TETRAETHYLENE PENTAMINE

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I. IDENTIFICATION[1-3]

Chemical Name: Tetraethylene pentamine
Synonyms:1,2-Ethanediamine,N-(2-aminoethyl)-N'-(2-((2-aminoethyl)amino)ethyl); Tetren 1,4,7,10,13-Pentaazatridecane; DEH 26; TEPA; Tetraethyl pentamine
CAS Number: 112–57–2
Molecular Formula: $C_8H_{23}N_5$
Structural Formula:
$NH_2–(CH_2–CH_2–NH)_3– CH_2–CH_2–NH_2$
DOT #: UN 2320

II. CHEMICAL AND PHYSICAL PROPERTIES[1-3]

Physical State: Liquid (yellow)
Molecular Weight: 189.31
Conversion Factors: 1 ppm = 7.74 mg/m^3
1 mg/m^3 = 0.129 ppm at 25°C (77°F)
Melting Point: -30°C (-22°F)
Boiling Point: 340.3°C (644.5°F) at 760 mm Hg
Vapor Pressure: 8.0×10^{-7} mm Hg at 25°C(77°F)
Saturated Vapor Concentration: 0.001 ppm
Vapor Density: 6.53 (Air = 1)
Odor Description and Threshold: ammonia-like odor
Flammability Limits: LEL: not available
UEL: not available
Flash Point: 163°C (325°F), open cup
Autoignition Temperature: 321°C (610°F)
Specific Gravity: 0.9980 at 20°C (68°F) (water = 1)
Solubility: soluble in most organic solvents and water
Reactivity: incompatible with oxidizing materials, acids, aldehydes, ketones, epoxides, acrylates, and organic halides
Log K_{ow}: 1.503

III. USES AND VOLUMES[1]

Used as a solvent for acid gases, resins and dyes, as a chemical intermediate for lubricating oil additives and surfactants, in papermaking, and as a coagulation aid for synthetic rubber latex.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral*

LD_{50} = 3990 mg/kg, rat (sex and strain not specified)[1,3]
LD_{50} = 2140 mg/kg, rat (female, strain not specified)[4]

2. *Eye Irritation*

Instillation of undiluted tetraethylene pentamine (TEPA) in the rabbit eye produced severe ocular irritation/corrosion, severe pain, corneal damage and severe conjunctivitis with incomplete healing 7 days after cessation of exposure. When exposure to undiluted material was followed by immediate washing, slight pain, moderate conjunctivitis and slight corneal injury were observed, and the eyes appeared normal 7 days after exposure. Ocular exposure to 10 or 1% aqueous solutions of tetraethylenepentamine produced no adverse effects in the rabbit eye.[5]

3. *Skin Absorption*

LD_{50} = 660 mg/kg, rabbit (sex and strain not specified)[1,3]

4. *Skin Irritation*

TEPA was been evaluated in the US DOT skin corrosion test. The clipped skin of six female New Zealand albino rabbits was exposed to 0.5 ml under an occlusive dressing for 4 hours, and examined for erythema, oedema and necrosis immediately following exposure, and 24–48 hrs thereafter. A 4-hr exposure resulted in slight redness and swelling and irreversible necrosis to the skin of 3/6 rabbits. The test material was considered to be corrosive under the conditions of this test.[6]

5. *Skin Sensitization*

In a Magnusson and Kligman maximization test, Dunkin-Hartley guinea pigs were used to evaluate the skin sensitization potential of TEPA.[7] Groups of 10 male and 10 female guinea pigs each received 0.1 mL intradermal induction doses via injection into two sites of the clipped shoulder skin with: 50% water emulsion of Freund's complete adjuvant (FCA), TEPA, and TEPA in FCA/water emulsion. Epicutaneous induction doses were administered 7 days later via application of 0.2 mL of the test material applied to a 2 × 4 cm filter paper patch that was left in place for 48 hrs. Animals were challenged 14 days later by applying 2 × 2 cm filter paper patches soaked with 50% TEPA under occlusive dressings that were left in place for 24 hrs. Seven days after the TEPA challenge exposure, animals were cross-challenged epicutaneously with 6 related alkylamines. One of the 20 guinea pigs challenged with TEPA showed a positive response and the authors considered the test material to be a weak dermal sensitizer. Moderate to strong cross-sensitization was observed when TEPA-induced guinea pigs were challenged with 25% N-hydroxyethylendiamine, 50% triethylenetetramine, or 25% N-(2-aminoethyl)piperazine.

