Safety Assessment of Tromethamine, Aminomethyl Propanediol, and Aminoethyl Propanediol as Used in Cosmetics

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ABSTRACT
This is a safety assessment of tromethamine, aminomethyl propanediol, and aminoethyl propanediol in cosmetics. These ingredients function as pH adjusters. The CIR Expert Panel reviewed relevant animal and human data related to these ingredients. The similarities in molecular structures, properties, functions and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of individual members of the group. The Panel concluded that tromethamine, aminomethyl propanediol, and aminoethyl propanediol are safe in the present practices of use and concentration described in this safety assessment in cosmetics.

INTRODUCTION
Tromethamine (also referred to as Tris and THAM) is used in cosmetics primarily as a pH adjuster. Aminomethyl propanediol (AMPD; 2-amino-2-methyl-1,3-propanediol) and aminoethyl propanediol (AEPD; 2-amino-2-ethyl-1,3-propanediol) function as pH adjusters in cosmetics.

The similarities in molecular structures, physicochemical properties, and functions and concentrations in cosmetics enable reading across the available toxicological data to support the safety assessment of the entire group.

The Cosmetic Ingredient Review (CIR) issued a safety assessment of aminomethyl propanediol in 1990, concluding that it is safe in the present practices of use up to 1%. This conclusion was amended in 2009 with a safe as used conclusion. The summaries of these safety assessments are provided below. New data received are incorporated in this report. Also included in the text is new information provided on the pH or form (i.e., free base, salt) of these ingredients used in various studies.

CHEMISTRY
Definition and Structure
The ingredients in this report are related by a core 2-aminopropane-1,3-diol structure, with differentiation between the three ingredients corresponding to varied substitution at the 2-position. Tromethamine is an organic amine proton acceptor, with substitution at the 2 position.

![Figure 1. Tromethamine](image1)

It is used in the synthesis of surface-active agents and as a biological buffer, because of the multitude of polar functional groups and alkalinity.

Aminomethyl propanediol and aminoethyl propanediol are substituted at the 2-position with a methyl or ethyl group, respectively.

![Figure 2. Aminomethyl propanediol and aminoethyl propanediol](image2)

Definitions and functions are provided in Table 1.

Physical and Chemical Properties
These ingredients are small, polar, and crystalline materials with high water solubilities and octanol water partition coefficients (free base) in the range of -1 to -2. Tromethamine is reported to be stable when exposed to light. Physical and chemical properties are presented in Table 2.

Method of Manufacture
Tromethamine is prepared by the reduction of tris(hydroxymethyl)nitromethane. Tromethamine may also be manufactured by additively reacting nitromethane with formaldehyde to yield tris(hydroxymethyl) nitromethane, which is then reduced, via hydrogenation with the aid of the catalyst, Raney® Nickel.
Impurities

A manufacturer reported that cosmetic grade tromethamine was 99% pure. Secondary amines, anhydrous were present at a maximum of 0.5% wt.; nitrosamines at 50 ppb (below the levels of detection), and water at 0.2% wt. Nickel, which may leach from the skeletal catalyst used in the manufacture of tromethamine, was present at < 10 ppm; other metals are not expected to be present due to non-use. Methanol, used as a solvent in the manufacture process, is limited to 3000 ppm; the typical value is < 100 ppm.

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 3). A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations.10,11

Tromethamine is used in 488 leave-on products and 70 rinse-off products. It was reported to be used up to 3.7% in leave-on nail creams and lotions. Other products include eye makeup up to 2%, fragrance preparations up to 0.2%, and skin care preparations up to 3.1%.

Aminomethyl propanediol was reported by the VCRP to be used in 131 leave-on products including 121 in the eye area in 2 rinse-off products (skin cleansing products and hair dyes and colors). It was reported to be used in leave-on products up to 2%. It is also reported to be used in skin cleansing products up to 0.5% and hair dyes and colors up to 0.9%. This is a decrease in use from 2007; concentrations of use are similar. It was reported that aminomethyl propanediol was used up to 2% in leave-on products and up to 1% in rinse-off products.7 These include: up to 2% in eye products; 0.08% - 1% in makeup preparations; 0.01% - 1% in skin care preparations and 1% in suntan preparations.

There were no reported uses for aminoethyl propanediol by the VCRP or concentrations of use by the Council.

Tromethamine was reported to be used in fragrance preparations up to 0.2%, that may be propellant and pump spray products, as well as in face powders and fragrance powders up to 0.05% that could possibly be inhaled. Aminomethyl propanediol was reported to be used in hair sprays up to 1.2% In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.12,15 Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.16-21

Non-Cosmetic

Tromethamine is used in the synthesis of surface-active agents, vulcanization accelerators, and pharmaceuticals. It is also reported to be used as an emulsifying agent for mineral oil and paraffin wax emulsions, leather dressings, textile specialties, polishes, cleaning compounds, and so-called soluble oils. It is used as an absorbent for acidic gases and as a biological buffer.22 Tromethamine was reported to be used as a commercial emulsifier.23

Tromethamine has several medical uses which include:

- Orally administered tromethamine citrate syrup (1.5-9 mmol/kg) is used to treat renal acidosis, adjusted to maintain urinary pH, and for chemolysis of renal calculi.24
- Intravenously administered tromethamine (15 mmol/kg or 3.5 L of 0.3 mol/L maximum) is used in the treatment of adult and infant respiratory distress syndromes and in the management of increased intracranial pressure after trauma, over several days.25-27
- Intravenously administered tromethamine is used to treat acidosis during pulmonary bypass and cardio surgery that requires hypothermic techniques.28-31
- Intravenously administered tromethamine is used to treat acidosis in burn victims.32
- Tromethamine (~60% of 0.15 mol/L) administered peritoneally has been used for the treatment of intoxication with salicylates, barbiturates and methyl alcohol (methanol).26,33,34
- Tromethamine, mixed with hydrochloric acid (to a pH of 9.2) or acetate, sodium bicarbonate and disodium phosphate (to a pH of 8.1), is used for peritoneal dialysis to treat acidemia in humans and will cause alkalization of the plasma.26

In veterinary medicine, tromethamine is an amine pH buffer prescribed for the prevention and correction of metabolic acidosis, usually as a 0.3 M solution (0.3 mEq/mL) in a 7.5% sodium bicarbonate (q.v.) solution.35

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Tromethamine is eliminated by the kidneys. Ionized tromethamine is rapidly and preferentially excreted in urine at a rate associated with the infusion rate. Urinary excretion continues over a period of 3 days; 75% or more appears in the
urine after 8 hours. Other studies report 50% - 75% of an i.v. dose was recovered in urine within 24 h. Recovery of orally administered tromethamine in urine from healthy adults is reported to be 64% and 77% after 2 and 3 days, respectively. Excretion of tromethamine is accompanied by osmotic diuresis, since clinical doses of tromethamine considerably adds to osmolarity of glomerular filtrate. Tromethamine may accumulate in patients with renal insufficiency, and produce an ‘osmolar gap’ with pseudohyponatremia.

