of 7 years there were 126 cases of dermatitis, 99 of whom were patch tested. 55.1% were positive to 1% TETA in water. The mean period between starting work and occurrence of dermatitis was 18.5 months.
(40)

Type: Patch-Test
Species: human

Remark: 1544 patients(dermatitis) without exposure to epoxy resin systems and 137 patients in occupational contact with epoxy resins were patch tested. 28 out of the 1544 patients were

positive to ethylenediamine; 12 of these were tested with TETA, 2 were positive. 400 out of the 1544 patients were also tested with TETA and re- sults were negative. Tests with 137 patients in occupational contact to resins resulted in coexistence of positive reactions to TETA and ethylenediamine and TETA and diethylenetriamine.

(41)

Type: Patch-Test
Species: human

Remark: A 58 years old woman with dermatitis due to exposure with epoxy resins showed positive reaction in the patch test to epoxy resin and TETA as well as to ethylenediamine.

(42)

Type: Patch-Test
Species: human

Remark: 12 out of 32 ethylenediamine-sensitive patients showed cross-sensitivity reaction to TETA in the patch test.

(43)

Type: Patch-Test
Species: human

Remark: 19 out of 71 patients with allergic epoxy resin dermatitis were also allergic to different hardeners. 3 of them showed positive reactions to TETA in epicutaneous testing.

(44)

Type: Patch-Test
Species: human

Remark: A shipwright''s yard worker complained a chronic dermatitis of the fingertips and palms. Beside other material he used epoxy resin SP 106. In the patch test a positive reaction to TETA was demonstrated after 48 and 96 h.

(45)

Type: Patch-Test
Species: human

Test substance: no data

Remark: 31 students and instructors at the same dental school were patch tested to contactants in dental components including TETA. None had any history of allergy. No positive allergic reactions were found.

(46)

Type: Patch-Test
Species: human

Test substance: no data

Remark: 2 out of 7 patients with airborn contact dermatitis of hands and face due to epoxy resins showed positive reactions in the patch test to TETA.

(47)

Type: Patch-Test
Species: human

Remark: 14 young female patients (12 of them were seborrhean) in occupational contact with araldite D and hardener 951 (mainly TETA) suffering from eczema were patch tested. 1 of the 14 women was positiv to 3% of the hardener in ethanol (48 h).

(48)

Type: other
Species: human

Remark: 20 workers (6 without, 8 with slight and 6 with severe dermatosis) were patch tested with technical TETA (1% in water). 5 of the 6 workers with severe dermatosis showed a positive reaction.

(34)

Type: other: see remarks
Species: human

Remark: 164 out of 328 workers from 11 factories producing electrical equipment showed slight dermatosis (21%, erytamotous itching patches) or severe eczemas (22%) caused by direct contact to araldite resin D or hardener TETA. TETA concentration in air was below analytic limits of 0.00015 mg/l.

(49) (50)

Type: other: see remarks
Species: human

Remark: 6 workers with diagnoses of occupational asthma were examined for sensitivity to epoxy resin systems and their components. In one worker asthma followed exposure to TETA fume in inhalation challenge testing. Skin sensitivity test was negative.

(51)

Type: other: see remarks
Species: human

Remark: 447 patients suffering from eczema, occupationally exposed to epoxy resins, have been tested with Epidian 5 (resin) and five concentrations of the hardener TETA. In Poland these health damages were characterized by a considerable percentage of those sensitized to TETA. The calculation of eczema incubation period and testing the allergen by several allergen concentrations demonstrated that the sensitivity to TETA was sometimes very enhanced.

(52)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male/female
Strain: other: Harlan-Wistar
Route of administration: oral feed
Exposure period: 7 days
Frequency of treatment: daily ad libitum
Post exposure period: no data
Doses: m: 0.5, 1.23, 2.98 g/kg b.w.; f: 0.47, 1.38, 2.63 g/kg b.w.
Control Group: no data specified
NOAEL: ,5

Method: other: 5 rats per dose and sex
GLP: no data

Test substance: no data

Remark: LOEL: 1.23 (m) and 1.38 (f) mg/kg b.w./day
remarks: no deaths occurred
Result: highest dose:
depression of body weight gain, decrease of relative and absolute liver weights, increase of relative kidney weights.
medium dose:
increase of relative kidney weights.

