

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

COPPER -TRIETHANOLAMINE COMPLEXES

Chemical Code # 1615 and 1826, Tolerance # 50335 and 50346
January 13, 2003

Note: The studies reviewed were conducted with triethanolamine.

I. DATA GAP STATUS¹

Chronic toxicity, rat:	No study on file
Chronic toxicity, dog:	No study on file
Oncogenicity, rat:	No study on file [several studies from the literature and NTP]
Oncogenicity, mouse:	No study on file [several studies from the literature and NTP]
Reproduction, rat:	No study on file
Teratology, rat:	No study on file
Teratology, rabbit:	No study on file
Gene mutation:	No study on file [publication and summary statement from NTP]
Chromosome effects:	No study on file
DNA damage:	No study on file
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 114624 were examined.

** Indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T030113

Compiled by J. Gee, 1/13/03

¹ The triethanolamine complexes of copper hydroxide (CC 1826) and copper sulfate (CC 1615) have been grouped with copper hydroxide for toxicological testing purposes. The required health effects studies mandated by SB950 have been waived for copper hydroxide and copper compounds grouped with it. No further testing of either copper complex is required under SB950 at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

National Toxicology Program, "Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344 Rats and B6C3F₁ Mice (Dermal Studies)." (1999.) This report is not on file with the Department. A summary of the study was obtained from the NTP web site. Triethanolamine (>98% purity) was applied to the skin of rats and mice for 13 weeks or 2 years. Included in the report were genotoxicity studies with *Salmonella typhimurium*, Chinese hamster ovary cells, *Drosophila melanogaster* and mouse peripheral lymphocytes. **13 weeks, rats:** Groups of 10 per sex were administered dermal doses of 0, 125, 250, 500 or 1000 mg/kg body weight in acetone or 2000 mg/kg TEA neat, 5 days per week for 13 weeks. Body weights were lower at 1000 mg/kg (F) and above (both sexes). Clinical observations of the skin were noted at 2000 mg/kg. Kidney weights were higher at 500 mg/kg and above. NOEL unclear from summary statements. **13 weeks, mice:** Ten per sex were administered dermal doses of 0, 250, 500, 1000 or 2000 mg/kg in acetone or 4000 mg/kg neat, 5 days per week for 13 weeks. Skin findings were noted at 4000 mg/kg. Body weights were lower at 250 mg/kg. Kidney weights of females in all groups were higher than controls and for males at 1000 mg/kg and higher. Acanthosis was noted in all treated groups. **2-year, rats:** Groups of 60 rats per sex were given dermal doses of 0, 63, 125 and 250 mg/kg (F) and 0, 32, 63 and 125 mg/kg (M), administered topically in acetone, 5 days per week for 103 weeks. Hours per day not stated. Ten/sex/group were evaluated at 15 months. Skin lesions (acanthosis, inflammation, ulcers) were increased in all treated groups of females and at 125 mg/kg for males. No skin neoplasms were observed. Renal tubule adenomas were observed in males at 0/50, 2/50, 6/49 and 4/50, controls through high dose, including animals with extended kidney evaluations. The incidence of hyperplasia in males was similar across groups but the severity increased at 32 and 125 mg/kg. There was no evidence of treatment-related kidney findings in females. The conclusion was that the evidence for carcinogenesis in males was "equivocal" and "no evidence" in female rats. **2-year, mice:** Sixty/sex/group were administered topical doses of 0, 200, 630 and 2000 mg/kg (M) or 0, 100, 300 and 1000 mg/kg (F), 5 days per week, in acetone. Ten/sex/group were evaluated at 15 months. Skin irritation was noted in all groups of treated males. Kidney weights were increased at 15 months in males at 630 and 2000 mg/kg. Acanthosis and inflammation of the skin were noted at the application site of males and females at 15 months and termination with the incidence increased at the high dose, both sexes and at 630 mg/kg in males. The summary states that the severity did not increase with dose. The incidences of liver adenomas, animals with multiple adenomas, and adenoma/carcinomas increased, especially at the high dose, in both sexes. The findings were confounded by a liver infection with *Helicobacter hepaticus* and the conclusion was the study with mice was "inadequate" due to the infection. **Genotoxicity:** No data were presented but the following