It is not known whether tromethamine is distributed into human milk.

**Dermal/Percutaneous**

**TROMETHAMINE**

Dermal absorption was < 1% when radiolabeled tromethamine hydrochloride (0.1% and 10%; 100 μL; vehicle not provided) was administered to dermatomed, thawed human skin in Franz cells. The receptor fluid was sampled at 2, 4, 6, 8, and 10 h. After washing, the retention of tromethamine hydrochloride in the dermis and epidermis was 0.13%-0.14% and 0.69%-0.22%, respectively. The test material was not retained in the horny layer. The washing waters contained more than 90% of the applied dose. Recovery of the test material by washing was > 90%.

**Oral**

**TROMETHAMINE**

In human subjects, daily administration of tromethamine citrate syrup (3 and 6 mmol/kg) produced urinary alkalization (pH increasing from a range of 5.6 - 6.8 to 7.2-7.3).

**Intravenous**

**TROMETHAMINE**

When administered intravenously (i.v.) in a bolus or over a short-term, tromethamine rapidly distributes into the intracellular spaces and raises the pH of plasma. Cells slowly take up the tromethamine; the rate of uptake increases when the pH is more alkaline. However, one study’s conclusion contradicts the findings of previous studies suggesting that tromethamine permeates very slowly into the intracellular space. A representative set of studies are presented here as well as the study with the opposite conclusion.

In rats of different ages (5 to 240 days old) the renal excretion of tromethamine was studied. In older rats the renal excretion of tromethamine was slower than in rats of other age groups. Stimulation of diuresis by i.p. injection of mannitol, thiazide, or by oral water load resulted in an increase in tromethamine excretion in 5- and in 240-day-old rats. The renal excretion of tromethamine was also increased by repeated administration of tromethamine in all age groups, except in newborn rats.

When 14C-tromethamine is administered i.v. to nephrectomized Sprague-Dawley rats (n = 21-26; with blood stabilized at pH 7.5, 7.4, 7.2), the authors concluded: 1) tromethamine diffuses very slowly into the intracellular spaces of various tissues; 2) the intracellular concentration of tromethamine increased faster with the higher pH; 3) the rate of increase of tromethamine was the same in spleen, heart, skeletal muscle, and brain tissue; 4) tromethamine diffusion into liver cells is rapid, which is not so for spleen, heart, skeletal muscle, and brain tissue; and 5) the intracellular steady state was only reached in the liver. The rats were nephrectomized and catheterized (venous and arterial). After administration of the test material, some of the rats were killed and necropsied at 60, 180, 360, 720, and 1440 min. The experiment was repeated (n = 26) with the blood stabilized at pH 7.4. The authors concluded that the mechanism of tromethamine therapy is its elimination of H+ ions from the extracellular space and the generation of bicarbonate that then penetrates the intracellular compartments.

When 14C-tromethamine (5 μci) was administered i.p. to nephrectomized Wistar rats (n = 6), the half-life in the plasma was 90 min. The half-times to equilibrium for tromethamine distributed to heart and skeletal muscle were 2.7 and 5 h, respectively. Distribution to the brain and cerebrospinal fluid were very slow and a constant tissue to plasma ratio in the brain was not obtained at 24 h. The rats were killed and samples of blood, cerebrospinal fluid, skeletal muscle and cerebral cortex analyzed at 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300, and 360 min after the test material was administered. In a second experiment, when administered i.p. to rats, the largest amount of 14C-tromethamine was collected in skeletal and heart muscle at 12 and 24 h. Accumulation was slower in brain tissue and cerebrospinal fluid.

Rabbits (strain and number not provided) were intravenously injected with tromethamine (5 - 100 mL/kg; 0.3 M at pH 5.5 and 7.4) daily for 1 – 99 days. The amount of tromethamine excreted in the urine reached a maximum at the end of infusion, and dropped rapidly after infusion stopped. Only a small quantity of chloride was excreted in the urine in any group. Rabbits administered tromethamine at pH 5.5 excreted a larger amount of chloride in the urine than those administered tromethamine at pH 7.4. The amount of tromethamine excreted in the urine reached a maximum at the end of infusion, and dropped rapidly after infusion stopped. Only a small quantity of chloride was excreted in the urine in any group. Rabbits administered tromethamine at pH 5.5 excreted a larger amount of chloride in the urine than those administered tromethamine at pH 7.4. At the end of the 7 hours, 44% and 77% of the infused tromethamine was found in the urine in the pH 7.4 and pH 5.5 groups, respectively. Blood sampling showed that the glucose concentrations decreased during the infusions, but returned to normal or above normal following the end of the infusions (tromethamine-induced hypoglycemia persisted longer than the tromethamine-neutralized). Both treatments caused transient hypoglycemia. Studies with extracted blood (tromethamine added to blood droplets) also determined that there was no deleterious effect on erythrocytes 0.3 M.

Tromethamine (121 mg/kg; 1 mmol/kg; pH 7.4) was primarily eliminated by the kidneys (82% was recovered in the
urine at 24 h) when administered i.v. to healthy subjects (n = 6) and subjects with metabolic acidosis (n = 20).\textsuperscript{40}

Tromethamine did accumulate in the tissues, but equilibrium was slow. The distribution of \textsuperscript{14}C-labeled tromethamine was determined between intra- and extracellular space of nephrectomized Sprague-Dawley rats (n = 5) as a function of time at constant plasma pH of 7.4.\textsuperscript{46} An equilibrium in the distribution of tromethamine between external and internal cellular spaces was observed at 6-12 h after administration. The authors concluded that tromethamine permeates very slowly into intracellular spaces, in contrast to previous conclusions that it quickly diffuses into intracellular spaces to restore normal intracellular pH. The authors concluded that tromethamine passed from extracellular spaces in a multi-exponential fashion, indicating that it passes to different body tissues at variable rates and is in ionized form when transferring across cellular membranes.