17-OCT-1994 (28)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: drinking water
Exposure period: 90 d
Frequency of treatment: daily
Post exposure period: no
Doses: 0, 120, 600, 3000 ppm (see remarks)
Control Group: other: concurrent no treatment (diet: cereal based NIH-31, purified AIN-76A, Cu-deficient AIN-76A)
NOAEL: = 3000 ppm

Method: other: 18 rats/sex and dose group, different diets: cereal based (NIH-31) or purified (AIN-76A) diet; hematology and plasma chemistry; necropsy and histopathology; statistical analyses
Year: 1996
GLP: no data
Test substance: other TS: trientine-2HCl: purity: > 99 %

Remark: test substance consumption:
NIH-31 diet: f:14, 70, 352 mg/kg bw; m:10, 55, 276 mg/kg bw
AIN-76A diet: f:13, 60, 323 mg/kg bw; m:10, 53, 270 mg/kg bw
Result: no death occurred; pobabely attributed to dosing with trien-2HCL: females: a significant trend toward an increased prevalence of uterine dilatation; no other findings

23-JUN-1997 (53)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: dermal
Exposure period: 17 days

Frequency of treatment: once daily (3rd - 19th day of gestation)
Post exposure period: no
Doses: ca. 4 mg/rat and day
Control Group: yes

Method: other: 10 rats per group. One drop of the test substance was rubbed into the shaved skin

GLP: no data
Test substance: no data

Remark: LOEL: no data
Result: pregnant and nonpregnant rats: reduced weight gain, progressive emaciation, apathy, lack of appetite, local inflammatory symptoms such as erythema, edema and superficial erosions. pregnant rats: increase of plasma sialic acid; increased activity of lactate dehydrogenase, aspertate aminotransferase and acid phosphatase in the serum; decreased plasma activity of alkaline phosphatase; reduced haptaglobin concentration; increased acti- vity of leucylnaphthylamidase in amniotic fluid. nonpregnant rats: decreased total plasma protein and elevated concentrations of seromucoid a. haptaglobin; in the serum increa- sed activity of lactate dehydrogenase, leucylnaphthylamidase and alkaline phosphatase; inhibited activity of aspartate and alanine aminotransferase.

(54)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: dermal
Exposure period: 17 days
Frequency of treatment: once daily
Post exposure period: no
Doses: ca 4 mg/rat and day
Control Group: yes

Method: other: 10 rats per group. No data about stage of pregnancy in pregnant rats. One drop of test substance was rubbed into the shaved skin.
GLP: no data
Test substance: no data

Remark: LOEL: no data
Result: pregnant and nonpregnant rats:
weight loss, hyperemia of liver and kidneys, dermis and subcutaneous tissue with inflammatory infiltrates.
pregnant rats: aspartate aminotransferase activity in the liver inhibited.
nonpregnant rats: increased activity of gammaglutamyltranspeptidase in the kidney and aspartate and alanine aminotransferases in the liver.

(55)

Species: rat **Sex:** no data
Strain: no data
Route of administration: oral unspecified
Exposure period: a) 4 months b) 10 months
Frequency of treatment: a) no data b) daily
Post exposure period: no data

Doses: a) 215 or 430 mg/kg b) 0.8 or 4 mg/kg
Control Group: no data specified

Method: other: no data
GLP: no data
Test substance: no data

Remark: LOEL: a) 215 mg/kg b.w. b) 0.8 mg/kg b.w./day, 10 months no dose effect relation; abstract, no further information available.
Result: 4 months both doses:
Excitability of the central nervous system decreased. Plasma levels of hippuric acid, protein and hemaglobin were decreased. Inhibited activities of catalase and peroxidase.
10 months both doses:
Increased excitability, stimulated tactile reflexes. Antitoxic, carbohydrate and protein function of the liver disturbed. Transient inhibition of nicotinamide coenzymes and stimulation of cytochrome oxidase.
17-OCT-1994 (31)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: drinking water
Exposure period: 90 d
Frequency of treatment: daily
Post exposure period: no
Doses: 0, 120, 600, 3000 ppm (see remarks)
Control Group: other: concurrent no treatment, (diet: cereal based NIH-31, purified AIN-76 A, Cu-deficient AIN-76A)
NOAEL: = 600 ppm

Method: other: 20 mice/sex and dose group; different diets: cereal based (NIH-31) or purified (AIN-76A); hematology and plasma chemistry; necropsy, histopathology, statistical analyses
Year: 1996
GLP: no data
Test substance: other TS: trientine-2HCl; purity: > 99 %

Remark: test substance consumption:
NIH-31 diet: f:22,107, 551 mg/kg bw; m:22,107, 487 mg/kg bw
AIN-76A diet: f:19, 99, 483 mg/kg bw; m:17, 92, 443 mg/kg bw
Result: diet AIN-76A, 3000 ppm: chronic interstititial inflammation and alveolar histocytic infiltration of the lung, spleen hemapoetic cell proliferation, liver periportal fatty change, kidney weight reduction, reduced renal cytoplasmatic vacuolization, body weight gain reduction
27-JAN-1998 (53)

Species: guinea pig **Sex:** female
Strain: no data
Route of administration: dermal
Exposure period: 55 days
Frequency of treatment: once daily
Post exposure period: no
Doses: ca.4 mg/animal and day
Control Group: yes

Method: other: starting exposition in pregnant guinea pigs on day 10 of gestation. One drop of the test substance was rubbed into the shaved skin.
GLP: no data
Test substance: no data

Remark: LOEL: no data
remarks: 6 out of 10 nonpregnant and 2 out of 9 pregnant exposed guinea pigs died before end of experiment. No further information about toxic effects available.

