Dimethylethanolamine (DMAE) [108-01-0] and Selected Salts and Esters

DMAE Aceglutamate [3342-61-8]
DMAE *p*-Acetamidobenzoate [281131-6] and [3635-74-3]
DMAE Bitartrate [5988-51-2]
DMAE Dihydrogen Phosphate [6909-62-2]
DMAE Hydrochloride [2698-25-1]
DMAE Orotate [1446-06-6]
DMAE Succinate [10549-59-4]
Centrophenoxine [3685-84-5]
Centrophenoxine Orotate [27166-15-0]
Meclofenoxate [51-68-3]

Review of Toxicological Literature (Update)

November 2002

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Review of Toxicological Literature

(Update)

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Executive Summary

Nomination

Dimethylethanolamine (DMAE) was nominated by the NIEHS for toxicological characterization, including metabolism, reproductive and developmental toxicity, subchronic toxicity, carcinogenicity and mechanistic studies. The nomination is based on the potential for widespread human exposure to DMAE through its use in industrial and consumer products and an inadequate toxicological database. Studies to address potential hazards of consumer (e.g. dietary supplement) exposures, including use by pregnant women and children, and the potential for reproductive effects and carcinogenic effects are limited. DMAE and related ethanolamines appear to interfere with choline uptake and utilization and may also generate nitrosamines. Further studies are recommended to address these data gaps with special attention to pharmacokinetics and the influence of dietary choline. Consideration should be given to whether the bitartrate salt of DMAE (a form commonly used in dietary supplements) or other DMAE derivative is more appropriate than the free base for use in toxicology studies.

Nontoxicological Data

Chemical Identification

The principal compounds related to DMAE [108-01-0] that have common commercial uses and are discussed in this report, are DMAE aceglumate [3342-61-8], DMAE *p*-acetamidobenzoate (an ester) [2811-31-6], DMAE *p*-acetamidobenzoate (a salt); Deaner® [3635-74-3], DMAE bitartrate [5988-51-2], DMAE dihydrogen phosphate [6909-62-2], DMAE hydrochloride [2498-25-1], DMAE orotate [1446-06-6], DMAE succinate; tonibral [10549-59-4], centrophenoxine; dimethylethanolamine *p*-chlorophenoxyacetate hydrochloride [3685-84-5], centrophenoxine orotate [27166-15-0], and meclofenoxate; DMAE *p*-chlorophenoxyacetate [51-68-3].

Commercial Availability, Production, and Production Processes

U.S. EPA IUR (Inventory Update Rule database) listed six U.S. producers producing at least 10,000 lb DMAE each annually: BASF, Dow Chemical Co., Elf Atochem, Huntsman Corp., ICI Americas, and Union Carbide. In 1996, SRI International listed Pelron Corporation as U.S. producers of (DMAE). Chemcyclopedia listed the following additional bulk supplies in 1992: Ashland Distribution Company; Mallinkrodt Laboratory Chemicals, Division of Mallinkrodt, Baker; and Quaker City Chemicals. Suppliers are also listed in Chemcyclopedia 2002 for the acrylate and methacrylate esters and the hydrochloride salt [13242-44-9]. ATOFINA Chemicals, Inc. offers DMAE and other ethanolamines.

Several companies are potential manufacturers of DMAE bitartrate: American International Chemical, Inc., Richman Chemical Inc., FoodTechSource.com, and ICC Chemical Corporation.

An aggregate production volume range of 50-100 million pounds was reported in non-confidential production volume information submitted by companies for chemicals under the 1998 TSCA Inventory Update Rule (http://www.epa.gov/oppt/iur/iur98/index.htm). DMAE was included in the 2000 OECD List of High Production Volume Chemicals, a list of chemicals produced at levels greater than 1,000 tonnes (2,205,000 lbs) per year.

DMAE is synthesized from equimolar amounts of ethylene oxide and dimethylamine. The amino group of DMAE forms salts by reacting with mineral and carboxylic acids. The hydroxyl group forms esters by reacting with carboxylic acids. Thus, the bitartrate is produced from DMAE and tartaric acid.

Uses

Based on the Organization for Economic Co-operation and Development Screening Information Data Set (OECD SIDS) estimates, 50% of the DMAE produced is used to make flocculants for wastewater treatment, 20% is used in the manufacture of flexible and rigid polyurethane foams and polyurethane lacquers, 20% is used in the manufacture of water-based paints and surface coatings, and the remaining 10% is used for ion exchange resins, pharmaceuticals, and corrosion inhibitor formulations. DMAE is used for solubilization of water-insoluble resin components for water-based coatings, a process achieved by reaction of DMAE with the resins.

Environmental Occurrence

DMAE is released into water as a result of its use in the production of polyurethane, acrylates, ion exchange resins and flocculants, and pharmaceuticals. DMAE is also released into the environment as a component of corrosion inhibitor formulations, paints, and surface coatings.

Coatings

No information on environmental occurrence in the United States was found. However, two industrial operations common in the United States, spray-painting and beverage can lacquering, are potential emitters of DMAE to the environment. Environmental releases to the atmosphere of DMAE might be expected from paint-spraying operations as suggested by the research conducted by the Statewide Air Pollution Research Center, University of California, which studied the potential for photo-oxidation of the compound. In the United Kingdom, DMAE has been identified as one of the major odoriferous components from the ovens drying beverage cans after coating with solvent-borne and water-borne lacquers.

Urethane Catalysts

Furniture and cabinets made of coated engineered wood products (particle board, medium-density fiberboard, and hardboard from wood particles and fibers) after installation in buildings emit volatile organic compounds [volatile organic compounds (VOCs)] from the wood glues, coatings, and overlay materials such as polyvinyl chloride. U.S. EPA sponsored a survey by Research Triangle Institute of emissions from finished samples of such engineered wood products. Coating compositions included two-component waterborne polyurethane formulations. DMAE was expected to be present in the volatile emissions; however, the analytical method used was not able to determine DMAE due to its polarity. However, another study showed DMAE is among VOCs that outgas from new carpets.

Amines were sampled evaporating from polyurethane foams applied in buildings. Air concentrations of reactants in the vicinity of freshly produced polyurethane foam insulation material were 4.0 mg MDI/m^3 and 6.7 mg DMAE/m^3. While concentrations of MDI in a closed space fell to < 0.05 mg/m^3 after two months, concentrations of 4.0 mg DMAE/m^3 were found to persist.

Environmental Persistence

A 1997 IUCLID report summarized environmental fate characteristics for DMAE:

- Photodegradation: DMAE underwent indirect photolysis in air with hydroxide ion as a sensitizer.
- Distribution: At 10 °C, DMAE was distributed 56% in water, 44% in air. At 20 °C, DMAE was distributed 39% in water and 61% in air.
- Biodegradation: In the presence of nonacclimated domestic sewage microorganisms at 25 °C, DMAE biodegraded rapidly after a lag period of about five days when subjected to the biochemical oxygen demand test. DMAE (released in wastewater from washout to control emissions from water-based paint spray booths) was “readily biodegradable” by activated

sludge in aerobic conditions. A concentration of 1,000 mg/L sludge, related to chemical oxygen demand, degraded 90% of DMAE after 13 days. At a concentration of 100 mg/L DMAE in 30 g/L sewage at 25 °C, 85% of the DMAE degraded after 20 days (4% after five days and 67% after 10 days). A concentration of 100 mg/L DMAE in 30 g/L sewage at 25 °C degraded with ammonia as an end product.

Human Exposure

Occupational Exposure

The National Occupational Exposure Survey estimated the total number of U.S. workers exposed to DMAE was 33,474, of which 5,559 were female.

Workplace Air Concentrations

NIOSH-sponsored industrial hygiene surveys conducted at four polyurethane foam insulation manufacturing facilities in 1979 found DMAE concentrations ranging from 0.02 to 0.22 ppm in workplace air at one facility and "very low" concentrations at another facility.

An authoritative review estimated that industrial DMAE exposure in the United Kingdom is controlled by process enclosure, local exhaust, or personal protection equipment to less than 2 ppm as an 8-hour time-weight average (TWA). Higher exposures of 2 to 4 ppm are possible during spray painting with water-based coatings. The magnitude of dermal exposure was estimated to be 0 to 0.1 $mg/cm^2/day$ with up to 1 $mg/cm^2/day$ for spent catalyst drumming in organic flocculants manufacture.

A time-weighted threshold limit value (TLV) for DMAE was established at 5 ppm as an internal exposure limit. The short-term exposure limit set was 25 ppm. DuPont (2002) regulates DMAE at 2.0 ppm as a company-based 8-hour TWA.

The TWA values for worker exposure in polyether block plants and in hot cure molding plants were up to 60 ppb total amine burden, which is comprised of 1,4-diazabicyclo[2,2,2]octane triethylenediamine (DABCO) and DMAE. The range of DMAE was < 1 to 87 ppb in polyether slabstock production, 7 to 1,100 ppb in hot cure molding, and < 10 ppb in cold cure molding and in conversion and cold block handling.

A United Kingdom study examined occupational exposure during DMAE production and its use in manufacturing polyurethane foams, flocculants, surface coatings and ion-exchange resins. Using the Estimation and Assessment of Substance Exposure (EASE) method, potential for skin exposure would be 0 to 0.1 $mg/cm^2/day$, and in the manufacture of organic flocculants, as high as 0.1 to 1 $mg/cm^2/day$.

Nonoccupational Exposure

Consumer Products Other Than Dietary Supplements

Individuals may ingest small quantities of DMAE through the consumption of salmon roe, mollusks (squid), and fish. DMAE may also be emitted from sealants, architectural coatings, coatings on furniture and cabinets, polyurethane foam cushions, and carpets in homes, commercial buildings, and vehicles.