**Cytotoxicity**

TROMETHAMINE

In cytotoxicity assays using multiple cell lines, the IC\textsubscript{50} for tromethamine ranged from 129.07 - 404.37 μg/ml. In the 2,5-Diphenyl-3-((4,5-dimethyl-2-thiazolyl) tetrazolium bromide (MTT) assay, after exposure for 24 h, the IC\textsubscript{50}s were ~330 μg/ml for 3T3 cells, ~160 μg/ml for 3T6 cells, ~340 μg/ml for HaCaT cells, ~180 μg/ml for NCTC 2544 cells, ~340 μg/ml for HeLa cells, and ~405 μg/ml for MCF-7 cells. In the neutral red uptake (NRU) assay, the IC\textsubscript{50}s were ~295 μg/ml for 3T3 cells, ~130 μg/ml for 3T6 cells, ~160 μg/ml for HaCaT cells, ~190 μg/ml for NCTC 2544 cells, ~190 μg/ml for HeLa cells, and ~315 μg/ml for MCF-7 cells.\textsuperscript{47}

**Physiological Effects**

TROMETHAMINE

Because tromethamine (in the form of R-NH\textsubscript{2}) is a proton acceptor with a pK of 7.8, it is an effective buffer that can be used to maintain the pH of body fluids.\textsuperscript{26} Oral administration of tromethamine (20 g) resulted in alkalinization of the body fluids in humans.\textsuperscript{48}

Tromethamine i.v. caused a decrease in blood glucose levels in rats (5 mmol/kg, pH 7.4), rabbits (0.3 M), dogs (10 mmol/kg, pH 6.1), and humans (1 mmol, 0.3 mol/L, pH 10.9).\textsuperscript{43,44,49,51} Tromethamine lowered the blood sugar of dogs after the removal of the pancreas when given a few hours after pancreatectomy, but had little or no effect on the blood sugar of pancreatectomized dogs if insulin was withheld for 18 hours or longer before tromethamine was administered.

Hypoglycemic effect of tromethamine was due to the release of insulin and its activity.\textsuperscript{51} Tromethamine-induced hypoglycemia is associated with a transient stimulation of insulin secretion in rats. A bolus injection of neutralized tromethamine (5 mmol/kg; pH 7.4) caused a transient increase of plasma insulin concentration (130 ± 20 μU/mL) but did not change the glucose concentration in male Wistar rats (n = 6). However, a continuous infusion of tromethamine (0.5 mol/kg/min) for 90 min decreased the plasma glucose concentration (8.7 ± 0.42 to 5.1 ± 0.33 mmol/L) after 30 min. The plasma insulin concentration was elevated during the first 20 min (max ± 122 ± 21 μU/mL after 10 min). In streptozotocin-diabetic rats (administered 48 h prior to the experiments), an infusion of tromethamine changed neither glucose nor insulin concentration in plasma.

**TOXICOLOGICAL STUDIES**

**Acute Toxicity**

**Oral – Non-Human**

TROMETHAMINE

The oral LD\textsubscript{50} for mice was reported to range from 3350 to 5500 mg/kg (Table 4). For rats, the LD\textsubscript{50} was > 5000 mg/kg. The LD\textsubscript{50} for rabbits was between 1000 and 2000 mg/kg.\textsuperscript{49,52,53}

**Dermal – Non-Human**

TROMETHAMINE

The dermal LD\textsubscript{50} of tromethamine for rats was reported to be > 5000 mg/kg for rats (Table 4).\textsuperscript{54}

**Subcutaneous – Non-Human**

TROMETHAMINE

The subcutaneous LD\textsubscript{50} was reported to be > 1000 mg/kg for mice and rats (Table 4).\textsuperscript{49}

**Intraperitoneal – Non-Human**

TROMETHAMINE

The intraperitoneal LD\textsubscript{50} of tromethamine for mice was reported to be ~3350 mg/kg (Table 4).\textsuperscript{55,56}
**Intravenous – Non-Human**

TROMETHAMINE

The intravenous LD₅₀ of tromethamine for mice was reported to be 16.5 mM/kg (Table 4). There were no mortalities reported at < 5000 mg/kg. The LD₅₀ for rats was reported to range between 3.28 and 4.04 g/kg and up to ~6000 mg/kg. There were no treatment related mortalities in rabbits administered tromethamine up to 500 mg/kg. In dogs, the LC₅₀ was reported to be >125 mg/kg.44,49,57,58

Dogs (breed not specified) exhibited profuse diuresis during i.v. treatment with tromethamine.37 Dogs (n = 5) were anesthetized and rendered apneic using succinylcholine chloride. Apnea was then induced by barbiturates. Under oxygen saturation, tromethamine (0.3 M; 1.1 ml/kg/min) was administered by i.v.

**Repeated Dose Toxicity**

**Oral – Non-Human**

TROMETHAMINE

The NOAEL for local toxicity was 100 mg/kg/d and ≥ 1000 mg/kg/d for systemic toxicity for Crl:CD(D) rats (n = 10) orally administered tromethamine (100, 300, 1000 mg/kg/d adjusted to pH 9) by gavage in a reproduction study.54 Males (n = 10) were treated for at least 2 weeks before breeding up to 29 days. Females (n = 12) were treated from 2 weeks prior to breeding, through gestation, and through 4 days of lactation for up to 54 days. There were no systemic effects but there was irritation to the forstomach.

When tromethamine (2500 mg/kg) was orally administered to rats (n = 38; strain not provided) for 15 days, there were no mortalities or clinical signs observed.54 When tromethamine (250-4000 mg/kg) was orally administered to male rats (n = 36; strain not provided) for 31 days, there were no mortalities or clinical signs observed except for moderate diarrhea in the highest dose.54 Dogs (n = 12/dose; strain not specified) orally administered tromethamine (250, 1000, 4000 mg/kg) for 30 days had no mortalities.54 Dogs in the mid dose group had occasional loose stools and vomiting. Dogs in the high dose group had frequent loose stools and vomiting. Urinalysis showed decreased urinary potassium in the mid and high dose groups. The authors considered the NOAEL to be 4000 mg/kg because none of the effects were considered permanent.

**Dermal – Non-Human**

TROMETHAMINE

There were no clinical signs observed in rabbits (strain and number not provided) dermally administered tromethamine (100%) on clipped skin for 4 h for 5 days.53

**Intravenous – Non-Human**

TROMETHAMINE

There were no clinical signs or mortalities observed in mice (strain and number not provided) administered i.v. tromethamine (10, 50 mL/kg; 0.155 M; pH 5.5, 7.4) for 10 days.44 Histological examination of the organs did not identify any adverse effects from the treatment.

Other than necrosis at the injection site (ear) and transient body temperature changes, there were no adverse effects to New Zealand White rabbits (n = 4/sex) administered tromethamine (0.5 g/kg; 0.3 M) for up to 20 days.58 Two rabbits/sex were necropsied within 24 h of the last dose. The remaining rabbits had a 20-days recovery before necropsy.

There were no effects on feed and water consumption or body temperature. Body weights fluctuated throughout the study in all animals, including control animals, but not in any treatment-related pattern. Of the treated rabbits, 7/8 had inflammatory lesions of the external ear. The lesions varied from swelling and redness to dry gangrene and erosion.

Weekly blood samples were normal for: total serum proteins, albumin/globulin (A/G) ratio, serum bilirubin, cephalin flocculation, serum transaminase, red blood cell count, differential counts, hemoglobin, microhematocrit, and platelet counts. White blood cell counts in excess of 13,000 were seen in 5/8 rabbits receiving tromethamine. In all cases, increased white blood cell counts coincided with dry gangrene in the external ear. Urinalysis findings were unremarkable.