Result: pregnant guinea pigs:
activity of gammaglutamyltranspeptidase significantly elevated in kidney and blood.
nonpregnant guinea pigs:
significantly increased activity of liver aspartate aminotransferase.

(56)

Species: guinea pig **Sex:** female
Strain: no data
Route of administration: dermal
Exposure period: once daily for 10 days, then every second day for 45 days
Post exposure period: no
Doses: ca.4 mg/animal and day
Control Group: yes

Method: other: 11 animals/group; exposure started on day 10 of gestation; one drop of the test substance was rubbed into the shaved skin
GLP: no data
Test substance: no data

Remark: LOEL: no data
Result: 7 out of 11 pregnant and 7 out of 11 nonpregnant guinea pigs died within the first 10 days. Surviving pregnant and nonpregnant animals showed weight loss with advanced emaciation; skin revealed inflammatory alterations indicated by erythema, edema and erosion. Surviving and nonsurviving ainmals showed all fatty degeneration of the liver, congestion of the kidney and brain, and brain edema. Pregnant animals showed necrotic changes in the placenta and miscarriage or mortification of fetuses.

(57)

Species: other: see remarks **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 1 h/d for 2 weeks, 5 d a week
Post exposure period: no data
Doses: 0.4 ml in 5 ml ethanol as aerosol in a 400 l chamber
Control Group: no data specified

Method: other: 1 guinea pig, 1 rabbit, 2 rats, 4 mice were exposed together in one chamber.
GLP: no data
Test substance: no data

Remark: LOEL: no data
no further information available
Result: no effects
17-OCT-1994 (29)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium, TA 100, TA 1535
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data
Test substance: no data

Remark: abstract, no further information available
(58)

Type: Ames test
System of testing: Salmonella typhimurium, TA 100,
Metabolic activation: no data
Result: positive

Method: other: no data
GLP: no data
Test substance: no data

Remark: 0.07 revertants per nmole;
abstract, no further information available
(59)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: no data
(60)

Type: Ames test
System of testing: Salmonella typhimurium, TA 92, 98, 100
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: no data
(60)

Type: Ames test
System of testing: Salmonella typhimurium, TA 98, 100, 1535, 1537, 1538
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data

Test substance: other TS: purified TETA-2Hydrochloride

(61)

Type: Ames test
System of testing: Salmonella typhimurium, TA 98, 100, 1535, 1537
Metabolic activation: with and without
Result: positive

Method: other: preincubation assay
GLP: no data
Test substance: other TS: technical grade (68.1%)

(62)

Type: Ames test
System of testing: Salmonella typhimurium, TA 98, 100, 1535, 1537, 1538
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: yes
Test substance: other TS: techn. grade; 2 samples: 56.4 and 68.5% purity

(63) (64)

Type: Mammalian cell gene mutation assay
System of testing: CHO cells
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS: purity 79.15%

Remark: no clear dose-response relationship

(65)

Type: Mammalian cell gene mutation assay
System of testing: CHO cells
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: purity 99.42%

(66)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS: purity 99.42%

(66)

Type: Unscheduled DNA synthesis
System of testing: rat hepatocytes
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS: purity 99.42%

(66)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS: purity 79.15%

(65)

Type: Unscheduled DNA synthesis
System of testing: rat hepatocytes
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS: purity 79.15%

(65)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS: purity 56.4%, technical grade

Remark: with metab. activation only at the lowest concentration (0.5 g/l) significant increase of SCEs/chromosome; no increase at 0.6 and 0.8 g/l.

(67)

5.6 Genetic Toxicity 'in Vivo'

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** no data
Route of admin.: unspecified
Exposure period: no data
Doses: no data

Method: other: no data
GLP: no data
Test substance: no data

Result: no effects

(68)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Route of admin.: i.p.
Exposure period: single injection
Doses: 185, 370, 600 mg/kg

Method: other: Bushy Run Research Center standard protocol
GLP: yes
Test substance: other TS: purity 68.5%, technical grade

Result: not clastogenic

(69)

Type: Micronucleus assay
Species: mouse **Sex:** no data
Route of admin.: i.p.
Exposure period: single injection
Doses: 130, 190, 250 mg/kg

Method: other: according to Schmid, W., Mitt. III der Komm. fuer Mutagenitaetsfragen, 53 (1975)
GLP: no data
Test substance: other TS: purified TETA-Dihydrochloride

Result: not clastogenic

(61)

Type: Micronucleus assay
Species: mouse **Sex:** no data
Route of admin.: oral unspecified
Exposure period: single application
Doses: 1500, 3000, 6000 mg/kg