conclusions were made. TEA was negative in *Salmonella typhimurium*, did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells *in vitro* with and without activation. It did not induce sex-linked recessive lethal mutations in germ cells of *Drosophila melanogaster* by feeding or injection and did not increase the incidence of micronuclei in peripheral erythrocytes of male and female mice by dermal applications. Full report is not on file. (Gee, 12/18/02)

No record number. "Lack of carcinogenicity of triethanolamine in F344 rats." (Maekawa, A., H. Onodera, H. Tanigawa, K. Furuta, J. Kanno, C. Matsuoka, T. Ogiu and Y. Hayashi, publ. in *J. Toxicol. Environ. Health* 19: 345 - 357 (1986)) Triethanolamine (99.0%), dissolved in drinking water, was given to groups of 50 Fischer (F344/DuCrj) rats per sex at 0, 1 or 2% for 104 weeks, followed by about 9 weeks of observation until week 113 when remaining animals were sacrificed. About week 69, doses for females were reduced by half, due to loss of body weight and mortality. Major organs and tissues were examined pathologically. Body weights in both sexes were lower in the treated groups and survival in females was dose related, being 84%, 68% and 58% in control through high dose. Absolute and relative weights of kidneys were increased with dose for both sexes. Although there was a statistically significant trend for hepatic tumors in males and uterine endometrial sarcomas and renal-cell adenomas in females, the authors concluded that, because the control incidences were lower than historical values, triethanolamine was not carcinogenic. There was, however, evidence for nonneoplastic toxicity to the kidneys, especially for females, as an increase in severity of chronic nephropathy, mineralization of the papilla, nodular hyperplasia of the pelvic mucosa, and hydronephrosis. **Possible adverse effects to kidneys.** No worksheet. (Gee, 1/13/03)

ONCOGENICITY, MOUSE

See also under Oncogenicity, rat.

No record number. "Chronic toxicity carcinogenicity studies of triethanolamine in B6C3F1 mice." (Konishi, Y., A. Denda, K. Uchida, Y. Emi, H. Ura, Y. Yokose, K. Shiraiwa and M. Tsutsumi, publ. in *Fundamental and Applied Toxicol.* 18 (1): 25 - 29 (1992)) Triethanolamine (special reagent grade, 1.9 % diethanolamine) was given to groups of 50 mice/sex in drinking water at 0, 1 or 2% for 82 weeks. [In another study, concentrations of 4 and 8% led to decreased water intake.] Appropriate organs were weighed and most required tissues were collected. Body weights in both sexes late in the study were slightly lower at 2% TEA. There was no affect on survival. There were no significant differences in organ weights. There was no treatment-related increase in tumors compared with controls. No adverse effects. Unacceptable (summary data only, missing parameters and tissues). No worksheet. (Gee, 12/19/02)

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

No study on file.

TERATOLOGY, RABBIT

No study on file.

GENE MUTATION

No study on file.

No record number. "Mutagenicity tests and in vitro transformation assays on triethanolamine." (Inoue, K., T. Sunakawa, K. Okamoto and Y. Tanaka, publ. in *Mutation Research* 101: 305 - 313 (1982)) Four assays were conducted with triethanolamine (purity not stated). *Rec* assay with *Bacillus subtilis* H17 and M45 strains (-S9), preincubation mutation assay with *Salmonella typhimurium* TA98, TA100 and *E. coli* WP2 (\pm S9), chromosomal aberration assay with CHL cells (- S9) and cell transformation (- S9) with primary hamster embryo cells. *Rec* assay was conducted with 0, 40, 200, 800, 2000 and 4000 μ g/disk with negative results. The assay with *Salmonella*, using a 20-minute preincubation step, was conducted with 0, 1, 5, 10, 50, 100, 500, 1000, 5000, 10000 and 20000 μ g/plate with no evidence of increased revertants with or without activation. Chromosome aberrations were not increased in CHL cells after 24 or 48 hours of treatment at 0, 5, 10, 25, 50 or 100 μ g/ml. Exposure of hamster embryo cells to 0, 25, 50, 100, 200 or 500 μ g/ml did not result in cell transformation. Positive controls were functional in all four assays. No worksheet. (Gee, 1/13/03)