In the treatment group, two of the four rabbits necropsied after recovery had grossly visible infarcts in the kidneys; there were none in the control group. No gross lesions were observed in any other organ or tissue. In 7/8 test animals with gross lesions of the ear, there were microscopic lesions of chronic cellulitis and necrosis at injection sites in the subcutaneous tissues of the ear. Those with kidney lesions also had chronic interstitial nephritis. Infiltrations of lymphocytes were observed in tissue sections of the liver and kidney of 3 treated rabbits. The infiltrations were observed in animals in the recovery and non-recovery groups. Peracute toxic nephrosis was observed in 1 rabbit, which also had urolithiasis.58

Treatment-related mortalities occurred a few days after starting the i.v. administration of tromethamine (100 ml 0.3 M at pH 5.5 and 7.4) to rabbits (strain not provided; n = 2-3).44 Tromethamine was administered i.v. over 5 h daily for 19 d. Other groups were administered tromethamine (5 and100 ml 0.3 M/kg at pH 5.5 and 7.4) over 5 h daily for 1 – 99 d.

The neutralized tromethamine was less toxic. Observed clinical signs included anorexia, bloody urine, hind leg paralysis, and irregular respiration. Observations at necropsy included abnormally red lungs, necrosis at the point of infusion, bleached liver, darkened spleen, bloated stomach, and lesions on the heart and kidney. Histologic evaluation of the
organs was negative. There were no treatment-related mortality or clinical signs to rabbits (strain not provided; n = 3) administered i.v. tromethamine (50 and 10 ml/kg 0.155 M; over 30 sec) once daily for 10 d. Histological evaluation of the organs was negative.

Rabbits (n = 5) administered tromethamine (1500, 3000 mg/kg; 0.2 mL/kg/min in Ringer’s solution; 0.34 M) by catheter placed in the jugular vein for 21 days had two mortalities (days 6 and 12) in the high dose group. Clinical signs included rapid, shallow breathing during infusion.

Catheterized dogs (n = 5) administered i.v. tromethamine (1500, 3000 mg/kg/d; 0.34 M in Ringer’s solution; 0.5 mL/kg/min) for 21 days exhibited sporadic convulsions and vomiting. One dog in the high dose group died during treatment. Three dogs in the low dose group had increased retention of bromosulfophthalein (BSP). Infarcts (multiple abscesses) of the liver were observed in three dogs in the low dose group. Colonies of bacteria, acute inflammatory exudate, and hypertrophy of the Kupffer cells were observed in the same livers.

Histological evaluation of the organs was negative.

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The no observed adverse effects level (NOAEL) for Sprague-Dawley rats (n = 6/sex) administered tromethamine i.v. (0.5 and 1.5 g/kg; 0.3 M) for 10 and 20 days was reported to be ~500 mg/kg. Rats were allowed 24 h or 7 d for recovery.

In the 10-d low dose group, all rats necropsied at 24 h and 5/6 rats in the 7-day recovery group had similar findings.58

Intraperitoneal – Non-Human

TROMETHAMINE

Tromethamine (30 mL/kg: 0.075 M) administered i.p. to dogs (n = 3) under anesthesia for 3 days caused no clinical signs during treatment. One dog died on day 3. This dog had heartworms and died under anesthesia; death was attributed to a collapsed lung and pulmonary disease. There were no histopathological signs attributed to the test substance.

Intratracheal – Non-Human

TROMETHAMINE

Tromethamine (in an unknown mixture with 0.9% saline; 2 mL; vehicle control in an experiment) did not decrease survival or average body weight of male Syrian hamsters (n = 28-29) when administered over the lifetime of the hamsters compared to hamsters in the no treatment group. There were no differences in survival (88 ± 22 vs. 78 ± 25 weeks) and mean body weights (116 ± 10 vs. 114 ± 6 g) between the vehicle and the no treatment groups.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

TROMETHAMINE

The NOAEL for reproduction and teratogenicity for tromethamine using rats was ≥1000 mg/kg/d. Female Crl:CD(D) rats (n = 10) were orally administered tromethamine (100, 300, 1000 mg/kg/d adjusted to pH 9) by gavage. Males (n = 10) were treated for at least 2 weeks before breeding up to 29 days. Females (n = 12) were treated from 2 weeks prior to breeding, through gestation, and through 4 days of lactation for up to 54 days.

Tromethamine had no effect on mating performance or conception. There were no effects to mating index, fertility index, gestation period, deliver index, and number of live pups. There were no adverse effects were observed to the F1 pups at birth.

GENOTOXICITY

In Vitro

TROMETHAMINE

Tromethamine (1 mg/mL; pH 7.4) was toxic but not mutagenic to Escherichia coli (CHY832) in an RK assay. The E. coli were killed at 42°C but not at 30°C.

AMINOETHYL PROPANEDIOL

In an in vitro mammalian chromosome aberration test using Chinese hamster lung (CHL/IU) cells, aminoethyl propanediol (75, 150, 300, 600, 1200 μg/mL in saline) was not genotoxic with and without metabolic activation when exposed for 24 and 48 h. Aminoethyl propanediol (156, 313, 625, 1250, 2500, 5000 μg/plate in water) was not mutagenic to S. typhimurium (strains TA98, TA100, TA1535, TA1537) and E. coli (strain WP2 uvr A), with or without metabolic activation.

Aminoethyl propanediol (12, 38, 119, 337, 1192 μg/mL with metabolic activation; 15, 44, 132, 397, 1192 μg/mL without) was not mutagenic to Chinese hamster ovary (CHO) cells in an in vitro mammalian cell gene mutation test with or
without metabolic activation. Aminoethyl propanediol was cytotoxic at 1192 μg/mL. The above study was repeated with the same results.

**CARCINOGENICITY**

**TROMETHAMINE**

When administered intratracheally as the vehicle control to male Syrian hamsters weekly for their entire lifespan, tromethamine (in an unknown mixture with 0.9% saline; 2 mL) did not induce tumors.

**IRRITATION AND SENSITIZATION**

**Irritation**

- **Dermal – Non-Human**
  - **TROMETHAMINE**
    
    In a Draize test, rabbits (strain and n not provided) were dermally administered tromethamine, both in solution (25%, saturation; pH 10.8) and as a crystalline product, to intact and abraded skin. There was no noticeable irritation produced by any state of the test material on intact skin. There was mild irritation by the crystals at saturated states on abraded skin. All signs of irritation were completely resolved in 48 h. The author concluded that tromethamine was a mild irritant under these conditions.

- Tromethamine (40% in distilled water) was not irritating to rabbits (n = 6) in a Draize test.

- In a dermal irritation test using New Zealand White rabbits (n = 3 males), tromethamine (0.5 g in enough water to make a paste) was not irritating when administered to shaved skin under semi-occlusion for 4 h. Test sites were observed at 1, 24, 48 and 72 h.