Pharmaceuticals

Riker Laboratories' prescription drug Deaner® (deanol *p*-acetamidobenzoate) was a U.S. prescription drug for more than 20 years until 1983 when it was withdrawn from the market. It was used to treat children with learning and behavior problems.

DMAE may be an impurity or a metabolite of ditilin (succinylcholine chloride). DMAE was found among hydrolysis and thermal degradation products of diphenhydramine, which is available as Benadryl® (the hydrochloride salt) and several generic over-the-counter antihistamines. Diphenhydramine is also a component of the antinausea drug dimenhydrinate. DMAE and 4-butylbenzoic acid were metabolites of the local anesthetic tetracaine hydrochloride (Hansen, 1970).

Dietary Supplements
A large number of dietary supplements contain DMAE. The predominant form, when specified, is DMAE bitartrate.

Regulatory Status
Regulations applicable to DMAE are as follows:

- **40 CFR 60.** Subpart YYY – Standards of Performance for Volatile Organic Compound (VOC) Emissions from Synthetic Organic Chemical Manufacturing Industry (SOCMI) Wastewater.
- **40 CFR 63.** National Emission Standards For Hazardous Air Pollutants For Source Categories.
- **40 CFR 63.100ff.** Subpart F-National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry.
- **21 CFR 173.** Secondary Direct Food Additives Permitted in Food for Human Consumption. Subpart A-Polymer Substances and Polymer Adjuvants for Food Treatment.
- **21 CFR 175.** Indirect Food Additives: Adhesives and Components of Coatings.

DMAE was included in the Organization for Economic Co-operation and Development (OECD) investigation of high production volume (HPV) chemicals to identify possible data gaps in assessing potential risks to human health and the environment. In the SIDS Initial Assessment Report, DMAE was characterized as "presently of low priority for further work."

Toxicology Data
Human Data
DMAE tartrate administered orally to humans produced mild mental stimulation. At 20 mg/day (0.084 mmol), there was a gradual increase in muscle tone and perhaps an increased frequency of convulsions in susceptible individuals. Larger doses produced insomnia, muscle tenseness, and spontaneous muscle twitches.

DMAE has been tested for its efficacy in treating a variety of diseases possibly related to deficiencies of acetylcholine with mixed results. Three reported no benefit from DMAE treatment (tardive dyskinesia; cognitive dysfunction; Alzheimer's disease). Benefits from DMAE treatment were found in other studies evaluating DMAE's ability to increase theta power or concentration. Centrophenoxine showed benefits for patients with organic psychosyndrome.

DMAE supplementation is contraindicated during pregnancy, lactation, and for treatment of people with symptoms of schizophrenia and clonic-tonic seizure disorders. DMAE antagonizes the depressant effects of barbiturates.

A large number of adverse health effects were associated with DMAE, including cardiovascular, neurological, and/or psychological effects. Specific attribution of adverse effects to DMAE is unlikely, as many of these products also contained *Ephedra vulgaris* alkaloids and other *Ephedra*

spp.

Treatment with DMAE for tardive dyskinesia was associated with serious cholinergic side effects (nasal and oral secretions, dyspnea, and respiratory failure).

Adverse effects were observed in one occupational study (manufacture of polyurethane foam insulation for refrigerators) and included disorders of the upper respiratory tract and nervous system, along with significant changes in the immune status. Workers were exposed to a mixture of DMAE, ethylenediamine, propylene oxide, and 4,4′-methylenediphenyl diisocyanate. Severe respiratory symptoms were observed in a single painter exposed to spray paint containing DMAE. Wheal and flare responses occurred after exposure of human volunteers to DMAE (undiluted, and 1:10 and 1:100 dilutions in saline) but were interpreted as an irritant response. DMAE failed to meet the current criteria for classification as a respiratory sensitizer.

Chemical Disposition, Metabolism, and Toxicokinetics

DMAE is absorbed and rapidly transported to the liver where much of it is metabolized. Approximately 280 nmol (25.2 µg) DMAE/gram plasma was observed in male mice about ten minutes after receiving 300 mg (3.30 mmol) DMAE/kg, intraperitoneally. Approximately 2.41, 1.30, and 0.20% of an administered dose of 30 mg/kg (0.13 mmol/kg) (with 100 µCi) of ^{14}C-cyprodenate was found in the liver, brain, and plasma, respectively, five minutes after intravenous dosing in male rats. After transport to the liver, a portion of centrophenoxine was converted to its constituent moieties, DMAE and *p*-chlorophenoxyacetic acid (PCPA), while the unmetabolized form was transported throughout the body by the circulatory system.

Daily oral exposures (deanol acetamidobenzoate, DMAE, or Deaner) of chinchilla rabbits or humans produced measurable plasma and cerebrospinal concentrations of the parent compound. The drugs were cleared from the plasma by 36 hours post-treatment.

In male Wistar rats, DMAE was oxidized rapidly to the *N*-oxide of DMAE, representing the primary urinary metabolite. However, only 13.5 % of the administered dose was eliminated by the 24 hour time point, suggesting that most of the DMAE was routed toward phospholipid biosynthetic pathways. In humans, 33% of an injected 1 g (10 mmol) dose of DMAE was excreted unchanged. It was suggested that the remaining dose might have been demethylated to ethanolamine directed toward normal metabolic pathways.

It is unclear to what extent DMAE is methylated and substituted into acetylcholine. Some reports indicated that the DMAE that crossed the blood-brain barrier was methylated to form choline and then incorporated into acetylcholine. Other investigators found that neither acute (*in vitro*) nor chronic (*in vivo*) treatments with [$^{2}H_{6}$]DMAE had the capacity to alter levels of acetylcholine in the brain tissues.

Choline may be formed by methylation of DMAE. *De novo* synthesis of choline typically involves conversion of phosphatidylethanolamine to phosphatidylcholine. Although small amounts may be synthesized, choline must be supplemented through the diet to maintain adequate physiological concentrations for optimal health.

Most of the body's choline is found as a component of phospholipids. Choline-containing phospholipids, especially phosphatidylcholine and sphingomyelin, are structural components of cell membranes and precursors for intracellular messenger molecules. Phosphatidylcholine is a required component of very low-density lipoprotein (VLDL) particles, necessary for the transportation of

cholesterol and fat from the liver to other sites in the body. Finally, choline is a precursor for the neurotransmitter, acetylcholine. As a possible precursor of choline, DMAE has been studied as a potential modulator of many of the above-mentioned biological processes.

Acute Exposures
Inhalation studies resulted in LC_{50} values in the mouse of 36.14 mmol/m^3. The upper range for the rat was reported at 70 mmol/m^3. Oral LD_{50}s ranged from 6.790 to 14.60 mmol/kg (mouse) to 2.94 to 67.31 mmol/kg (rat). Dermal LD_{50}s were derived only for rabbits and ranged from 13.5 to 34.86 mmol/kg.

Signs of toxicity from inhalation exposures included irritation to the mucous membranes of the eyes and upper respiratory tract and incoordination; blepharospasms and lacrimation; excessive salivation; ocular, oral, and nasal discharge and encrustation; respiratory difficulties; decreased motor activity; coordination loss, and swelling and bleeding of extremities from excessive preening (high-dose only); and a substantial body-weight loss. Discolored lungs, liver, kidneys, and spleen were observed in rats that died and in two high-dose survivors.

DMAE, classified as corrosive (occlusive or semi-occlusive dressings), was moderately lethal in rabbits after acute percutaneous exposures. Moderate to severe erythema and edema with ecchymoses, necrosis, and ulceration occurred after DMAE application for 24 hours, and progressed to local desquamation, alopecia, and scarring. Application of 0.75 mg (0.0083 mmol) DMAE to the eyes of rabbits produced severe irritation. Moderate to severe corneal injury, iritis, and severe conjunctival irritation (with necrosis) was observed in all rabbits treated with 0.005 mL (4 mg; 0.05 mmol) DMAE.

Short-term Exposures
All high-dose (586 ppm; 24 mmol/m^3) F344 rats died between days four through eight, and four of fifteen mid-dose (288 ppm; 11.8 mmol/m^3) males died on days eight through twelve after inhalation exposure to DMAE (six hours/day, five days/week, nine exposures in eleven days). Signs of toxicity included respiratory distress, ocular and nasal irritation, and corneal opacity. Male and female New Zealand White rabbits treated dermally with DMAE (up to 2.0 mL/kg/day (1800 mg/kg/day; 20 mmol/kg/day) developed severe skin irritation. Microscopic examination revealed no treatment-related effects in regions other than treated skin.

Male Wistar rats (24-month-old) dosed orally with centrophenoxine (100 mg/kg body weight [0.640 mmol/kg]) once a day for four weeks had significant differences in malondialdehyde (MDA), phospholipid content, superoxide dismutase (SOD) activity, glutathione (GSH), and protein thiol (PrSHs) relative to tissue levels from untreated young and old rats.

Subchronic and Chronic Exposures
Male and female F344 rats exposed to DMAE (8 to 76 ppm; 0.3 to 3.1 mmol/m^3, six hours/day, five days/week, thirteen weeks) produced corneal opacity in mid- and high-dose rats; an increase in audible respiration was demonstrated in the high-dose group. Histopathologic changes in nasal tissue were observed, including rhinitis, squamous metaplasia, degeneration of respiratory epithelium, atrophy of olfactory epithelium, and microcysts in respiratory epithelium. Nasal lesions were limited to the anterior nasal cavity. Chronic exposures of mice to emissions from freshly foamed polyurethane insulation [6.7 mg/m^3 DMAE (0.075 mmol/m^3)] produced disturbances in blood composition including increased leukocyte count and decrease in erythrocytes and hemoglobin content.