CHROMOSOME EFFECTS

No study on file.

See under Gene Mutation above.

DNA DAMAGE

No study on file.

See under Gene Mutation above.

NEUROTOXICITY

Not required at this time.

OTHER - TRIETHANOLAMINE

50335 - 007 114623 "The Alkanolamines Handbook", 1988, The Dow Chemical Company, page 148. This page contains a very brief summary regarding the toxicity of the alkanolamines.

Oral: Stated to be of low acute toxicity.

Vapor: Vapors can be irritating to the eyes and nose and exposure should be kept below the TLVs.

Eyes: Triethanolamine and their solutions have an irritating action on the eyes but no corneal injury is expected.

Skin: undiluted triethanolamine is slightly to moderately irritating to the skin with a burn possible from prolonged contact.

50335 - 007 114624 "Final Report of the Safety Assessment for Triethanolamine, Diethanolamine, monoethanolamine." (The Expert Panel of the Cosmetic Ingredient Review, 5/19/83) Record consists of 55 pages containing summary data for the ethanolamines. The overall conclusions of the Panel were that TEA was safe for cosmetics designed for discontinuous, brief use followed by rinsing of the skin. TEA should not be used in products containing N-nitrosating agents as N-nitrosodiethanolamine (NDELA), which is carcinogenic in lab animals, may result. Acute oral toxicity: Table 4 presents the results of the LD50 determination of a number of studies of several purities using rats. Values ranged from a low of 4.19 g/kg (78.6%

purity) to 9 g/kg for higher purity. Subchronic and chronic oral toxicity: Results of several studies were presented in Table 5. Rats and guinea pigs were used with dosing lasting from 60 days to 6 months. Studies were conducted between 1940 and 1976. From the summary statements of results, the liver, kidney and peripheral optic nerves appeared to be the targets for effects. The NOEL of 0.08 g/kg/day was obtained from a 1951 study using rats and TEA of unknown purity. The other studies showed some affect at all doses. Acute dermal toxicity: TEA of 91.8 and 88.1% purity (both containing 6% DEA) was applied to skin of rabbits for 24 hours occluded. Both elicited mild to moderate erythema but no edema, with a return to normal by day 6 or 10. Subchronic and chronic dermal toxicity: A 6.5% solution of TEA applied for 1 hour, 5 days/week, for 6 months to rats produced no observed toxic effects. A 13% solution caused changes in the liver and central nervous system function (no specifics). Primary skin irritation: TEA (99%), applied to the skin of rabbits for 1, 3 or 10 applications of 24 hours, was considered to cause slight to moderate irritation. Dermal sensitization: Studies with guinea pigs did not indicate sensitization. Other affects: High concentrations of TEA were irritating to the rabbit eye. Genotoxicity: TEA up to 100 mg/plate was negative with and without activation with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. TEA alone was negative with *Bacillus subtilis* for mutagenicity. TEA up to 10^{-1} M was negative for UDS with primary rat hepatocytes. Oncogenicity: TEA, 99% or >80%, was negative when applied to mouse skin for 14 to 18 months. When fed to ICR-JCL mice at 0, 0.03 or 0.3% for a life span, the incidence of malignant tumors (not identified) for females was 2.8, 27 and 36% and males, 2.9, 9.1 and 3.6%. Developmental and reproductive effects: Pregnant rats were exposed dermally to 0.1 to 0.15% TEA in hair dye on days 1, 4, 7, 10, 13, 16 and 19 of gestation. No affects were reported in a 1976 study. (Gee, 12/18/02)