- **Intradermal – Non-Human**
  
  Intradermally administered tromethamine (0.1 mL) was severely irritating to rabbits (strain and n not provided) at a pH of 10.4 (0.2, 0.3 M) and at pH 7.4 (0.6, 1 M). The cause of local necrosis around the infusion site was investigated using intravenous Trypan blue dye. The irritation caused by the solutions was evaluated by observing the amount of extravasated dye. The neutral tromethamine (pH 5.5) had reduced irritation/local necrosis. At pH 7.4, tromethamine was not irritating at lower doses (0.2, 0.3 M). The authors suggested that the pH of the tromethamine is the probable cause of the dermal irritation.

- **Dermal – Human**
  
  A cosmetic product containing tromethamine (3.1%; neat) was not irritating when administered in a patch test (n = 11) for 48 h.

- **Ocular**
  
  Tromethamine (0.1 g; finely ground) was not an ocular irritant when instilled into the eyes of New Zealand White rabbits (n = 3). The eyes were observed at 1, 24, 48, and 72 h with a hand slit lamp. Fluorescein was used at 24 h. There was slight/moderate redness and chemosis at 1 h; the irritation effects cleared by 24 or 72 h. No damage to the iris or cornea was observed.

  Tromethamine (100%) was not an ocular irritant when administered to rabbits (strain and n not provided).

**Sensitization**

- **Non-Human**
  
  Aminoethyl propanediol (0.05% - 0.5%; 0.5 mL) was not a sensitizer to male Hartley guinea pigs (n = 10) in a Buehler sensitization assay. Some of the guinea pigs showed mild erythema during the first five applications at 0.5% of the induction period, so the concentration was reduced to 0.05% the last five applications. Challenge was at 0.5% and 1%. No further data on the physical or chemical characteristics of the test material were provided.

  In a sensitization assay, aminoethyl propanediol (0.05% - 1% in saline; 0.5 mL; 85.34% pure) was not a sensitizer to male Hartley guinea pigs (n = 10) when the induction was administered intradermally. Some of the guinea pigs showed mild erythema during the initial five applications at 1% of the induction period, so the concentration was reduced to 0.05% the last five applications. Challenge was at 0.5% and 0.01%. No further data on the physical or chemical characteristics of the test material were provided.
AMINOMETHYL PROPANEDIOL

In a peptide reactivity assay for screening contact allergens, it was concluded that aminomethyl propanediol (4 nM) is not expected to cause dermal sensitization. The peptide consisted of seven amino acids with an acetylated N-terminus (acetylated-asparagine-lysine-lysine-cysteine-aspartic acid-leucine-phenylalanine) and was incubated for 24 h. The positive control was diethyl maleate; the negative control was the vehicle, acetonitrile. The average depletion values for the test substance, the negative control, and positive control were 4.22 ± 1.84%, 4.83 ± 1.66%, and 96.13 ± 0.21%.

**Human**

**TROMETHAMINE**

In a human repeated insult patch test (HRIPT; n = 101) of a mascara containing tromethamine (1.8%; ~0.2 g), there were no signs of irritation or contact sensitization observed. In HRIPTs (n = 102) of mascaras containing tromethamine (2%), there were no signs of irritation or sensitization observed. In an HRIPT (n = 102) of a water-based eyeliner stick containing tromethamine (2%), there were no signs of irritation or sensitization observed. The authors concluded that this product is not contraindicated for usages entailing repeated applications on human skin.

**AMINOETHYL PROPANEDIOL**

In a patch test of 16 components of metalwork fluids (MWF; n = 160; including current metalworkers exposed to MWF, some with occupational dermatitis), only one had a positive reaction to aminoethyl propanediol (1% aq.) on day 3 of observation. This subject was not among the subjects that were exposed to MWF. The authors used industrial grade metalwork chemicals; aminoethyl propanediol was reported to be 85% pure. In a follow up study on just metalworkers (n = 144) exposed to MWF, only one tested positive for aminoethyl propanediol (2% pet.). Analysis of 17 different MWFs revealed that aminoethyl propanediol was present at 0.06% - 0.39% with a median of 0.09%.

**CLINICAL USE**

**TROMETHAMINE**

Tromethamine (20 g in 3.3% glucose) was administered i.v. to male subjects (n = 4) with respiratory acidosis due to emphysema or carcinoma of the lung over 40 min. Blood pH increased, O2 tension decreased, and CO2 tension remained unchanged (except for in 1 subject where it decreased) over the administration time. Urinary pH increased within 20 min of the start of infusion with the exception of the same subject; the increase happened at 40 min.

**Case Studies**

**TROMETHAMINE**

A 30-year-old woman developed severe respiratory acidosis following cardiac surgery. After she was administered tromethamine (120 g in water) by gastric tube over 24 h, the acidosis was resolved but she developed severe diarrhea. She also developed tetany which was controlled with calcium gluconate. Her arterial pH rose from 7.1 to 7.45 and she had no further acidosis. While she died from other complications, there were no adverse effects from the tromethamine treatment observed at autopsy.

A 40-year-old man, who had a 9-rib thoracoplasty, presented with extensive pneumonia. He was unconscious within 12 h with slow, gasping respirations. A tracheotomy and 100% oxygen were not helpful. O2 saturation was 97%, CO2 tension was 160 mm Hg, and pH was 6.95. He was administered tromethamine (30 g in water; 10%) over 1 h. Arterial blood was then at 92% saturation and CO2 tension was 80 mg Hg with a pH of 7.2. Additional tromethamine (10 g) was administered after 5 h. O2 saturation was 49%, CO2 tension was 68 mm Hg, and the pH was 7.29. No adverse effects from the tromethamine treatment were reported.

**SUMMARY OF DATA FROM THE AMINOMETHYL PROPANEDIOL SAFETY ASSESSMENTS**

**2009**

Aminomethyl propanediol is a substituted aliphatic alcohol used as a cosmetic ingredient. It occurs in solid and liquid forms and is soluble in both water and alcohols.

Aminomethyl propanediol functions as a pH adjuster in cosmetic products and is also a fragrance ingredient. Aminomethyl propanediol is used in concentrations up to 2%.

Inhalation of a hair spray containing 0.50% Aminomethyl propanediol for 1 h was nontoxic to rats. When both albino rats and Syrian Golden hamsters were exposed in a 13-week subchronic inhalation toxicity study to a hair spray formulation containing 0.1350% aminomethyl propanediol for 4 hours per day, 5 days per week, no significant compound-related adverse effects were observed.

Cosmetic formulations containing 0.40% aminomethyl propanediol were moderate ocular irritants.
Aminomethyl propanediol was not mutagenic, with and without metabolic activation, in *S. typhimurium* strains TA1535, 1537, 98, and 100.

In a primary irritancy test of a cosmetic formulation containing aminomethyl propanediol at 0.26%, scattered incidences of questionable responses were observed in two thirds of the panelists. In addition, 2 of 15 panelists had slight redness at least once during the observation period.

A cosmetic formulation containing 0.073% aminomethyl propanediol was not a primary irritant, and it was neither a fatiguing agent nor a sensitizer. In another study, a cosmetic formulation containing 0.50% aminomethyl propanediol was not a sensitizer.