In a local lymph node assay (LLNA), groups of 4 female BALB/c mice each were exposed cutaneously on the dorsum of both ears to 25 uL of TEPA in vehicle (acetone:olive oil; 4:1), or 25 uL vehicle alone, for 3 consecutive days.[12] Test material concentrations used were 2.5, 5, 10 and 20% (v/v). A further group of 4 mice served as a negative control. Five days after initiation of exposure, all mice were administered an i.v. injection of 250 uL phosphate buffered saline containing 20 uCi of ^{3}H-methyl thymidine. Five hours later all mice were killed and the draining auricular lymph nodes were polled for each experimental group. A single cell suspension of lymph node cells was prepared by mechanical disaggregation. Incorporation of ^{3}H-methyl thymidine was measured by scintillation counting and expressed as group mean dpm. A stimulation index (SI) relative to the concurrent vehicle-treated control group was calculated. The calculated SI for 10% and 20% solutions was greater than 3, and on that basis the authors concluded that TEPA was positive in the LLNA.[12]

TEPA has been classified as a skin sensitizer (Xi;R43) in Annex I of the EU Dangerous Substances Directive.

6. *Inhalation Toxicity*

Very slight irritation was observed in rats exposed to what was reported to be a saturated atmosphere for 7 hours.[5]

7. *Other*

LD_{50} i.p. = 205 mg/kg, rat (sex and strain not specified).[3]
LD_{50} i.v. = 320 mg/kg, mouse (sex and strain not specified).[3]

B. Subacute Toxicity

No data found for tetraethylenepentamine.

C. Subchronic Toxicity

Groups of 5 New Zealand White rabbits/sex/dose were exposed percutaneously to 0, 50, 100, or 200 mg/kg of TEPA for 6 hrs/day, 5 days/weeks for 4 consecutive weeks.[9] The control animals were exposed to 1 mL/kg (1 mg/kg) water. All rabbits exposed to 100 or 200 mg/kg showed dose-related signs of skin irritation. No clinical signs of toxicity were observed, nor were there any significant differences between the controls and treated groups in body weights, clinical chemistry, organ weights, gross pathology or histopathology. The NOAEL for the study was set at 50 mg/kg/day for local effects and 200 mg/kg/day for systemic effects.

D. Chronic Toxicity/Carcinogenicity

A group of 50 male C3H/HeJ mice was exposed three times per week throughout their entire lifespan to 25 microliters (approx. 6.25 mg) of TEPA applied to a clipped site on the back of each animal. Control mice were similarly exposed to water. No significant effect on mean survival was observed when control and TEPA-treated mice were compared. No epidermal tumours were observed in the TEPA-treated mice, however 20 cases of hyperkeratosis and 13 cases of epidermal necrosis were recorded, indicating that chronic dermal exposure to TEPA induced irritation but not epidermal hyperplasia or dermal fibrosis. The authors concluded that there was no evidence of an oncogenic effect of TEPA under the conditions of this study.[10]

E. Developmental/Reproductive Toxicity

No data found for TEPA. TEPA is a copper-chelating agent, similar to trietheylenetetramine

(TETA). High oral doses of TETA produced maternal toxicity and developmental effects in animals that were attributed to copper deficiency.[13]

F. Genotoxicity/Mutagenicity

TEPA was tested in *S. typhimurium* strains TA1535, TA1537, TA97, TA98, and TA100 with and without S-9, at doses of 0.03, 0.10, 0.33, 1.0, 3.3, 6.6, or 10.0 mg/plate, in accordance with a standard NTP protocol. TEPA was positive in TA100 without metabolic activation and in TA98 with or without metabolic activation.[1] In another Ames assay, TEPA was tested in the same 5 strains of *S. typhimurium* at doses of 0.001, 0.003, 0.01, 0.03, 0.1 mg/plate, with and without S-9.[11] Under the conditions of this test, TEPA was negative with/without metabolic activation.