A decrease in plasma triglyceride and cholesterol was observed in rats receiving 10 mg/kg (0.10 mmol/kg) per day DMAE orotate for six months, without any signs of fatty acid infiltration of the liver. A four-month continuous inhalation exposure of rats to high concentrations of DMAE (2.76 mg/m^3; 0.031 mmol/m^3) resulted in a disturbance in the "dynamic equilibrium between processes of inhibition and excitation" with "prevalence for excitation." A 90-day feeding study resulted in a NOAEL and LOAEL of 180 and 890 mg (2.00 and 10.0 mmol) DMAE/kg, respectively.

Synergistic/Antagonistic Effects
DMAE (175 to 350 mg/kg [1.95 to 3.90 mmol/kg], subcutaneously) was reported to potentiate the central action of cardiazol, strychnine, morphine, chlorpromazine, evipan, and phenobarbital in rats. Treatment with DMAE for seven to fourteen days increased levels of chlorpromazine in the brains of rat, relative to treatment with chlorpromazine alone..

DMAE bitartrate administered simultaneously with paracetamol (acetaminophen), protected rats and mice from hepatotoxic effects of paracetamol possibly by enhancing the elimination of free paracetamol and its glucuronide. DMAE *p*-chlorophenoxyacetate, given prior to pentetrazole, reduced the threshold for pentetrazole-induced generalized tonic-clonic crisis. Chicks injected intraperitoneally with small doses of DMAE *p*-acetamidobenzoate before tremorine potentiated the tremorine-induced tremor response. Large doses prior to tremorine suppressed the tremor response.

Reproductive and Teratological Effects
No histopathological changes in the gonads were observed after repeated exposure to DMAE in a 90-day inhalation study in rats.

DMAE induced maternal toxicity as demonstrated by changes in body weight gain in the mid- and high-dose (30 and 100 ppm; 1.20 and 4.10 mmol/m^3) groups and ocular changes in the mid- and low-dose groups (30 and 10 ppm; 1.20 and 0.41 mmol/m^3). Sporadic, inconsistent alterations in gestational parameters included significant decreases in viable implants per litter, percentage live fetuses/litter, and litter size in rats exposed to 10 ppm (40mg/m^3; 41 mmol/m^3). A significant decrease in the percentage of male fetuses in rats exposed to 30 ppm (1.20 mmol/m^3) was reported. Inhaled DMAE induced an inconsistent pattern of skeletal variations reported as poorly ossified cervical centrum, bilobed thoracic centrum, bilobed sternebrae, unossified proximal phalanges of the forelimb, and increased incidences of split cervical centra, and bilobed thoracic centrum. A NOAEL of 100 ppm (4.10 mmol/m^3) or greater was established for embryofetal toxicity and teratogenicity. A NOAEL for maternal toxicity was estimated at 10 ppm (0.41 mmol/m^3).

Pups derived from pregnant rats dosed with DMAE (gestation day 12 through postnatal day 10) demonstrated diminished behavioral decrements (motor activity in the pups; striatal dopamine release in adults) induced by postnatal hypoxia.

Carcinogenicity
There was no statistically significant increase, or morphological difference, in the incidence of neoplasms in any organ in female C3H/HeN mice given drinking water with 10 mM (900 µg/mL) DMAE for 105 weeks, or in female C3H/HeJ(+) mice given 15 mM (1300 µg/mL) DMAE for 123 weeks.

Anticarcinogenicity
Centrophenoxine was reported to potentiate the antitumor activity of chlorambucil *in vivo*. Tumorigenic LM cell cultures enriched with choline or DMAE enhanced the antineoplastic action of 5-fluorouracil by threefold.

Genotoxicity
DMAE failed to demonstrate genotoxicity in the *Salmonella typhimurium* assay, *Drosophila melanogaster* sex-linked recessive lethal assay, sister chromatid exchange assays, or hypoxanthine-guanine phosphoribosyl transferase forward gene mutation tests (HGPT). No significant increases in the incidence of micronucleated polychromatic erythrocytes were observed in Swiss-Webster mice at DMAE dose levels ranging from 270 to 860 mg/kg body weight (3.00 to 9.60 mmol/kg).

Immunotoxicity
DMAE has been classified as a potential skin sensitizer, although this classification has not been supported by human experiences with DMAE under normal handling procedures. DMAE, evaluated in the guinea pig maximation test was without any clear evidence of skin sensitization.

Other Data
NIH 3T3 clone-7 fibroblasts treated with DMAE (0.1, 0.25, 0.5, or 1 mM [9.0, 22.0, 45.0, or 90.0 µg/mL] for 17 hours, with the addition of [methyl-^{3}H]thymidine for the last hour, enhanced DNA synthesis 12- and 33-fold, respectively. The addition of insulin (500 nM) to DMAE-supplement media greatly enhanced the modest (15- to 20-fold) mitogenic effect of insulin. NIH 3T3 clone-7 fibroblasts treated with the protein kinase C inhibitor GF 109203X, followed by DMAE (90.0 µg/mL, 17 hours) enhanced insulin-induced DNA synthesis ~ 8.4-fold. Detectable (~ 2-fold) enhancement of DNA synthesis occurred with 0.1 mM (9.0 µg/mL) DMAE alone, while maximal enhancement of DNA synthesis occurred with 1 mM (90.0 µg/mL) DMAE. In NIH 3T3 cells overexpressing the *Drosophila* ethanolamine kinase, ethanolamine (50 to 200 µM) inhibited the mitogenic response induced by DMAE in the presence of insulin.

Supplementation with DMAE (50 µM or 1 mM; 4.5 or 90 µg/mL) reduced docosahexaenoic acid-induced cell death in OLN 93 cell from 48% to 6% (3 days) or 20% (20 hours), possibly by preventing the translocation of activated ERK1 to the nucleus. Further studies suggested that DMAE supplementation reduced the synthesis of ethanolamine phosphoglycerides, prevented its externalization to the outer membrane leaflet, and thereby rescued the cells from apoptotic death. DMAE, at concentrations ranging from 10 to 100 µg/mL (110 to 1110 µM), inhibited dimethylsulfoxide-induced differentiation of Friend leukemia cells.

Infusion of DMAE (0.3 mg (3.3µmol)/kg/min, intravenously) in bile-duct fistulated rats for 15 hours enriched phosphatidylcholine content in hepatic membranes and was accompanied by a significant ($p<0.01$) decrease in the hepatic concentration of triacylglycerols. Infused through a bile-duct cannula, DMAE resulted in an increase in biliary phospholipid secretion, increased canicular membrane fluidity, and decreased biliary phospholipid hydrophobicity, without a change in its transporter activity.

DMAE and Choline
Choline has recently been identified as an essential human nutrient, used in the biosynthesis of the phospholipids, phosphatidylcholine, and sphingomyelin and as a precursor of intracellular messenger molecules. Perturbations in choline metabolism will affect a range of cellular structures and functions.

DMAE (200 µM for 20 minutes) was found to be a potent inhibitor of choline uptake *in vitro*. DMAE acted as a choline oxidase inhibitor. In isolated perfused kidney studies, DMAE significantly decreased both the rate of [^{14}C]choline removal and the rate of [^{14}C]betaine addition to the

perfusate. DMAE also significantly inhibited [^{14}C]betaine production in cortical, outer, and inner medullary regions of rat kidney in tissue slice experiments.

Although pregnancies progressed equally well for all treatment groups and litters of similar sizes were delivered, only 18/253 offspring derived from pregnant rats maintained on a choline-deficient diet supplemented with 1% DMAE survived for more than 36 hours postpartum. The pups demonstrated moderate degrees of glycogen and fatty infiltrations in their livers. Measurable amounts of DMAE (72.2 ± 12.7 nmol/g) were observed in their brains. In addition, levels of choline and acetylcholine in the brains were elevated 53% and 36%, respectively.

One study reported that the DMAE-induced perturbations of choline uptake and metabolism caused neural tube defects and craniofacial hypoplasia in neurulating mouse embryos *in vitro*. Incubation of mouse embryos for 26 hours in DMAE-containing medium resulted in a statistically significant, dose-dependent increase in malformation rate and severity. DMAE-treatment reduced choline uptake by 70% in the 375 µM group (33.7 µg/mL). Follow-on studies conducted in gastrulation/neurulation stage mouse embryos suggested that DMAE decreased [^{14}C]choline incorporation into phosphocholine, phosphatidylcholine, and sphingomyelin to 25%, 35%, and 50% of control values, respectively, and increased the levels of labeled betaine was threefold. DMAE treatment produced a 15% increase in embryonic ceramide, an important cell-signaling molecule.

LM fibroblasts, when grown in DMAE-containing, serum-free medium, incorporated DMAE into membrane phospholipids. These cells, when injected into nude mice, reduced the frequency of lung metastasis relative to that of serum- and choline-fed cells.

Addition of DMAE to cultured hepatocytes isolated from choline-deficient rats resulted in the biosynthesis of phosphatidyldimethylethanolamine in the place of phosphatidylcholine and negatively impacted normal VLDL secretions.

Choline deficiency results in the depletion of intracellular methyl-folate and methionine with a simultaneous increase in intracellular *S*-adenosylhomocysteine and homocysteine concentrations. Elevated homocysteine levels are a significant risk factor of atherosclerosis and other cardiovascular and neurological disorders.

Structure-Activity Relationships
Di- and triaminoethanols
Di- and triaminoethanols can give rise to *N*-nitrosodiethanolamine (NDELA), a potent carcinogen, via nitrosation resulting from reaction with nitrite or nitrous oxide.