**1990**

Aminomethyl propanediol is a substituted aliphatic alcohol.1 It occurs in solid and liquid forms and is soluble in both water and alcohols. Aminomethyl propanediol functions as an emulsifying agent for cosmetic creams and lotions, and as a neutralizing agent in hair sprays. Aminomethyl propanediol is used in concentrations up to 5%. All uses at concentrations above 1% involve neutralization of the aliphatic alcohol with fatty acids.

In industry, aminomethyl propanediol is used in the synthesis of surface-active agents, as a vulcanization accelerator, in pharmaceuticals, and as emulsifying agents for a variety of products.

According to the classification of Hodge and Sterner, a hair spray containing aminomethyl propanediol was practically nontoxic to albino rats. Additionally, when both albino rats and Syrian Golden hamsters were exposed in a subchronic inhalation toxicity study to hair spray formulations containing aminomethyl propanediol, no significant compound-related adverse effects were observed.

Cosmetic formulations containing aminomethyl propanediol were also non- to minimally irritating to rabbit skin.

Cosmetic formulations containing aminomethyl propanediol were moderate ocular irritants.

Aminomethyl propanediol was not mutagenic, with and without metabolic activation, in *S. typhimurium* strains TA1535, 1537, 98, and 100.

In a primary irritancy test of a cosmetic formulation containing aminomethyl propanediol, scattered incidences of questionable responses were observed in two-thirds of the panelists. In addition, 2 of 15 panelists had slight redness at least once during the observation period.

A cosmetic formulation containing aminomethyl propanediol was not a primary irritant, and it was neither a fatiguing agent nor a sensitizer. In another study, a cosmetic formulation containing aminomethyl propanediol was not a sensitizer.

**SUMMARY**

Tromethamine is an aliphatic compound that functions as a pH adjuster. Aminomethyl propanediol and aminoethyl propanediol are substituted aliphatic compounds. Aminomethyl propanediol was previously reviewed by the Panel and found to be safe as used.

Tromethamine is used in 480 leave-on cosmetic products up to 2% and 69 rinse-off products up to 3.7% in a rinse-off nail product. Aminomethyl propanediol was reported in the VCRP data to be used in 131 leave-on and 2 rinse-off products up to 2%. There were no reported uses of aminoethyl propanediol.

Tromethamine has several medical uses, including treatment for acidosis under several circumstances.

Tromethamine is eliminated by the kidneys in mammals. There was little dermal absorption in human skin.

Tromethamine was cytotoxic to multiple cell types in the range of 129 – 405 µg/ml.

Tromethamine administered i.v. caused a fall in blood glucose levels in rats, rabbits, dogs, and humans.

The oral LD₅₀ for mice was reported to range from 3350 to 5500 mg/kg. For rats, the LD₅₀ was > 3000 mg/kg. The LC₅₀ was between 1000 and 2000 mg/kg. The dermal LD₅₀ of tromethamine for mice and rats was reported to be > 1000 mg/kg and > 2000 mg/kg for rabbits. The intraperitoneal LD₅₀ of tromethamine for mice was reported to be ~3350 mg/kg.

The LOAEL for tromethamine for rats was reported to be 2500 ppm when incorporated into feed for 3 months. The local NOAEL for orally administered tromethamine was 300 mg/kg/d for 14 – 37 days. Tromethamine at 1000 mg/kg caused loose stool and vomiting in dogs.

There were no adverse clinical signs in rabbits dermally administered tromethamine at 100% on clipped skin for 4 h for 5 days.

Intravenous toxicity of tromethamine was minimal at neutral pH. However, at a more alkaline pH range, gangrene at the injection sites, tissue necrosis, inflammatory lesions, visible infarcts in the kidneys, bleached liver, darkened spleen, and lesions on the heart were reported. Anorexia, bloody urine, and paralysis were also observed.

Intratracheal administration of 2 mL tromethamine in an unknown mixture with 0.9% saline did not decrease survival or mean body weights of hamsters when administered over their lifetime.

There were no adverse effects on reproduction by tromethamine up to 1000 mg/kg/day to rats.

Tromethamine was toxic, but not mutagenic, to *E. coli* in an RK assay. Aminoethyl propanediol was not mutagenic in three chromosome aberrations tests using Chinese hamster lung cells, CHO, and bacteria up to 5000 µg/plate.

Tromethamine at 2 ml did not induce tumors when administered intratracheally to hamsters weekly for their entire
Tromethamine was a mild irritant to rabbits at 25% with a pH of 10.8. At 40%, tromethamine was not irritating. Intradermal injections of tromethamine were severely irritating to rabbits at pH 10.4 but were only mildly irritating at pH 7.4. Tromethamine was mildly irritating at 25% with a pH of 10.8 and not irritating at 40% in distilled water. Tromethamine in a paste with water was not irritating to the shaved skin of rabbits.

Aminoethyl propanediol was not a sensitizer to guinea pigs at 0.05%. It was an irritant at 0.5%. Aminomethyl propanediol was not predicted to be a dermal sensitizer in a peptide reactivity assay.

In a patch test of subjects, some with professional contact of metalwork fluids that contain aminoethyl propanediol, only 1/160 had a positive reaction.

A cosmetic product containing 3.1% tromethamine was not irritating in a patch test. Tromethamine was not an ocular irritant to rabbits at 100%. Aminoethyl propanediol was not a sensitizer to guinea pigs up to 1%.

Five products (including mascara, eyeliner stick, and body lotion) containing tromethamine up to 2% were not irritating or sensitizing in HRIPTs using up to 102 subjects. There was only one positive reaction among 233 subjects with past or present exposure to metalworking fluids to aminoethyl propanediol at 85%.

Tromethamine at 20 g administered i.v. was not toxic to subjects being treated for respiratory acidosis.

**DISCUSSION**

The similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients together and interpolating using the available toxicological data to support the safety of the entire group.

The Panel discussed the issue of incidental inhalation exposure from tromethamine in fragrance preparations up to 0.2% that may be spray products as well face powders and fragrance powders up to 0.05%. The limited data available from inhalation studies, including acute and chronic exposure data, suggest little potential for respiratory effects at relevant doses. Aminomethyl propanediol was not toxic to hamsters and rats in subchronic inhalation studies.

The Panel believes that the sizes of a substantial majority of the particles of these products, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. These ingredients are reportedly used at concentrations up to 2% in cosmetic products that may be aerosolized and up to 0.05% in other products that may become airborne. The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the tromethamine, aminoethyl propanediol, and aminomethyl propanediol and on data that shows that these ingredients are not irritants. Coupled with small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel’s approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel considered other data available to characterize the potential for these ingredients to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. The Panel noted that tromethamine has seen long-time been used to treat acidosis-related ailments and as a biological buffer. Tromethamine did not penetrate skin and toxicity studies, including reproductive/developmental toxicity, showed that these ingredients were not toxic at levels far greater than those that could result from cosmetic-use exposures. This information along with negative dermal irritation/sensitization assays, including tests of products containing these ingredients, reassured the Panel that there are no safety concerns for these ingredients.