No record number. "Absorption, distribution, metabolism and excretion of intravenously and dermally administered triethanolamine in mice." (Stott, W. T., J. M. Waechter, Jr., D. L. Rick and A. L. Mendrala, publ. in: *Food and Chemical Toxicology* 38 (11): 1043 - 1051 (2000)) ^{14}C -Triethanolamine (98.6% radiopurity) and non-labeled TEA (99.6%) were used. Male C3H/HeJ mice (27) were injected iv with aqueous ^{14}C -TEA at 1 mg/kg. Blood was collected from 3 mice at 0.083, 0.167, 0.5, 1, 2, 4, 6, 12 and 24 hours post-dosing. Urine, feces and CO_2 were collected at 12 and 24 hours. At termination, the liver and kidneys were excised. The radioactivity in urine, feces, CO_2 , liver, kidneys and carcass were determined. Dermal applications of 2000 mg/kg TEA (neat) without occlusion, 1000 mg/kg in acetone (unoccluded), 2000 mg/kg (neat, occluded) and 2000 mg/kg in water (neutralized, occluded) were made to approximately 2 cm^2 of skin. For comparison, three F344 rats were dosed with 1000 mg/kg TEA (neat), occluded. Radioactivity at timed intervals in urine, feces, livers, kidneys, carcass and skin was determined. Results: Clearance from blood following iv injection was biphasic with $t_{1/2}$ of 0.3 hr, first phase, and $t_{1/2}$ of 10 hours, second phase, with radioactivity still detectable at 24 hours. Following dermal application of 2000 mg/kg, neat, unoccluded, TEA reached peak levels in blood by 3 hours post-dosing with a half-life of absorption of 0.7 hours. Elimination from blood followed a bi-exponential pattern with $t_{1/2}$ s of 1.9 and 31 hours. Radioactivity was still detectable at 48 hours. Excretion was primarily in the urine (49 - 69% of total dose, 58 - 79% of absorbed dose), followed by feces (16 - 28% of total dose, 19 - 32% of absorbed dose) regardless of route or vehicle. Excretion in urine was primarily in the first 24 hours. Tissue/organ distribution was carcass > liver > kidney. Results with F344 male rats given TEA were similar. Analysis of urine by ion-exchange liquid chromatography indicated most of the excreted material was unchanged TEA. No mono- or diethanolamine were found in urine. Greater than 82% of dermally applied TEA was absorbed by mice. Supplemental data. No worksheet. (Gee, 12/19/02)

No record number. "Subchronic dermal toxicity study of triethanolamine in C3H/HeJ mice."

(DePass, L. R., E. H. Fowler and H.-W Leung, publ. in: *Food Chemical Toxic.* 33 (8): 675 - 680 (1995)) Triethanolamine (98.2%) was applied to the skin of C3H/HeJ male and female mice, 15/sex/dose, at 0 (acetone), 10, 33 and 100% (undiluted), three times per week (Monday, Wednesday and Friday), for 95 days, with 37 applications. Based on body weight, doses were calculated to be 0.14, 0.46 or 2.0 g/kg for males and 0.16, 0.54 or 2.3 g/kg for females. Ten mice per sex per dose level were used for hematology and clinical chemistry evaluations. Testes, liver, kidneys, brain, heart, spleen and thymus were weighed. Most organs/tissues were examined histologically from control and high dose animals. No clinical signs or skin irritation were noted. The only pathology was a slight thickening of the treated skin of males and females consisting of an increase of one to three cell layers. The incidences of males/females from control through high dose were: 2/0, 14/12, 13/14 and 12/15, with slightly more evidence at 100 % TEA and was considered to be associated with mild irritation. Effects on liver and kidneys were not observed (no data). Supplemental data. No worksheet. (Gee, 12/19/02).