Ethanolamine [141-43-5]
Ethanolamine has had wide industrial use without reports of human injury. Undiluted ethanolamine applied to human skin resulted in redness after 90 minutes. Ethanolamine is naturally found in mammals. Ethanolamine is methylated to choline, metabolized to form serine and glycine, and deaminated to form urea (rabbits). Both cultured rat and chick neurons were able to methylate ethanolamine phospholipids, free ethanolamine, or phosphorylethanolamine to form choline.

In an oral subchronic toxicity study (90-day), lethality and microscopic pathological changes occurred at 1.28 g/kg in rats with changes in liver or kidney weight observed at lower doses. The primary toxic effects reported for inhalation studies (mice, rats, guinea pigs, rabbits, cats, and dogs) included respiratory tract irritation and nonspecific degenerative changes in the liver and kidneys. Skin irritation and lethargy was observed at 5 and 12 ppm. Applied directly to the eye (rabbit),

ethanolamine resulted in severe damage.

LM fibroblasts grown in the presence of ethanolamine resulted in fewer and less invasive, lung metastases in the nude mouse relative to metastases induced by trimethylethanolamine-supplemented serum. Tumors derived from these LM cells had significant reductions in the specific activity of several mitochondrial enzymes. Significant changes were also observed in the fatty acid composition of plasma membranes, microsomes, and mitochondria. Ethanolamine failed to inhibit dimethylsulfoxide-induced cell differentiation in Friend leukemia cells until concentrations of 100 µg/mL were reached.

The addition of 1 or 2 mM ethanolamine to NIH 3T3 cells produced a slight (4.5- to 5-fold) increase in DNA synthesis. The combination of ethanolamine (1 mM) and insulin (500 nM) increased insulin-induced DNA synthesis by only 2.1-fold. The addition of choline (1 or 5 mM) further enhanced the combined effects of ethanolamine and insulin.

Diethanolamine [111-42-2]
The most consistent results from twelve human cancer studies of metalworking fluids were a small excess in stomach cancers associated with the use of cutting fluids containing diethanolamine. Synthetic metalworking fluids were also associated with weak to moderate risks for cancer of the liver, esophagus, pancreas, prostate, larynx, and the hematopoietic system. The IARC Working Group concluded that there was inadequate evidence of carcinogenicity in humans (IARC, 2000; cited by NTP, 2002).

Diethanolamine was absorbed following intravenous, dermal, and oral administration to male F344 rats, with most of the compound retained in liver and kidney tissues. The primary route of elimination was via the urine. Steady state tissue concentrations were reached at about four weeks. The elimination half-life was estimated at one week. Similar studies performed in $B6C3F_1$ mice gave similar results.

Ranges for oral LD_{50}s for diethanolamine in rats have been reported at 780 to 1820 mg/kg; for mice, the LD_{50} for intraperitoneal and subcutaneous exposures was 2300 and 3553 mg/kg, respectively. Toxic symptoms included increased blood pressure, diuresis, salivation, and papillary dilation. A 90-day NOAEL (species not provided) was reported to be 20 mg/kg. Long-term (90 days) dietary exposures to 170 mg/kg resulted in uncharacterized microscopic lesions and death. Mild skin irritation was noted in rabbits at concentrations exceeding 5%; 50% concentrations produced severe ocular irritation. Single oral injections (100 to 3200 mg/kg) or inhalation (25 ppm, continuously, 216 hours) of diethanolamine (rats) resulted in increased relative and absolute liver weights, respectively and clinical chemistry changes. Renal changes included increased absolute and relative tissue weights, necrosis and cytoplasmic vacuolization of the renal tubular epithelium, and increased blood urea nitrogen levels.

Male B6C3F1 mice exposed to dietary diethanolamine revealed a significant reduction in phosphocholine, glycerophosphocholine, choline, phosphatidylcholine, and *S*-adenosylmethionine. Body weight gain and liver weights were unaffected and there was no evidence of fatty livers in the treated animals. Diethanolamine (dermally, five day per week for four weeks) resulted in a dose dependent reduction in phosphocholine, glycerophosphocholine, and choline.

The National Toxicology Program investigated the dermal carcinogenic potential of diethanolamine in male and female F344/N rats and $B6C3F_1$ mice and concluded that there was clear evidence for carcinogenic activity of diethanolamine in both male and female $B6C3F_1$ mice at the exposure levels

used. A significant increase in the incidences of hepatocellular adenoma, combined hepatocellular adenoma or carcinoma, hepatocellular carcinoma, and hepatoblastoma were found. Nonneoplastic changes included cytoplasmic and syncytial alterations. In mice, a positive trend was observed for renal tubule adenoma. A dose-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma or carcinoma (combined), and an increase in the incidences of renal tubule adenoma in male mice were found. An increased incidence in thyroid gland follicular cell hyperplasia was found in dosed male and female mice relative to vehicle controls.

Diethanolamine tested positive after a seven-day exposure in a single transformation study in SHE cells. Diethanolamine (500 µg/mL) reduced ^{33}P incorporation into phosphatidylcholine in Syrian hamster embryo (SHE) cells. Choline uptake by the SHE cells was inhibited in a concentration-dependent fashion in the presence of diethanolamine. Incubation of SHE cells in the presence of both diethanolamine and excess choline (30 mM) prevented the incorporation of diethanolamine into phospholipids.

A loss in cellular respiratory control was observed in hepatic mitochondria isolated from male Sprague-Dawley rats treated with diethanolamine in the drinking water for up to three weeks.

Monomethylethanolamine [109-83-1]

Acute oral LD_{50} values were 1908 (male rats) and 1391 (female rats) mg/kg; the dermal LD_{50} (rabbit) was 1070 µL/kg. Intraperitoneal LD_{50}s were 1330 (rat) and 125 (mouse) mg/kg. Administered subcutaneously (mouse), monomethylethanolamine resulted in a LD_{50} of 1802 mg/kg. Signs of toxicity included chromodacryorrhea, ataxia, somnolence, respiratory effects, gastrointestinal hypermotility, diarrhea, dermatitis, and affected both the seizure threshold (producing comas). Dermally monomethylethanolamine was classified as skin corrosive and caused a severe hyperemia of the conjunctivae, edema, and profuse discharge when applied to the eye.

No maternal or fetal toxicity was associated with maternal exposures to 150 ppm seven hours a day from gestation day seven through fifteen (Nelson et al., 1984). Pregnant dams exposed to a choline-deficient diet supplemented with 1.0% monomethylethanolamine beginning on gestation day six through 15 days post-partum resulted in pups that weighed significantly less than pups from the choline-deficient group. None of the 120 pups from the ten exposed litters survived past 36 hours postpartum. The pups showed a moderate degree of glycogen and fatty infiltrations in their livers. Measurable amounts of DMAE (11.7 ± 1.8 nmol/g) were detected in the brains of one-day-old pups. Monomethylethanolamine-supplementation resulted in elevated levels of both choline and acetylcholine relative to choline-deficient derived pups. In the monomethylethanolamine-supplemented pups, phosphatidylcholine and phosphatidyl aminoethanol levels in the brain were significantly ($p<0.05$) lower relative to the choline-deficient-fed pups.

LM fibroblasts grown in the presence of monomethylethanolamine resulted in fewer and less invasive lung metastases (42%) in the nude mouse than LM fibroblasts grown in serum- or choline-supplemented serum. Tumors derived from these cells injected into nude mice had significantly reduced activities in several mitochondrial enzymes. Significant changes were observed in the fatty acid composition of plasma membranes, microsomes, and mitochondria.

Monomethylethanolamine, classified as having a mild potential to induce skin sensitization, gave a positive response in the guinea pig maximation test.

Monomethylethanolamine (1mM) induced an increase in DNA synthesis (ten-fold) in NIH 3T3 cells; in combination with insulin, it induced DNA synthesis by almost six-fold. Choline (1 or 5 mM)

further enhanced the combined effects without potentiating the mitogenic effects of monomethylethanolamine alone.

Methyldiethanolamine [105-59-9]
Radiolabeled methyldiethanolamine was readily absorbed from dermal applications in rats, with the highest concentrations found in the liver and kidneys. Nonlinear kinetic behavior following intravenous administration of 500 mg/kg suggests saturation of metabolism at high doses. Elimination is primarily through the urine, with an excretion half-life in excess of 30 hours after dermal application.

The oral LD_{50} for both Sprague-Dawley rats was 1945 mg/kg; dermal LD_{50}s were 10,244 and 11,336 mg/kg (male and female New Zealand White rabbits, respectively). Methyldiethanolamine was classified as mildly irritating to the skin and to the eyes of rabbits. Short-term and subchronic studies of dermally applied methyldiethanolamine resulted in changes in weight gain, dose-related skin irritations, an increase in adrenals gland weight, and hematological and clinical chemistry changes.

Methyldiethanolamine failed to induce genotoxic or immunotoxic effects. In reproductive toxicity/teratogenicity studies, NOAELs for maternal and embryofetal toxicity/teratogenicity of methyldiethanolamine were estimated at 250 and 1000 mg/kg/day or greater, respectively. Signs of maternal toxicity were anemia and severe skin irritation including necrosis, ecchymoses, exfoliation, crusting, excoriation, erythema, and edema.

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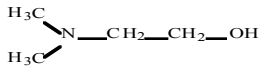
1.0 Basis for Nomination

Dimethylethanolamine (DMAE) was nominated by the NIEHS for toxicological characterization, including metabolism, reproductive and developmental toxicity, subchronic toxicity, carcinogenicity and mechanistic studies. The nomination is based on the potential for widespread human exposure to DMAE through its use in industrial and consumer products and an inadequate toxicological database. Studies to address potential hazards of consumer (e.g. dietary supplement) exposures, including use by pregnant women and children, and the potential for reproductive effects and carcinogenic effects are limited. DMAE and related ethanolamines appear to interfere with choline uptake and utilization and may also generate nitrosamines. Further studies are recommended to address these data gaps with special attention to pharmacokinetics and the influence of dietary choline. Consideration should be given to whether the bitartrate salt of DMAE (a form commonly used in dietary supplements) or other DMAE derivative is more appropriate than the free base for use in toxicology studies.