The Expert Panel cautions that products containing these ingredients could form nitrosamines and formulators should continue to avoid the formation of nitrosamines.

**CONCLUSION**

The CIR Expert Panel concluded that tromethamine, aminomethyl propanediol, and aminoethyl propanediol* are safe in the present practices of use and concentration in cosmetics as described in this safety assessment.

* Were this ingredient not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.
### Table 1. Definitions and functions of the ingredients in this safety assessment.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Definition</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromethamine CAS No. 77-86-1</td>
<td>An aliphatic compound that conforms to the structure in Figure 1.</td>
<td>Fragrance ingredient; pH adjuster</td>
</tr>
<tr>
<td>Aminomethyl propanediol CAS No. 115-69-5</td>
<td>A substituted aliphatic diol that conforms to the structure in Figure 2.</td>
<td>Fragrance ingredient; pH adjuster</td>
</tr>
<tr>
<td>Aminoethyl propanediol CAS No. 115-70-8</td>
<td>A substituted aliphatic diol that conforms to the structure in Figure 2.</td>
<td>pH adjuster</td>
</tr>
</tbody>
</table>

### Table 2. Chemical and physical properties of tromethamine, aminomethyl propanediol, and aminoethyl propanediol.

<table>
<thead>
<tr>
<th>Property</th>
<th>Tromethamine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Form</td>
<td>Crystalline powder</td>
<td>22</td>
</tr>
<tr>
<td>Color</td>
<td>White</td>
<td>22</td>
</tr>
<tr>
<td>Odor</td>
<td>Slight, characteristic</td>
<td>74</td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>121.14</td>
<td>22</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20°C</td>
<td>~1.3</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>1.32</td>
<td>73</td>
</tr>
<tr>
<td>Vapor pressure mmHg @ 25°C</td>
<td>2.20(\times)10^{-5}</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>0.000267</td>
<td>73</td>
</tr>
<tr>
<td>Melting Point °C</td>
<td>171-172</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>169</td>
<td>73</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>219-220</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>288 (decomposition)</td>
<td>73</td>
</tr>
<tr>
<td>Solubility g/L water</td>
<td>550</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>678-689</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>0.0791</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>0.022</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>0.020</td>
<td>22</td>
</tr>
<tr>
<td>Other Solubility g/L</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>Insoluble</td>
<td>74</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Practically insoluble</td>
<td>4</td>
</tr>
<tr>
<td>Benzene</td>
<td>Practically insoluble</td>
<td>4</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Practically insoluble</td>
<td>4</td>
</tr>
<tr>
<td>log K_{ow} @ 20°C</td>
<td>-2.31</td>
<td>74</td>
</tr>
<tr>
<td>Disassociation constants (pKb) @ body temperature</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>@ 25°C</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>7.8</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>8.22</td>
<td>73</td>
</tr>
</tbody>
</table>

| Aminomethyl Propanediol             |              |           |
| Physical Form                        | Liquid or crystals | 22        |
| Color                               | Colorless liquid  | 74        |
| Odor                                | Liquid-amine odor; crystals-odorless | 74        |
| Molecular Weight g/mol              | 105.14        | 22        |
| Melting Point °C                    | 109-111       | 22        |
|                                     | 105.14        | 73        |
| Boiling Point °C @ 10 mm Hg         | 151-152       | 22        |
|                                     | 151          | 73        |
| Water Solubility g/L @ 20°C         | .250          | 74        |
| Other Solubility Alcohol            | Soluble       | 22        |
| log K_{ow} @ 20°C                   | <-0.8         | 74        |
| Disassociation constants (pKa, pKb) @ 25°C |                |           |
|                                      | 8.76          | 73        |
Table 2. Chemical and physical properties of tromethamine, aminomethyl propanediol, and aminoethyl propanediol.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminoethyl propanediol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Form</td>
<td>Crystalline</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>119.16</td>
<td>22</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20 °C</td>
<td>1.08</td>
<td>73</td>
</tr>
<tr>
<td>Vapor pressure mm Hg @ °C</td>
<td>0.0021 a</td>
<td>73</td>
</tr>
<tr>
<td>Melting Point °C</td>
<td>37.5-38.5</td>
<td>22</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>152-153</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>259-260</td>
<td>73</td>
</tr>
<tr>
<td>Water Solubility</td>
<td>Miscible</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>&gt; 950</td>
<td>73</td>
</tr>
<tr>
<td>Other Solubility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohols</td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>log Kow @ 20 °C</td>
<td>-1.02</td>
<td>73</td>
</tr>
<tr>
<td>Disassociation constants (pKa, pKb) @ 25°C</td>
<td>9.03</td>
<td>73</td>
</tr>
</tbody>
</table>

a Converted from 0.29 Pa.

Table 3. Frequency of use according to duration and exposure of the ingredients in this safety assessment. 9-11

<table>
<thead>
<tr>
<th>Use type</th>
<th>Uses</th>
<th>Maximum Concentration (%)</th>
<th>Uses</th>
<th>Maximum Concentration (%)</th>
<th>Uses</th>
<th>Maximum Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tromethamine</td>
<td></td>
<td>Aminomethyl propanediol</td>
<td></td>
<td>Aminoethyl propanediol</td>
</tr>
<tr>
<td>Total/range</td>
<td>558</td>
<td>0.00009-3.7</td>
<td>133</td>
<td>0.25-2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Duration of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leave-on</td>
<td>488</td>
<td>0.0002-3.7</td>
<td>131</td>
<td>0.25-2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rinse-off</td>
<td>70</td>
<td>0.00009-3.1</td>
<td>2</td>
<td>0.5-0.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Diluted for (bath) use</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Exposure type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye area</td>
<td>75</td>
<td>0.8-2</td>
<td>121</td>
<td>0.27-2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental ingestion</td>
<td>1</td>
<td>0.002-0.03</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental inhalation-sprays</td>
<td>10</td>
<td>0.2-2</td>
<td>NR</td>
<td>1.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Incidental inhalation-powders</td>
<td>NR</td>
<td>0.0002-0.05</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dermal contact</td>
<td>531</td>
<td>0.00009-3.1</td>
<td>16</td>
<td>0.25-1.4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hair-noncoloring</td>
<td>11</td>
<td>0.001-0.8</td>
<td>NR</td>
<td>1.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hair-coloring</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nail</td>
<td>1</td>
<td>3.7 a</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>13</td>
<td>0.00009-0.03</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Baby</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = None Reported; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

a In a rinse-off product.
Table 4. Acute toxicity data for tromethamine.