TEPA was also tested for gene mutations in Chinese Hamster Ovary (CHO) cells with and without S-9 and was negative at all doses.[11] Statistically significant and concentration-related effects on sister-chromatid exchange (SCE) frequencies were observed with or without S-9 in CHO cells exposed to TEPA.[11] TEPA also produced a statistically significant increase in unscheduled DNA synthesis (UDS) in rat hepatocytes at four of six test concentrations.[11]

TEPA was also tested in a mouse micronucleus assay.[11] Young adult Swiss-Webster mice (6–8 weeks old) were dosed via single i.p. injection with 200, 400 or 625 mg/kg TEPA. Triethyelenemelamine (0.3 ml/kg) was used as a positive control, water (10 ml/kg) served as the negative control. Blood samples were taken 30, 48, and 72 hrs after dosing and micronuclei in peripheral polychromatic erythrocytes were stained with Giemsa to determine the polychromatic:normochromtic erythrocyte ratio. No increase in the incidence of micronuclei was observed in erythrocytes from TEPA-treated mice.

These results suggest that TEPA has limited mutagenic potential, since it was positive in the SCE and UDS assays, was equivocal in the Ames assay, and was negative in the CHO gene mutation assay and the mouse micronucleus assay.

G. Metabolism and Pharmacokinetics

No data found for TEPA.

V. HUMAN USE AND EXPERIENCE

A case report of occupational contact dermatitis has been reported.[8] A male spray painter who had previously been diagnosed with hand dermatitis was patch tested with several epoxy resin hardeners used in 2-component epoxy resin paints cured with amine hardeners. A positive reaction to patch exposure to 1% TEPA was observed.

VI. RATIONALE

TEPA is a liquid with an ammonia-like odor and a very low vapor pressure at room temperature. Consequently, inhalation exposure is unlikely to occur unless it is heated, or where fogs or mists are produced. It is corrosive to skin and eyes. It has low acute toxicity via the oral route and is moderately toxic via the dermal route. TEPA was positive in the local lymph node assay in the mouse, produced weak dermal sensitization reactions in a maximization assay in the guinea pig, and has been reported as a human dermal sensitizer in a patch test of an occupationally exposed subject. Moderate to strong cross-sensitization reactions with N-hydroxyethyelendiamine, triethylenetetramine, and N-(2-aminoethyl) piperazine have been reported in the guinea pig. TEPA has limited mutagenic potential, since it was positive in SCE and UDS assays, was inconsistent in the Ames assay, and was negative in the CHO gene mutation assay and the mouse micronucleus assay. Aside from dermal irritation, no significant adverse effects were observed in a 28-day study in the rabbit in which NOAELs of 50 mg/kg/day for local effects and 200 mg/kg/day for systemic effects were established. Chronic dermal exposure to mice had no effect on the incidence of dermal tumours or lifespan of the exposed animals but did result in signs of dermal irritation.

An OEL Guide of 1 ppm, skin has been established for the related material triethylenetetramine. An ACGIH TLV® of 1 ppm, skin was established for dieth-ylenetriamine, based upon irritation and sensitization. The occupational exposure value for several related materials is 1 ppm (8 hr TWA). Based on the NOAELs of 50 and 200 mg/kg/day for TEPA, an OEL Guide of 5 mg/m^3 (~1 ppm) should provide adequate protection against possible irritation and systemic toxicity. A skin notation is recommended based on the dermal LD_{50} in rabbits. A DSENS notation is also recommended based on the animal and human evidence for skin sensitization with TEPA and the strong potential for cross-reactivity with similar materials.

VII. RECOMMENDED OEL

Based on its low vapor pressure, TEPA is likely to be present in workplace air primarily as an aerosol. An OEL Guide of 5 mg/m^s (~1 ppm) (aerosol), skin, DSEN is proposed.

VIII. REFERENCES

Databases consulted during this review include: HSDB; RTECS; TOXLINE; TSCATS; DART

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