2.0 Introduction

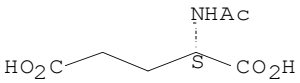
Chemical Structures of DMAE and selected salts and esters:

DMAE [108-01-0]



DMAE aceglumate [3342-61-8]

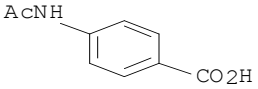
CM 1



CM 2

DMAE *p*-acetamidobenzoate (an ester) [2811-31-6]

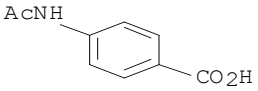
CM 1



CM 2

DMAE *p*-acetamidobenzoate (a salt); Deaner®
[3635-74-3]

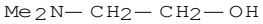
CM 1



CM 2

DMAE bitartrate [5988-51-2]

CM 1



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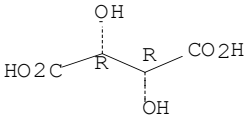
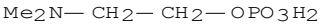
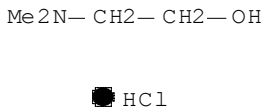


DMAE dihydrogen phosphate [6909-62-2]

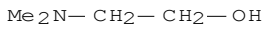


DMAE hydrochloride [2498-25-1]

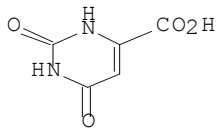


DMAE orotate [1446-06-6]

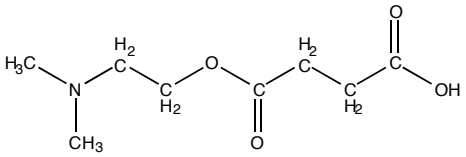
CM 1



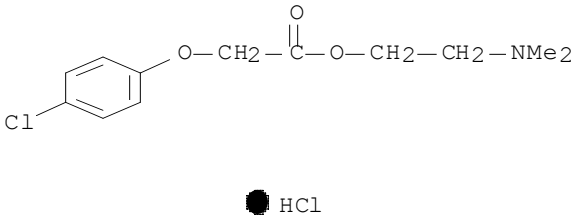
CM 2



DMAE succinate; Tonibral [10549-59-4]

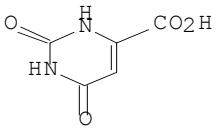


Centrophenoxine; dimethylethanolamine *p*-chlorophenoxyacetate hydrochloride [3685-84-5]

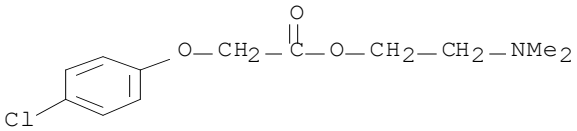


Centrophenoxine orotate [27166-15-0]

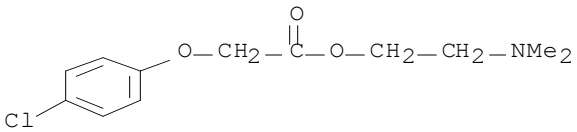
CM 1



CM 2



Meclofenoxate; Dimethylethanolamine *p*-chlorophenoxyacetate [51-68-3]



2.1 Chemical Identification and Analysis

DMAE [108-01-0] ([$C_4H_{11}NO$]; mol. wt. = 89.919) is also called:

Ethanol, 2-(dimethylamino)- (8CI, 9CI) (CA INDEX NAME)
Dimethylethanolamine
(2-Hydroxyethyl)dimethylamine
(Dimethylamino)ethanol
(*N,N*-Dimethylamino)ethanol
β-(Dimethylamino)ethanol
β-Dimethylaminoethyl alcohol
β-Hydroxyethyldimethylamine
2-(Dimethylamino)ethanol
2-(Dimethylamino)-1-ethanol
2-(Dimethylamino)ethyl alcohol
2-(*N,N*-Dimethylamino)ethanol
Amietol M 21
Bimanol
Dabco DMEA
Deanol
Dimethol
Dimethyl(2-hydroxyethyl)amine
Dimethyl(hydroxyethyl)amine
Dimethylmonoethanolamine
DMEA
Ethanolamine, dimethyl-(2 -hydroxyethyl) dimethylamine
Kalpur P
Liparon
N,N-Dimethyl(2-hydroxyethyl)amine
N,N-Dimethyl-*β*-hydroxyethylamine
N,N-Dimethyl-2-aminoethanol
N,N-Dimethyl-*N*-(2-hydroxyethyl)amine
N,N-Dimethyl-*N*-(*β*-hydroxyethyl)amine
N,N-Dimethylethanolamine
N-Dimethylethanolamine
N-(2-Hydroxyethyl)-*N,N*-dimethylamine
N-(2-Hydroxyethyl)dimethylamine
Norcholine
PC CAT DMEA
Propamine A
Rexolin
Texacat DME
Thancat DME
3D CONCORD

DMAE aceglumate [3342-61-8] ([$C_7H_{11}NO_5 \bullet C_4H_{11}NO$]; mol. wt. = 278.31) is also called:

L-Glutamic acid, *N*-acetyl-, compound with 2-(dimethylamino)ethanol (1:1) (9CI) (CA INDEX NAME)
Dimethylethanolamine aceglumate
Ethanol, 2-(dimethylamino)-, *N*-acetyl-L-glutamate (salt) (1:1) (8CI)
Ethanol, 2-(dimethylamino)-, *N*-acetyl-L-glutamate (1:1) (salt) (9CI)
Glutamic acid, *N*-acetyl-, compound with 2-(dimethylamino)ethanol (7CI)
Glutamic acid, *N*-acetyl-, compound with 2-(dimethylamino)ethanol (1:1), L- (8CI)
2-(Dimethylamino)ethanol acetylglutamate
2-(Dimethylamino)ethanol *N*-acetylglutamate
Cleregil
CR 121
Deanol aceglumate
Otrun
Risatarun

DMAE *p*-acetamidobenzoate (an ester) [2811-31-6] ([$C_{13}H_{18}N_2O_3$]; mol. wt. = 250.29) is also called:

Benzoic acid, 4-(acetylamino)-, 2-(dimethylamino)ethyl ester (9CI) (CA INDEX NAME)
Dimethylethanolamine *p*-acetamidobenzoate
Benzoic acid, *p*-acetamido-, 2-(dimethylamino)ethyl ester (7CI, 8CI)
2-Dimethylaminoethanol *p*-acetamidobenzoic acid ester

2-Dimethylaminoethyl *p*-acetamidobenzoate
CY 37
Dimethylaminoethanol *p*-acetamidobenzoate
Dimethylaminoethyl *p*-acetamidobenzoate
Nervoton

DMAE *p*-acetamidobenzoate (a salt); Deaner® [3635-74-3] ([$C_9H_9NO_3$•$C_4H_{11}NO$]; mol. wt. = 270.33) is also called:

Benzoic acid, 4-(acetylamino)-, compound with 2-(dimethylamino)ethanol (1:1) (9CI) (CA INDEX NAME)
Dimethylethanolamine *p*-acetamidobenzoate
Benzoic acid, p-acetamido-, compound with 2-(dimethylamino)ethanol (6CI, 7CI)
Benzoic acid, p-acetamido-, compound with 2-(dimethylamino)ethanol (1:1) (8CI)
Ethanol, 2-(dimethylamino)-, 4-(acetylamino)benzoate (salt) (9CI)
Ethanol, 2-(dimethylamino)-, compound with p-acetamidobenzoic acid (1:1)
Ethanol, 2-(dimethylamino)-, *p*-acetamidobenzoate (salt) (8CI)
2-Dimethylaminoethanol *p*-acetamidobenzoate
2-(Dimethylamino)ethanol *p*-acetylaminobenzoate
Deanol acetamidobenzoate
Diforene

DMAE bitartrate [5988-51-2] ([$C_4H_{11}NO$•$C_4H_6O_6$]; mol. wt. = 239.23) is also called:

Ethanol, 2-(dimethylamino)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt) (9CI) (CA INDEX NAME)
Dimethylethanolamine bitartrate
Ethanol, 2-(dimethylamino)-, tartrate (1:1) (8CI)
Ethanol, 2-(dimethylamino)-, [R(R*,R*)]- 2,3-dihydroxybutanedioate (1:1) (salt)
2-Dimethylaminoethanol bitartrate
2-Dimethylaminoethanol tartrate
Dimethylaminoethanol bitartrate
N,N-Dimethylethanolamine-tartaric acid salt

DMAE dihydrogen phosphate [6909-62-2] ([$C_4H_{12}NO_4P$]; mol. wt. = 169.12) is also called:

Phosphoric acid, mono[2-(dimethylamino)ethyl] ester (8CI, 9CI) (CA INDEX NAME)
Dimethylethanolamine dihydrogen phosphate
Ethanol, 2-(dimethylamino)-, dihydrogen phosphate (7CI)
Ethanol, 2-dimethylamino-, phosphate (6CI)
2-(Dimethylamino)ethanol dihydrogen phosphate
2-(Dimethylamino)ethyl dihydrogen phosphate
Demanyl phosphate
N,N-Dimethylaminoethanol monophosphate
N,N-Dimethylethanolamine phosphate
P-DMEA
Pancar
Panclar
Phosphoryldimethylcolamine
Phosphoryldimethylethanolamine

DMAE hydrochloride [2498-25-1] ([$C_4H_{11}NO$•ClH]; mol. wt. = 125.62) is also called:

Ethanol, 2-(dimethylamino)-, hydrochloride (8CI, 9CI) (CA INDEX NAME)
Dimethylethanolamine hydrochloride
2-(Dimethylamino)ethanol hydrochloride
2-(*N,N*-Dimethylamino)ethanol hydrochloride
Deanol hydrochloride
Dimethylaminoethanol-hydrochloride
Dimethylethanolamine hydrochloride
N,N-Dimethyl-2-aminoethanol hydrochloride
N,N-Dimethylaminoethanol hydrochloride

DMAE orotate [1446-06-6] ([$C_5H_4N_2O_4$•$C_4H_{11}NO$]; mol. wt. = 275.24) is also called:

4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-, compound with 2-(dimethylamino)ethanol (1:1) (9CI) (CA INDEX NAME)
Dimethylaminoethanol orotate
Ethanol, 2-(dimethylamino)- 1,2,3,4-tetrahydro-2,6-dioxo-4-pyrimidinecarboxylate (salt) (9CI)
Ethanol, 2-(dimethylamino)-, orotate (salt) (8CI)
Orotic acid, compound with 2-(dimethylamino)ethanol (7CI)
Orotic acid, compound with 2-(dimethylamino)ethanol (1:1) (8CI)

DMAE succinate; Tonibral [10549-59-4] ([$C_8H_{15}NO_4$] mol. wt. = 189.21) is also called:

Butanedioic acid, mono[2-dimethylamino)ethyl] ester (9CI) (CA INDEX NAME)
Dimethylaminoethanol succinate
Succinic acid, 2-(dimethylamino)ethyl ester (7CI)
Succinic acid, mono[2-(dimethylamino)ethyl]ester (8CI)
Mono[2-(dimethylamino)ethyl]succinate
3D CONCORD

Centrophenoxine; DMAE *p*-chlorophenoxyacetate hydrochloride [3585-84-5] ([$C_{12}H_{16}ClNO_3$•Cl H]; mol. wt. = 294.20) is also called:

Acetic acid, (4-chlorophenoxy)-, 2-(dimethylamino)ethyl ester, hydrochloride (9CI) (CA INDEX NAME)
Acetic acid, (*p*-chlorophenoxy)-, 2-(dimethylamino)ethyl ester hydrochloride (6CI, 8CI)
Acefen
Acephen
Centrophenoxine hydrochloride
Cerutil
2-(Dimethylamino)ethyl (*p*-chlorophenoxy)acetate hydrochloride
Dimethylaminoethyl 4-chlorophenoxyacetate hydrochloride
Dimethylaminoethyl *p*-chlorophenoxyacetate hydrochloride
Helfergin
Lucidril
Lucidryl hydrochloride
Meclofenoxate hydrochloride
Meclophenoxate hydrochloride

Centrophenoxine orotate ($C_{12}H_{16}ClNO_3 \bullet C_5H_4N_2O_5$; mol. wt. = 423.77) is also called:

2-(Dimethylamino)ethyl (4-chlorophenoxy)acetate (1:1) (9CI)(CA INDEX NAME)
4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-, compound with 2-(Dimethylamino)ethyl (4-chlorophenoxy)acetate (1:1) (9CI)
Acetic acid, (4-chlorophenoxy)-2-(dimethylamino)ethyl ester 1,2,3,6-Tetrahydro-2,6-dioxo-4-pyrimidinecarboxylate (9CI)
Acetic acid, (p-chlorophenoxy)-2-(dimethylamino)ethyl ester orotate (8CI)
Orotic acid, compound with 2-(dimethylamino)ethyl (*p*-chlorophenoxy)acetate (1:1) (8CI)
Meclophenoxate orotate

Meclofenoxate; DMAE *p*-chlorophenoxyacetate [51-68-3] ([$C_{12}H_{16}Cl\ NO_3$]; mol wt. = 257.71) is also called:

Acetic acid, (4-chlorophenoxy)-, 2-(dimethylamino)ethyl ester (9CI) (CA INDEX NAME)
Acetic acid, (*p*-chlorophenoxy)-, 2-(dimethylamino)ethyl ester (6CI, 8CI)
(*p*-Chlorophenoxy)acetic acid *β*-(dimethylamino)ethyl ester
(*p*-Chlorophenoxy)acetic acid 2-(dimethylamino)ethyl ester
2-(Dimethylamino)ethyl (*p*-chlorophenoxy)acetate
Analux
ANP 235
Cerebon
Cetrexin
Clocete
CPH
Dimethylaminoethyl *p*-chlorophenoxyacetate
EN 1627
Licidril
Meclofenoxane
Meclofenoxate
Meclophenoxate
Proseryl

Also interchangeable with centrophenoxine in most sources, but Registry (2002) restricts centrophenoxine to the hydrochloride salt.

Sources: Registry (2002)

Some industrial analytical methods for DMAE from air industrial settings are named below.

- DMAE in air was sampled on a high-capacity, carboxylic acid-functionalized resin and determined by Fournier transform infrared spectrophotometry (FITR). The limit of detection was 0.98 ppm v/v, and the limit of quantification was 2.89 ppm v/v (Seeber et al., 1998).
- The Crompton method uses 38C-17G1-R2 XAD-8 resin (250 mg/110 mg), and the Huntsman method uses Chromosorb-102 resin (API, 2000).
- Isotachophoretic systems were used for determining DMAE (Sollenberg and Hansen, 1987). Air was pumped through impinger flasks with 20 mM hydrochloric acid gas or by adsorption of silica gel (Hansen et al., 1984).

In a study of sampling and analysis of DMAE in air, the chemical was quantitatively determined with a detection limit of about 0.01 ppb for a 5-L sample by the following method. Air of a

known volume was passed through a short glass tube containing Chromosorb 102. The amines were adsorbed and were then thermally desorbed onto a gas chromatographic column to be separated from other components and detected by flame ionization detector. The retention time was 0.92 minutes (Bugler et al., 1992).

Several analytical methods were used to determine DMAE compounds in forensic and toxicological analysis: off-line coupling of thin layer chromatography (TLC) and electron-impact mass spectrometry (EIMS) to determine meclofenoxate (Brzezinka et al., 1999); reversed-phase high performance liquid chromatography (HPLC) to determine meclofenoxate (Eigendorf et al., 1989; Eigendorf et al., 1990); capillary zone electrophoresis deanol acetamidobenzoate [3635-74-3] (Hudson et al., 1995); HPLC to determine meclofenoxate and its degradation products [detector not mentioned in abstract] (Yang and Thyrion, 1998); and principal components analysis of standardized TLC data in different eluent systems to identify meclofenoxate (Musumarra et al., 1985).

2.2 Physical-Chemical Properties

DMAE is moderately flammable and is normally stable (HSDB, 1996). In its anhydrous state, it is compatible with aluminum, but in an aqueous mixture, it is highly corrosive to aluminum, copper alloys, zinc, and galvanized iron (Dow, 2001a).

DMAE [108-01-0]

Property	Information	Reference
Physical state	Liquid	Budavari (2001)
Color	Colorless	HSDB (1996)
Melting point, °C	-58.6	Huntsman Corp. (1997)
Boiling point, °C	134	Weast and Astle (1980)
Vapor pressure at 20 °C	21 mm Hg torr	Oxford (2001)
Flash point, °C	39-41	IUCLID (1997)
Odor	Amine odor	HSDB (1996)
Density at 20 °C/4 °C	0.8866 g/mL	Weast and Astle (1980)
Solubility:		
Water at pH 7	≥ 1 M	Registry (2002) (calculated)
Organic Solvents	Soluble in ethanol, diethyl ether	Weast and Astle (1980)
Log of the octanol-water partition coefficient (log K_{OW}; Log P)	-0.565 ± 0.257	Registry (2002) (calculated)
pKa	8.88 ± 0.20	Registry (2002) (calculated)

DMAE Acetate [1421-89-2]

Property	Information	Reference
Molecular weight	131.17	Registry (2002)
Solubility in water at pH 7	≥ 1 M	Registry (2002)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	0.331 ± 0.267	Registry (2002)

DMAE Aceglumate (a Salt) [3342-61-8]

Property	Information	Reference
Solubility in water	Soluble	Budavari (2001)

DMAE p-Acetamidobenzoate (Ester or Salt) [2811-31-6] or [3635-74-3]

Property	Information	Reference
Physical state	**Crystals**	**Budavari (2001)**
Melting point, °C	159-161.5	Budavari (2001)
Solubility in water at pH 7	0.1 M	Registry (2002) (calculated)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	1.380 ± 0.508	Registry (2002) (calculated)
pKa	8.19 ± 0.28	Registry (2002) (calculated)

DMAE Benzoate [2208-05-1]

Property	Information	Reference
Molecular weight	193.24	Registry (2002)
Solubility in water at pH 7	> 0.01 to < 0.1 M	Registry (2002)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	2.083 ± 0.490	Registry (2002)

DMAE Bitartrate [5988-51-2]

Property	Information	Reference
Physical State	Crystals	Budavari (2001)
Solubility in water	Soluble	Budavari (2001)

DMAE Carbamate [4220-32-0]

Property	Information	Reference
Molecular weight	132.16	Registry (2002)
Solubility in water at pH 7	> 1 M	Registry (2002)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	0.527 ±0.346	Registry (2002)

DMAE Phenylacetate [36882-00-5]

Property	Information	Reference
Molecular weight	207.27	Registry (2002)
Solubility in water at pH 7	≥ 0.01 to < 0.1 M	Registry (2002)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	2.120 ± 0.278	Registry (2002)

DMAE Succinate [10549-59-4]

Property	Information	Reference
Molecular weight	189.21	Registry (2002)
Solubility in water at pH 7	≥ 1 M	Registry (2002)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	0.137 ± 0.307	Registry (2002)

Centrophenoxine [3685-84-5]

Property	Information	Reference
Physical State	Crystals	Budavari (2001)
Melting point, °C	135-139	Budavari (2001)
Solubility:		
Water	In cold water	Budavari (2001)
Organic Solvents	In cold isopropyl alcohol, acetone (sparingly)	Budavari (2001)

Meclofenoxate [51-68-3]

Property	Information	Reference
Solubility in water at pH 7	0.1 M	Registry (2002) (calculated)
Log of the octanol-water partition coefficient (log K_{OW}; LogP)	2.250 ± 0.316	Registry (2002) (calculated)
pKa	8.17 ± 0.20	Registry (2002) (calculated)

Physical-chemical properties were not found for DMAE dihydrogen phosphate [6909-62-2], DMAE hydrochloride [2498-25-1], DMAE orotate [1446-06-6], or centrophenoxine orotate [27166-15-0].