Method: other: according to several published methods
GLP: no data
Test substance: other TS: purified TETA-2Hydrochloride

Result: not clastogenic

(61)

5.7 Carcinogenicity

Species: mouse **Sex:** male
Strain: other: C3H/HeJ
Route of administration: dermal
Exposure period: life-time
Frequency of treatment: 3 times a week
Post exposure period: no
Doses: ca. 1.2 mg/mouse and application
Control Group: other: deionized water

Method: other: see remarks
GLP: no data
Test substance: other TS: purity 79.15% (analytic)

Remark: method: no further data available
remarks: 50 animals per group; 0.025 ml of 5% aqueous solution applied; dose highest one that resulted in neither skin irratation nor reduced weight gain. No increased mortality. Dosage very low compared to LD50.
Result: No treatment related skin tumors, no evidence of increased incidence of any other tumor.

(70)

Species: mouse **Sex:** male
Strain: other: C3H/HeJ
Route of administration: dermal
Exposure period: 2 years
Frequency of treatment: 3 times/week
Doses: 0, 0.2 or 2.0 % in ethanol

Remark: 50 animals/group
Result: No effects were observed on any parameter, including mortality, body weights and incidence of tumorous or non-tumorous lesions.
Source: DOW Europe S.A., Switzerland
24-MAY-1994 (71)

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: day 6-15 of gestation
Frequency of treatment: once daily
Doses: 75, 325, 750 mg/kg
Control Group: yes

Method: other: test substance diluted in water
GLP: no data
Test substance: other TS: purity > 98%

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).
(72)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: day 0-21 of gestation
Frequency of treatment: daily ad libitum
Doses: 0.17, 0.83, 1.66% in the diet (170, 830, 1660 mg/kg b.w. and day)
Control Group: yes

GLP: no data
Test substance: other TS: purity > 99%, TETA-4Hydrochloride

Remark: litter size unchanged, all described effects significant and dose related. Authors comment: teratogenicity of the drug in part due to induced Cu deficiency and Zn toxicity.

Result: Controls (n=7): no resorbed or abnormal fetuses.
0.17%
dams(n=5): no effects except reduced liver copper and increased kidney zinc concentration. Fetuses: 5.8% resorbed (3/52), whole fetus and liver Zn conc. elevated, Cu liver conc. reduced.

0.83%
dams (n=9): reduced weight gain, decreased Cu conc. in liver and plasma, Zn conc. 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%
dams (n=5): reduced food consumption;
highly signif. reduced weight gain and copper concentration in liver and plasma. Zn conc. in kidney and muscle, manganese conc. in muscle and iron conc. in liver increased.
Fetuses: 18.8% resorbed (9/48); 100% abnormalities (39/39) like hemorrhages, edema, reduced ossification of caudal vertebrae and phalanges; fetal weight and length reduced.
Trace elements same results as in medium dose.

(73) (74) (75) (76)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: day 0-21 of gestation
Frequency of treatment: daily ad libitum
Doses: 0, 0.83 or 1.67% in diet combined with 0.05 or 0.5 mg Cu/kg diet
Control Group: yes

Method: other: 4 rats per group
GLP: no data
Test substance: other TS: purity > 99%

Remark: litter size not altered by test substance or 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 per kg b.w. and 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 concentraion was lowered to 6.5% (3/46) by high Cu concentration. Types of abnormalities: hemorrhage, edema, hydronephrotic kidneys, micrognathia and domed skulls. The lowered teratogenetic 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.

(77) (78) (79)

Species: rabbit **Sex:** female
Strain: other: New Zealand
Route of administration: dermal
Exposure period: day 6-18 of gestation
Frequency of treatment: 6 h each day

Doses: 5, 50, 125 mg/kg dissolved in 2 ml distilled water

Control Group: yes
NOAEL Teratogenicity: 125 mg/kg bw

Method: other: 22 rabbits per group; application occlusive
GLP: no data
Test substance: other TS: purity 95%

Result: No embryotoxic or teratogenic drug related effects at any dose.
Maternal toxicity:
125 mg/kg induced delayed weight gain and death of 2 out of 22 rabbits. Strong local irritations of the skin at 50 and 125 mg/kg and slight reversible irratations at 5 mg/kg. No reduction of copper concentrations in urine and plasma.
(80)

Species: other: chicken **Sex:** no data
Strain: other: White Leghorn
Route of administration: other
Exposure period: once in 3 days old embryos
Doses: 0.051, 0.102, 0.204 or 0.408 mg per egg dissolved in 5 ul acetone
Control Group: other: solvent

Method: other: injection on the inner shell membrane
GLP: no data
Test substance: other TS: technical grade

Result:

	deaths of embryos	malformed survivors
0.051 mg	1 out of 30	2 out of 29
0.102 mg	3/30	3/27
0.204 mg	10/30	4/20
0.408 mg	20/20	----
acetone	1/100	0/100