<table>
<thead>
<tr>
<th>Species (n)</th>
<th>Dose(s)</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice, strain not provided (10)</td>
<td>2000, 3500, 5000, 7000, 10000 mg/kg by gavage</td>
<td>LD₅₀ = 5500 mg/kg</td>
<td>52</td>
</tr>
<tr>
<td>Swiss mice (10)</td>
<td>1000, 2000, 3000 mg/kg as 5% and 20% solutions by gavage</td>
<td>LD₅₀ &gt;3000 mg/kg. No toxicity noted. Abundant urine output for some mice.</td>
<td>47</td>
</tr>
<tr>
<td>Mice, strain not provided (not provided)</td>
<td>2000, 2500, 3530, 5000, 7000 mg/kg by gavage</td>
<td>LD₅₀ = ~3350 mg/kg</td>
<td>54</td>
</tr>
<tr>
<td>Wistar rat (10)</td>
<td>1000 and 3000 mg/kg by gastric tube as 20% solution</td>
<td>No toxicity noted. Abundant urine output was recorded for some rats.</td>
<td>49</td>
</tr>
<tr>
<td>Wistar rat (10)</td>
<td>1000, 2000, 3000 mg/kg by gavage as 5% and 20% solutions by gavage</td>
<td>LD₅₀ &gt;3000 mg/kg. No toxicity noted. Abundant urine output for some rats.</td>
<td>49</td>
</tr>
<tr>
<td>Wistar rat, female (3)</td>
<td>5000 mg/kg in water by oral gavage; 3 doses with 2-day intervals</td>
<td>LD₅₀ &gt; 5000 mg/kg. No deaths or clinical signs.</td>
<td>38</td>
</tr>
<tr>
<td>Rabbits, strain not provided (not provided)</td>
<td>Delivered neat by gavage</td>
<td>LC₅₀ between 1.00 - 2.00 g/kg. Weakness and collapse. Coma preceded deaths. No CNS signs or convulsions. Toxicity was due to alkalinity; neutralization reduced toxicity.</td>
<td>53</td>
</tr>
<tr>
<td>Wistar rats (3)</td>
<td>5000 mg/kg for 24 h under semioclusion on shaved skin</td>
<td>No mortalities or clinical signs.</td>
<td>55</td>
</tr>
<tr>
<td>Mice, strain not provided (5)</td>
<td>500 or 1000 mg/kg as 5% solution by subcutaneous injection</td>
<td>500 mg/kg caused irritation at the injection site. 1000 mg/kg caused the formation of lesions. LD₅₀ &gt; 1000 mg/kg</td>
<td>49</td>
</tr>
<tr>
<td>Rat, strain not provided (5)</td>
<td>500 or 1000 mg/kg as 5% solution by subcutaneous injection</td>
<td>500 mg/kg caused irritation at the injection site. 1000 mg/kg caused the formation of lesions. LD₅₀ &gt; 1000 mg/kg</td>
<td>49</td>
</tr>
<tr>
<td>Mice, strain not provided (10)</td>
<td>2000, 2500, 3250, 3600, 4000, mg/kg by intraperitoneal injection at 0.015 ml/g</td>
<td>LD₅₀ = ~3350 mg/kg.</td>
<td>55</td>
</tr>
<tr>
<td>Male CD-1 mice (4-11)</td>
<td>100 mg/kg after drug-induced hypothermia/shock using lipopolysaccharide</td>
<td>Hypothermic response was reduced at 4, 24, and 48 h. No other effects were reported.</td>
<td>56</td>
</tr>
<tr>
<td>Mice, strain not provided (10)</td>
<td>0.3 M. i.v. injection (pH 5.5, 10.4) with and without dextrose or sodium chloride and observed for 24 h.</td>
<td>LD₂₅ = 16.5 mM/kg. Mice convulsed immediately before dying. Neutralizing the pH and the additives did not change toxicity.</td>
<td>44</td>
</tr>
<tr>
<td>Mice, strain not provided (10)</td>
<td>100, 200, 400, 500, 1000, 3000, 5000, 6000, 7000 mg/kg as 1% solution</td>
<td>No mortality at doses &lt; 5000 mg/kg. 6000 mg/kg, 40% mortality; 7000 mg/kg, 100%. Muscle weakness accompanied by respiratory difficulty prior to death. LD₅₀ = ~ 6100 mg/kg</td>
<td>49</td>
</tr>
<tr>
<td>Sprague-Dawley rat (3/sex)</td>
<td>2.0, 2.5, 3.0, 3.5 g/kg of 0.6M; 4.0 and 4.5 g/kg of 0.9M in saline injected over 1 min followed by 2-h observations then necropsy.</td>
<td>Most rats died during treatment or within 10 min of treatment. The rest survived the observation period.</td>
<td>38</td>
</tr>
</tbody>
</table>

Lethargy was observed sporadically in rats at 3-4 g/kg dose groups. All had lesions of acute toxic hepatitis. The lesion was characterized by pyknosis of the nuclei of the hepatocytes and cloudy swelling of the cytoplasm of hepatocytes. However, the lesions did not constitute a consistent characteristic lesion as did the...
Table 4. Acute toxicity data for tromethamine.

<table>
<thead>
<tr>
<th>Species (n)</th>
<th>Dose(s)</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, strain not provided (10)</td>
<td>100, 200, 400, 500, 1000, 3000, 5000, 6000, 7000 mg/kg as 1% and 2% solutions</td>
<td>No observations of toxicity at &lt; 3000 mg/kg. 5000 mg/kg, 30% mortality; 6000 mg/kg, 60%; and 7000 mg/kg, 70%. LD₅₀ = ~6000 mg/kg.</td>
<td>49</td>
</tr>
<tr>
<td>Male Wistar rats (6)</td>
<td>0.5 mmol/kg/min @ pH 10.9 or 7.4</td>
<td>Both pH levels were well tolerated for 50-70 min; then metabolic alkalosis developed, then death. Plasma concentration increased linearly to 53.7 ± 9.09 mmol/L @ 60 min. No effects observed to BP, heart rate, ECG, and Na⁺ and K⁺ plasma or erythrocyte concentration. The authors stated that depressed ventilation was the cause of death. When infusion was stopped at 20 min, the rats recovered.</td>
<td>37</td>
</tr>
<tr>
<td>Rabbit, strain not provided (5)</td>
<td>250 and 500 mg/kg as 5% solution</td>
<td>No treatment-related mortality. Changes in respiratory rate and amplitude were observed.</td>
<td>49</td>
</tr>
<tr>
<td>Dog, breed not provided (5)</td>
<td>125 mg/kg as 5% solution</td>
<td>Alterations in respiratory rate and amplitude. LC₅₀ &gt; 125 mg/kg</td>
<td>49</td>
</tr>
</tbody>
</table>
REFERENCES


53. Machle W, Scott EW, and Teon JF. The physiological response of animals to some simple mononitroparaffins and to certain derivatives of these compounds. *Journal of Industrial Hygiene and Toxicology*. 1940;22(8):315-332.