2.3 Commercial Producers and Suppliers

2.3.1 Producers

U.S. EPA IUR (Inventory Update Rule database) (2000) listed six U.S. producers producing at least 10,000 lb DMAE each annually: BASF, Dow Chemical Co., Elf Atochem, Huntsman Corp., ICI Americas, and Union Carbide. In 1996, SRI International listed Pelron Corporation as a U.S. producer of DMAE.

Several companies are potential manufacturers of DMAE bitartrate, according to their Web sites. American International Chemical, Inc. (undated) offers DMAE *L*-bitartrate monohydrate in 20-kg cartons DMAE, 32.9 to 36.4% purity. Richman Chemical Inc. (undated) offers DMAE bitartrate. No other information is given. FoodTechSource.com (undated) offers DMAE bitartrate powder, hygroscopic, 100 g- and 500 g-sizes. The Pharmaceutical Division of ICC Chemical Corporation (undated) of New York City offers DMAE bitartrate under "Nutritional Raw Materials" on its Web site. No amounts are given.

2.3.2 Suppliers

The following bulk suppliers were listed in Chemcyclopedia 2002 (Block, 2002) were: Ashland Distribution Company; Dow Chemical Co. [producer]; Mallinkrodt Laboratory Chemicals, Division of Mallinkrodt, Baker; Quaker City Chemicals, and Union Carbide [producer]. The IUCLID (1997) review stated that DMAE is shipped in road and rail tank cars, tank containers, ISOtanks, drums, and other, smaller packages. [In general, ISO tanks are available in insulated and noninsulated versions with capacities ranging from 17,500 L (4,623 gal) to 24,000 L (6,300

gal) (isotank.com, undated).] BASF (1997) and Huntsman Corp. (1997) [both producers] provide DMAE in bulk containers and in nonreturnable 55-gal steel drums (396-400 lb DMAE net weight). Suppliers are also listed in Chemcyclopedia 2002 (Block, 2002) for the acrylate and methacrylate esters and the hydrochloride salt [CAS RN 13242-44-9]. ATOFINA Chemicals, Inc. (2000) offers DMAE and other ethanolamines for ultraviolet-cured coating systems.

In a Google Internet search for DMAE and "mg," about half of 80 hits identified the form as DMAE bitartrate. Thirteen of these products were in dosage forms containing 350-351 mg DMAE bitartrate, which corresponds to 130 mg DMAE. Other products contained 20 to 250 mg DMAE bitartrate, with 100-mg dosage forms in 11 products. Individual products for which the form of DMAE was not evident contained DMAE or its salt(s) in 15 to 250 mg-dosages. Seventeen products in this unspecified-form group used amounts of 100 mg.

DMAE may also be supplied as part of a drug salt form. Lucidryl (meclofenoxate hydrochloride) is made by Bracco de Mexico, according to The Life Extension Foundation (1999) and a three-month supply can be obtained legally by crossing the border. [The Bracco Web site could not be easily searched on April 17, 2002, to confirm whether or not they still carry this product.] A European product, Tratul® (not to be confused with a cimetidine product by Gador, which is also called Tratul [Budavari, 2001]) is sold as an anti-inflammatory, analgesic composition by Gerot Pharmazeutica (undated) available in suppositories and vials as diclofenac-deanol.

Several suppliers of children's nutritional supplements advertise products containing DMAE for the treatment of attention deficit/hyperactivity disorder. Suppliers listing unspecified DMAE include A.D.D. Warehouse (undated), Good4all.net (2002), and The Mineral Connection (2002). Those listing DMAE bitartrate include Brain Child Nutritionals (undated-a and undated-b) and The Mineral Connection (2002).

3.0 Production Processes

DMAE is synthesized from equimolar amounts of ethylene oxide and dimethylamine (Budavari, 2001). The amino group of DMAE forms salts by reacting with mineral and carboxylic acids. The hydroxyl group forms esters by reacting with carboxylic acids. Thus, the bitartrate is produced from DMAE and tartaric acid (Dow, 2001a).

Amino alcohols were determined in water and air "at levels of their" maximum allowable concentrations, 0.5 mg/L and 0.5 ng/m^3, respectively. The amino alcohols were derivatized with hydrogen chloride and acetic anhydride for determination by GC (Stan'kov et al., 2000).

4.0 Production and Import Volumes

An aggregate production volume range of 50-100 million pounds was reported in non-confidential production volume information submitted by companies for chemicals under the 1998 TSCA

Inventory Update Rule (http://www.epa.gov/oppt/iur/iur98/index.htm). DMAE was included in the 2000 OECD List of High Production Volume Chemicals, a list of chemicals produced at levels greater than 1,000 tonnes (2,205,000 lbs) per year (2001).

OECD (1997) estimated that DMAE is used in these proportions: 20% for flexible and rigid polyurethane foams and polyurethane lacquers, 50% for water flocculants, 20% for paints and surface coatings, and 10% for ion exchange resins, pharmaceuticals, and corrosion inhibitor formulations.

5.0 Uses

5.1 Industrial Uses

Coatings

DMAE is used for solubilization of water-insoluble resin components for water-based coatings (ATOFINA Chemicals, Inc., 2000), a process achieved by reaction of DMAE with the resins (Huntsman Corp., 1997). Water-based DMAE coatings are used on aluminum cans (Dow, 2001a). In an extensive survey of architectural coatings by the California Air Resources Board (CARB, 1999), DMAE was ranked 77th by weight in a list of 88 ingredients commonly found in waterborne coatings. It ranked 165th by weight among 186 ingredients used in waterborne or organic-solvent-based coatings.

A recent French study of about 30 water-based paint formulations available to vehicle manufacturers all contained glycol ethers, *N*-methylpyrrolidone, [*N*-methylpyrrolidinone], and alkanolamines (DMAE was mentioned as an example) (Jargot et al., 1999).

DMAE hemisuccinate is named in a patent for organic polymers made from isocyanates to make cathodic electrocoating [Desoto, Inc., U.S.A.] (Lin, 1982), and DMAE bitartrate was part of an aqueous cathodic coating composition to which maleic acid was added to reduce discoloration by metal ions [PPG Industries, Inc., U.S.A.] (Lucas, 1983). DMAE is used to produce methacrylate monomers for polymers as antistatic agents, electrically conducting materials (Huntsman Corp., 1997).

Emulsifying and Dispersing Agents

DMAE is used as an amino resin stabilizer and as an intermediate in the synthesis of dyes, textiles, and auxiliaries (HSDB, 1996).

DMAE fatty acid soaps are used as emulsifying and dispersing agents for waxes and polishes resistant to water that are used on metal, leather, glass, wood, ceramic ware, floors, furniture, and automobiles, and DMAE esters are common emulsifying agents in the textile industry (Dow, 2001a). DMAE hydrochloride is used in manufacturing Procter & Gamble detergent

compositions (Kandasamy et al., 2000). DMAE hemisuccinate has been used to make amphoteric surfactants (Nieh and Naylor, 1984).

Gas Treating

Alkyl alkanolamines are used to eliminate hydrogen sulfide from natural gas and refinery off-gasses (Dow, 2001a). Two out of 73 titles resulting from a CAPLUS search linking DMAE to environmental pollution indicated that DMAE is used to remove hydrogen sulfide from gas mixtures.

Urethane Catalysts

DMAE is one of at least 60 amine compounds used as catalysts in the manufacture of polyurethane and polyisocyanurate foams. Polyurethane formulations require about 0.1 to 5.0% amine catalyst (API, 2000). DMAE reacts with isocyanates, limiting the amount of DMAE emissions during the foaming reaction (Dow, 2001a).

One study evaluated amine catalyst use in polyurethane production in the United Kingdom. At a factory making polyether slabstock, the "typical total throughput" of chemicals was 300 kg per minute: 200 kg polyol per minute, 100 kg per minute 80:20 diisocyanates, and 0.6 kg/minute amine. At a typical factory for making polyester slabstock, with a throughput of 300 kg per minute, 0.5 to 1.5 kg per minute would be used. At a typical factory for making a molding, the estimated throughput was 12 kg per minute and the rate of amine use was 0.02 kg per minute (Bugler et al., 1992). DMAE in vapor phase is also used to catalyze polyurethane-based inks (Huntsman Corp., 1997) to catalyze coatings (U.S. EPA ORD, 1994), and for curing epoxy resins (HSDB, 1996).

API (2000) lists 55 other amine catalysts used in polyurethane manufacture. The di-DMAE ether, that is, bis(2-dimethylaminoethyl) ether [CAS RN 3033-62-3] may be the most widely used amine catalyst in polyurethane manufacture.

Water Treatment

DMAE is used to make flocculants for wastewater treatment (Dow, 2001a; Huntsman Corp., 1997), to inhibit corrosion in return-condensate boiler and steam systems by controlling pH (Dow, 2001a; HSDB, 1996), and to synthesize Type II resins for anion exchange (Dow, 2001a).