Malformations occurred in the eyes, wings and abdominal wall. Oedema, enlarged lymph sacs and stunting and twisting of the backbone. ED50 for embryotoxicity: 0.155 mg per egg.
(81)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: TETA-2Hydrochloride is used in the therapy of Wilson''s disease (inherited metabolic desease characterised by copper accumulation predominantly in liver, cornea, brain, and kidney) when the drug of choice (Penicillamine) is not tolerated. All authors reported no serious side effects.
(82) (83) (84) (85) (86) (87) (88) (89) (90) (91)

Remark: In primary biliary cirrhosis treatment TETA is an unsuitable drug due to gastrointestinal side effects, skin rash and rhabdomyolysis (one out of 4 patients 48 h after 1. dose)

(92)

Remark: There was no evidence of teratogenicity in 4 patients who became pregnant while taking TETA-2Hydrochoride against Wilson''s disease (6 pregnancies).

(89)

Remark: 6 out of 20 employees working with ethoxylin cast resin and the hardener TETA suffered from work related eczematous dematosis. 8/20 showed slight skin irratations like erythemaand itching. In epicutaneous skin test 5 out of 6 workers with strong dermatosis were sensitized to TETA (technical grade).

(93)

Remark: Serum monoamine oxidase activity in 15 workers handling with epoxy resin and hardener TETA was significantly elevated compared to a control group. Increased activity reflect possibly increased amine metabolism in the connective tissue.

(94)

Remark: 12 workers exposed to araldite and hardener TETA were examined 2 to 4 times at intervals of 6 months. After 1 year there was a decrease in the relative percentage of lymphocytes and a corresponding increase in neutrophils. 5 workers reported subjective symptomes like drowsiness, headache, gastric pain, fatigue, weakness and decreased appetite. 7 showed dermatosis.

(95)

Remark: No significant improvement occurred in hand eczema of 23 nickel-sensitive patients treated with 300 mg TETA/d in a double blind study.

(96)

Remark: Plasma levels were measured in 4 male and 4 female patients receiving treatment for excess copper. Maximal plasma levels of 0.3- 15 mg/l (male) and 1.0- 2.2 mg/l (female) were seen 3 h after oral administration of 8.3 mg/kg b.w..

The free form of the drug was not detected, indicating chelation with metal ions (predominantly copper).
test substance: TETA-2Hydrochloride

(97)

Remark: Using the oral copper loading test and the 24 h urine excretion test on patients with Wilson''s disease it could be
shown, that longterm therapy with 1.2 g/d TETA (more than 3 months) led to a decreased intestinal copper absorption and to an increased urine copper excretion.
test substance: TETA-2Hydrochloride

(98)

5.11 Additional Remarks

Type: Biochemical or cellular interactions

Remark: Female F-344 rats received i.m. 0.75 mmol/kg TETA prior to 0.068 or 0.10 mmol/kg nickeldichloride (i.p. or i.m.). In rats killed 6 h after injection of TETA and nickelchloride, Ni concentration in liver, kidney, spleen, lung and heart averaged 3.4, 0.72, 0.27, 0.22, and 0.12 times corresponding Ni concentrations in contol rats that received only nickelchlorid. Ni-induced hyperglycemia and hyperglucagonemia were not prevented. TETA markedly reduced plasma Ni conc. and increased urine Ni excretion during 6 h after injection. Test substance: purified TETA-4Hydrochloride

(99)

Type: Biochemical or cellular interactions

Remark: Norwegian hooded rats received 100 mg TETA per rat with the diet for 3 days and the urine copper concentration was determined. The basal copper excretion of 65.1 nmol/24 h rose after drug application to 305.9 nmol/24 h. Test substance: TETA-2Hydrochloride

(100)

Type: Biochemical or cellular interactions

Remark: Female mixed-breed dogs were administered 150 mg TETA orally in gelantine capsules twice daily for 23 days and serum and 24 h urine were analysed on day 0, 9, 15, and 23. Cu concentration in serum was unchanged but increased in urine from 0.119 to 0.663 mg/24 h. Zn and Fe concentration in plasma and urine were not changed. Predictive value reduced by low number of animals (n=3). Test substance: TETA-4Hydrochloride

(101)

Type: Biochemical or cellular interactions

Remark: Nickel-poisened rats survived at a nickel:TETA ratio of 1:1. Urinary and biliary excretion of nickel was significantly enhanced.

(102)

Type: Biochemical or cellular interactions

Remark: Sodium diethyldithiocarbamate and D- pencillamine are significantly more effective upon acute toxicity of nickel carbonyl in rats than TETA.

