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)

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