(103)

Type: Biochemical or cellular interactions

Remark: The distribution of radioactive nickel, iron, manganese, and tin in plasma was studied in rats which received i.p. injections of their salts with or without i.m. injection of TETA. TETA was most effective in reducing nickel, followed by iron, manganese and tin.

test substance: no data

(104)

Type: Biochemical or cellular interactions

Remark: A single i.p. application of TETA decreased significantly the total body burden of zinc 24 h after i.v. injection of Zn chloride (0.14 mg/kg). Simultaneous peroral administration of TETA with Zn increased whole body burden of Zn, indicating possibly enhanced absorption of zinc.
test substance: TETA-2Hydrochloride

(105)

Type: Biochemical or cellular interactions

Remark: In a comparative study on the effects of 7 chelating drugs on trace metal and biochem. alteration in the rat TETA is one of the drugs producing least effects on the levels of trace metals and biochem. parameters.
test substance: no data

(106)

Type: Biochemical or cellular interactions

Remark: TETA is an effective antidote to acute nickel carbonyl poisoning (4.35 mg/l for 15 min) when it is administered 10 min after and not 10 min before exposure in rats.
test substance: no data

(107)

Type: Biochemical or cellular interactions

Remark: In a comparative study with 16 chelating agents TETA has been shown to be one of the most effective drugs enhancing urinary excretion of copper in the rat.
test substance: no data

(108)

Type: Biochemical or cellular interactions

Remark: 6 daily i.p. injections of 146 mg/kg TETA enhanced significantly excretion of all essential trace metals in rats. In serum levels there were no significant changes indicating redistribution.
test substance: no data

(109)

Type: Biochemical or cellular interactions

Remark: In cadmium preexposed rats 500 mg/kg TETA reduced the hepatic Cd burden but did not elicit any influence on other tissues except pancreas.
test substance: TETA-hydrochloride

(110)

Type: Toxicokinetics

Remark: The maximal plasma concentration 2 h after a single oral administration of 25 mg/kg was 8 microg/ml in fasted, 3 in nonfasted rats(max after 1h) and 24 microg/ml after

intraduodenal application. Bioavailability 4 h after administration was 6.6, 2.3,and 17.6%, respectively. Plasma levels after i.v. administration of 0.1 mg per rat were 0.0013 mg/ml 10 min. after injection and 0.00045 mg/ml after 4 h. The urinary excretion of unchanged TETA during 24 h was 3.1% of the oral dose and total urinary excretion including not identified metabolites amounted to 35.7% of the dose. Main absorption by permeation across the plasma membrane of intestinal epithelial cells. Binding to the brush border membran was totally inhibited by 0.05 mmol copper.
test substance: TETA-2Hydrochloride

(111)

(1) BUA Report No. 89 "Triethylentetramin", VCH, Weinheim, (1992)

(2) Beilsteins Handbuch der organischen Chemie, Band 4, Springer Ver- lag, Berlin, 255 (1922)

(3) Bayer AG, DIN-Safety Data Sheet Triethylentetramin 18.06.93

(4) Keith, L.H. & Walters, D.B., Compendium of safety data sheets for research and industrial chemicals, Part 3, Verlag Chemie, Wein- heim, 1670-1671 (1985)

(5) Kuehn, R. & Birett, K., Merkblaetter gefaehrlicher Arbeitsstoffe, Band 6, Blatt Nr. T 43, Ecomed Verlag, Landsberg (1982)

(6) Wilson, A.L., Ind. Eng. Chem. 27, 867-871 (1935)

(7) Hommel, G., Handbuch der gefaehrlichen Gueter, Springer Verlag, Berlin, Merkblatt 569 (1988)

(8) Hann, R.W. & Jensen, P.A., Water quality characteristics of ha- zardous materials, Texas A & M University, 3 S. (1974)

(9) Hart, A.W., In: Kirk-Othmer, Encycl. chem. technol., Bd. 7, New York, 22-39 (1965)

(10) Leo, A. et al., Chem. Reviews 71, 525&575 (1971)

(11) Fiedler, H., Chemical and physical properties worksheet (CAS Nr. 112-24-3), unveroeffentlicht (1989)

(12) Calculation Bayer AG, WV-UWS/Produktsicherheit, 1992

(13) Spitz, R.D., Diamines and higher amines, aliphatic, In: Kirk- Othmer, Encyclopedia of chemical technology, Vol.7, 580-602 (1979)

(14) Safety Data Sheet Dow Europe S.A., August 1993

(15) Baldwin, W.C.G, Pr. Roy. Soc. A, 167, 539-554 (1937)

(16) Atkinson, R., Ed., AOP, Rate of hydroxyl radical and ozone reaction from chemical structure, Version SRC 1.31, Syracuse Res. Co. University of California, Riverside, USA (1990)

(17) Hansen, E.B. et al., J. Anal. Toxicol. 9, 167-171 (1985)

(18) Bayer AG data

(19) unpublished report CRL I89039 from AKZO, 1989

(20) DOW Chemical Company, unpublished data (1978)

(21) unpublished report CRL I89044 from AKZO, 1989

(22) Van Wijk, R.J. et al., Environ. Toxicol. Chem. 13, 167-171 (1994)

(23) Dombrowicz, E. et al., Acta Pol. Pharm. 42, 184-191 (1985)

(24) unpublished report CRL F90088 from AKZO, 1990

(25) Schafer, E.W. et al., Arch. Environm. Contam. Toxicol. 12, 355-382 (1983)

(26) Lallier, R., C. R. Acad. Sc. Paris, Ser. D. 262, 1460-1463 (1966)

(27) Chatterjee, M. et al., Int. J. Environm. Stud. 24, 87-95 (1985)

(28) Chemical Hygiene Fellowship, Carnegie-Mellon University, Special Report 39-54 (1976); cited in BG Chemie, Toxikologische Bewertung Nr. 181, Triethylentetramin (1991)

(29) Bayer AG, Untersuchung von E 570 und Haerter T, unveroeffentlichter Bericht (1957)

(30) Smyth, H.F. et al., J. Ind. Hyg. Toxicol. 31, 60-62 (1949)

(31) Stavreva, M., Khig. Zdraveopaz. 22, 179-182 (1979); article in russian, data from TOXLINE abstract

(32) Kowalski, Z. et al., Chem. Abstracts 59, 6889 (1963)

(33) Srivastava, A. et al., Chemosphere 17, 839-844 (1988)

(34) Pletscher, A. et al., Z. Unfallmed. Berufskrankh. 47, 163-176 (1954)

(35) Maisey, J. et al., Contact Dermatitis 18, 133-137 (1988)

(36) Thorgeirsson, A., Acta Derm. Venereol. 58, 332-336 (1978)

(37) Markicevic, A. et al., Chem. Abstracts 61, 16688 (1964)

(38) Ormerod, A.D. et al., Contact Dermatitis 21, 326-329 (1989)

(39) Van Putten, P.B. et al., Contact Dermatitis 10, 146-150 (1984)

(40) Krajewska, D. and Rudzki, E., Contact Dermatitis 2, 135-138 (1976)

(41) Rudzki, E. and Krajewska, D., Contact Dermatitis 2, 311-313 (1976)

(42) Rudzki, E., Contact Dermatitis 4, 53 (1978)

(43) Balato, N. et al., Contact Dermatitis 15, 263-265 (1986)

(44) Jolanki, R. et al., Acta Derm. Venereol., S 134, 90-94 (1987)

(45) Camarasa, J.G. and Serra-Baldrich, E., Contact Dermatitis 20, 382 (1989)

(46) Oshima, H. et al., Contact Dermatitis 24, 138-139 (1991)

(47) Tosti, A. et al., Contact Dermatitis 19, 220-222 (1988)

(48) Welcker, A., Dermatol. Wochenschr. 132, 871-876 (1955)

(49) Grandjean, E., Brit. J. Industr. Med. 14, 1-4 (1957)

(50) Grandjean. E., Z. Praeventivmed. 2, 77-98 (1957)

(51) Fawcett, I.W. et al., Clinic. Allergy 7, 1-14 (1977)

(52) Rudzki, E. et al., Med. Pr. 32, 59-62 (1981); article in polish, data from TOXLINE abstract

(53) Greenman D.L. et al., Fundam. Appl. Toxicol. 29, 185-193 (1996)

(54) Dobryszycka, W. et al., Arch. Toxicol. 33, 73-80 (1974)

(55) Woyton, J. et al., Toxicol. Appl. Pharmacol. 32, 5-10 (1975)

(56) Dobryszycka, W. et al., Arch. Immunol. Therap. Exp. 23, 867-870 (1975)

(57) Szacki, J. et al., Arch. Immunol. Therap. Exp. 22, 123-128 (1974)

(58) Hedenstedt, A., Mutat. Res. 53, 198-199 (1978)

(59) Hulla, J. E. et al., Environ. Mutagen. 3, 332-333 (1981)

(60) Warren, G. et al., Mutat. Res. 88, 165-173 (1981)

(61) Heinz, N. and Schroeder, H.F., Drug Res. 31, 950-953 (1981)

(62) Mortelmans, K. et al., Environ. Mutagen. 8, S7, 1-119 (1986)

(63) Union Carbide Corporation, Bushy Run Res. Center, Report 50-43 (1987)

(64) Union Carbide Corporation, Bushy Run Res. Center, Report 50-9 (1987); cited in BG Chemie, Toxikologische Bewertung Nr. 181, Triethylentetramin (1991)

(65) Union Carbide Corporation, Bushy Run Res. Center, Report 43-127 (1981); cited in BG Chemie, Toxikologische Bewertung Nr. 181, Triethylentetramin (1991)

(66) Union Carbide Corporation, Bushy Run Res. Center, Report 44-11 (1981); cited in BG Chemie, Toxikologische Bewertung Nr.181, Triethylentetramin (1991)

(67) Union Carbide Corporation, Bushy Run Res. Center, Report 50-99 (1987); cited in BG Chemie, Toxikologische Bewertung Nr. 181, Triethylentetramin (1991)

(68) National Toxicology Program, Annual Plan for Fiscal Year 1986, report NTP-86-086, 72 (1986)

(69) Union Carbide Corporation, Bushy Run Res. Center, Report 50-122 (1987)

(70) Depass, L.R. et al., Fundam. Appl. Toxicol. 9, 807-811 (1987)

(71) Young, J.T., Grandjean, M. and Swaim, L.D., unpublished report of the DOW Chemical Corporation (1986)

(72) Ciba-Geigy Ltd., Report on TK 10458, report No. 830035 (1984), cited in BG Chemie, Toxikologische Bewertung Nr. 181, Triethyl- tetramin (1991)

(73) Cohen, N.L. et al., Fed. Proc. Fed. Am. Soc. Exp. Biol. 41, 944 (1982)

(74) Keen et al., Inflammatory Dis. Copper (Proc. Symp.) 109-121 (1982)

(75) Keen, C.L. et al., Lancet I, 1127 (1982)

(76) Keen, C.L. et al., Proc. Soc. Exp. Biol. Med. 173, 598-605 (1983)

(77) Cohen, N.L. et al., Drug-Nutr. Interactions 2, 203-210 (1983)

(78) Hurley, L.S. et al., Teratology 25, 51A (1982)

(79) Keen, C.L. et al., Teratology 25, 53A (1982)

(80) Union Carbide Corporation, Bushy run research center, Project report 50-127 (1988); cited in BG Chemie, Toxikologische Bewer- tung Nr. 181, Triethylentetramin (1991)

(81) Korhonen, A. et al., J. Appl. Toxicol. 3, 112-117 (1983)

(82) Bachmann, H. et al., Eur. Neurol. 29, 301-305 (1989)

(83) Brewer, G.J. et al., Semin. Neurol. 7, 209-219 (1987)

(84) Dubois, R.S. et al., J. Pediat. Gastroent. Nutr. 10, 77-81 (1990)

(85) Fromtling, R.A., Drugs of Today 23, 507-508 (1987)

(86) Haslam, R.H.A. et al., Dev. Pharmacol. Ther. 1, 318-324 (1980)

(87) Scheinberg, I.H. et al., New Engl. J. Med. 317, 209-213 (1987)

(88) Walshe, J.M., Lancet II, 1401-1402 (1969)

(89) Walshe, J.M., Lancet II, 643-647 (1982)

(90) Walshe, J.M., Prog. Clin. Biol. Res. 34, 271-280 (1979)

(91) Walshe, J.M., Quart. J. Med. 42, 441-452 (1973)

(92) Epstein, O. and Sherlock, S. Gastroentrology 78, 1442-1445 (1980)

(93) Pletscher, A. et al., Z. Unfallmed. Berufskrankh. 47, 163-176 (1954)

(94) Yano, E., Toxicol. Letters 37, 27-32 (1987)

(95) Zielhuis, R.L., J. Occup. Med. 3, 25-29 (1961)

(96) Burrows, D. et al., Contact Dermatitis 15, 55-57 (1986)

(97) Miyazaki, K. et al., Chem. Pharm. Bull. 38, 1035-1038 (1990)

(98) Loessner, S.R. et al., Acta Neurol. Scand. 83, 364-366 (1991)

(99) Sunderman, F.W. et al., Toxicol. Appl. Pharmacol. 38, 177-188 (1976)

(100) Gibbs, K. and J.M. Walshe, Clinic. Sci. Mol. Med. 53, 317-320 (1977)

(101) Allen, K.G.D. et al., Am. J. Vet. Res. 48, 28-30 (1987)

(102) Athar, M. et al., Fundam. Appl. Toxicol. 9, 26-33 (1987)

(103) Baselt, R.C., et al., Res. Communic. Chem. Pathol. Pharmac., 18, 677-689 (1977)

(104) Dwivedi,R.S. et al., Chemosphere 11, 925-932 (1978)

(105) Eybl, V. et al., Arch. Toxicol. Suppl. 13, 370-372 (1989)

(106) Misra, M. et al., Bull. Environm. Contam. Toxicol. 41, 172-184 (1988)

(107) Mitchell, J. et al., Clinical Toxicol. 12, 606-607 (1978)

(108) Planas-Bohne, F., Toxicol. Appl. Pharmacol. 50, 337-345 (1979)

(109) Tandon, S.K. et al., Environm. Res. 35, 237-245 (1984)

(110) Tewari, P.C. et al., Clin. Exp. Pharmacol. Physiol. 15, 71-75 (1988)

(111) Kobayashi, M. et al., Yakugaku Zasshi 110, 759-763 (1990)