Other Industrial Uses

Other uses of DMAE include as a chemical intermediate (HSDB, 1996), as a corrosion inhibitor in steel-reinforced concrete (CCIA, undated; FHWA DOT, 2000), and as "paper auxiliaries" (Huntsman Corp., 1997).

5.2 Pharmaceuticals and Dietary Supplements

DMAE salts such as *p*-acetamidobenzoate (deanol, Deaner®, Pabenol) have been used in humans to treat central nervous system disorders believed to be associated with hypofunction of cholinergic neurons; in the treatment of learning and behavioral problems; hyperkinetic behavior (Stenbäck et al., 1988); Huntington's chorea, tardive and levodopa-induced dyskinesias (De Silva, 1977; McGrath and Soares, 2000; and Soares and McGrath, 1999); chronic fatigue; and neurasthenia (American Hospital Formulary Service, 1984; cited by HSDB, 1996). Deaner® was recommended for treating schizoid and schizophrenic patients in a 1958 article in the American Journal of Psychiatry (Toll, 1958). Salomon et al. (1971) described a clinical trial of Panclar (DMAE monophosphate), described as a psychostimulant, in a neuropsychiatric clinic. Meclofenoxate hydrochloride (centrophenoxine hydrochloride) is used to enhance cognition in the elderly in Europe, Japan, Mexico and Australia (Hendler and Rorvik, 2001b).

DMAE *p*-chlorophenoxyacetate and its hydrochlorides (centrofenoxine, meclofenoxate) were named in a review article as showing some efficacy in treating brain injuries, including cerebral atrophy, brain injury, postapopletic disorder, chronic alcoholism, and barbituate intoxications (Schmidt and Broicher, 1970; Vojtechovsky et al., 1970; Herrschaft et al., 1974; and Kugler, 1977; all cited by Zs.-Nagy, 2002). The Life Extension Foundation Web site (2002a, 2002b) states that in Europe, centrofenoxine in combination with piracetam may improve memory and mental energy. The article states that the drug is not available in the United States but may be ordered from pharmacies in Europe. The Giampapa Institute (2001) Web site lists health claims for centrofenoxine that include improving memory, increasing mental energy, removing lipofuscin and potassium from the skin, heart, and brain, and protecting the brain against free radical damage, stroke, and injury.

Other salts used for pharmaceutical purposes include the aceglumate (Clérégil; Risatarun); the hemisuccinate (Tonibral; Rishiaril); and the bitartrate (Liparon), which was reported as a geriatric drug by Friederichs (1971). None of these salts were listed in the 1998 Physicians' Desk Reference, so they are apparently no longer widely prescribed as prescription drugs. Riker's Deaner® was the only one marketed ethically in the United States.

DMAE carbamate was listed among glaucoma drugs in article citations (Chiou, 1981; Zimmerman, 1980). DMAE freebase and its medicinal salts are widely advertised on the Internet to enhance cognitive performance and other physiological functions by increasing acetylcholine concentrations in the brain. Another claim made is that DMAE enhances lucid dreams (Whole Health Discount, 2002).

In Budavari (1996 [CD-ROM]), the DMAE substructure is part of numerous more complex pharmaceuticals, including the antihistamines paracarbinoxamine, diphenhydramine (Dow, 2001a), doxylamine, medrylamine, *p*-methyldiphenhydramine, moxastine, orphenadrine,

embramine, phenyltoloxamine dihydrogen citrate; the antiemetics, including dimenhydrinate (of which DMAE is a metabolite), and trimethobenzamide; the local anesthetics dimethisoquin (e.g. Quotane® is the hydrochloride), hydroxytetracaine, and tetracaine hydrochloride (of which DMAE is a metabolite); and the antiestrogens/antineoplastic agent tamoxifen (Dow, 2001a), and droloxifene. In addition, the DMAE moiety may be found in the narcotic analgesic dimenoxadol, the anticholinergic chlorphenoxamine, the antidepressant noxiptilin, the antipsychotic zotepine, the antitussive dimethoxanate, the antiviral tromantadine, the mydriatic (ophthalmic and anticholinergic) cyclopentolate, the peripheral vasodilator and *β*-adrenergic blocker moxisylate.

Yavin and Brand (2001 [Yeda Research and Development Co. Ltd., Israel]) were awarded a world patent for compositions containing DMAE or other *N*-methylethanolamines to relieve oxidative stress such as ischemia from strokes, cardiac arrest, oxidative distressed pregnancy, and neurodegenerative conditions such as aging and Alzheimer's disease.

The Natural Medicines Comprehensive Database (2002) indicated DMAE might be effective for improving exercise performance. En Garde Health Products (1997) claimed a buffered aqueous solution of DMAE enhances production of acetylcholine; sharpens concentration and memory; enhances muscle strength and coordination; improves mood; and fights fatigue. As of May 17, 2002, the Web site of En Garde makes fewer claims – that deanol enhances function of mind, memory, and muscle (2002).

The Natural Medicines Comprehensive Database (2002) review on DMAE lists a number of salts, including deanol aceglumate, deanol benzilate, deanol bisorcae, deanol cyclohexylpropionate, deanol hemisuccinate.

DMAE and related compounds have been used in topical preparations. DMAE orotate [CAS RN 1446-06-6] was mentioned in a European patent application (Ismail, 1985) for vitamin E-containing drugs with vasodilators for skin protection and treatment. DMAE capsules were marketed on the Internet for "skin and collagen support," and "skin repair and maintenance" (Whole Health Discount, 2002). DMAE was indexed in the CAPLUS record for a World patent on "compositions for rapid transdermal delivery of pharmaceutically active agents" (Kirby and Pettersson, 2000) [Transdermal Technologies, Inc., U.S.A.]. DMAE may have been one of the drugs, a solvent, or a solute modifier. Most of the drugs listed are herbal and/or used in dietary supplements. The example was for a composition containing theophylline for "promoting cellulite removal." Johnson and Johnson Consumer Companies, Inc. (2002) have a European application on topical compositions that contain alkanolamines such as DMAE for reducing skin inflammation. In one embodiment of the invention, a composition contained 3.00% DMAE. Perricone (2001) has a U.S. patent for alkanolamine compositions for treatment of topical scars. DMAE at 0.1 to 10 weight percent was "particularly preferred." Perricone (1997) patented

compositions containing DMAE for treating skin damage and aging, and it is marketed for that purpose via the Internet (Whole Health Discount, 2002).

DMAE and related compounds are found in drug formulations for various purposes. DMAE was probably one of the basic amines for self-emulsifying oral preparations of antiretroviral pyranones containing 0.1 to 10% basic amines to enhance bioavailability in a World patent assigned to Pharmacia and Upjohn Co., U.S.A (Morozowich and Gao, 1999). Meclofenoxate was in formulations in a German patent for "transdermal or transmucosal dosage forms containing nicotine for smoking cessation" [LTS Lohmann Therapie-Systeme A.-G., Germany] (Theobald and Frick, 2001).

Cosmetics

DMAE was used in cosmetics with skin-protection claims and for hair. Chabrier (1998, 2000) was issued French patents for cosmetic and dermatological compositions containing 5 to 20% meclofenoxate to prevent or repair "dermo-epidermal alterations" [no company affiliation]. DMAE hydrochloride [2498-25-1] was in a Japanese patent for anti-aging skin cosmetics containing biphenyl compounds [Kanebo, Ltd., Japan] (Hikima, 1998). Acetylcholine precursors are described as firming muscles (Perricone, 1996). DMAE was indexed in a European patent application for hair cosmetic compositions, including dyes [Kao Corporation, Japan] (Tajima et al., 2002).

Miscellaneous Uses

A recent article states that DMAE hemisuccinate is used with other chemicals to analyze blood for cholesterol and dehydrocholesterol (Johnson et al., 2001).

6.0 Environmental Occurrence and Persistence

6.1 Environmental Occurrence

DMAE is released into the environment during the production and use of a variety of products. Based on European estimates, approximately 75% of total DMAE is used in the production of polyurethane, acrylates, ion exchange resins and flocculants, and pharmaceuticals. While DMAE is cross-linked in the production of polyurethane, resulting in minimal releases to water, up to 50% of the DMAE used in the preparation of ion exchange resins or flocculants may be released to water. For the purposes of the European assessment, it was assumed that the industrial wastewater was directed to a treatment plant, where, based on the physico-chemical properties of DMAE, 97% would be removed by degradative processes. Final concentrations in receiving rivers were estimated at 30 µg/L. DMAE (approximately 5%) could also be released into water through corrosion inhibitor formulations and into air (3%) or water (2%) from paint and surface coating applications (OECD, 1997).

Coatings

Two industrial operations common in the United States, spray-painting and beverage can lacquering, are potential emitters of DMAE to the environment. Environmental releases to the atmosphere of DMAE might be expected from paint-spraying operations as suggested by the research conducted by the Statewide Air Pollution Research Center, University of California, which studied the potential for photo-oxidation of the compound (Pitts et al., 1980). In the United Kingdom, DMAE has been identified as one of the major odoriferous components from the ovens drying beverage cans after coating with solvent-borne and water-borne lacquers (Casper and Redman, 1995).

Urethane Catalysts

Furniture and cabinets made of coated engineered wood products (particle board, medium-density fiberboard, and hardboard from wood particles and fibers) emit volatile organic compounds (VOCs) from the wood glues, coatings, and overlay materials such as polyvinyl chloride (PVC) after installation in buildings. U.S. EPA sponsored a survey by Research Triangle Institute of emissions from finished samples of such engineered wood products. Coating compositions included two-component waterborne polyurethane formulations. DMAE was expected to be present in the volatile emissions; however, the analytical method used was not able to determine DMAE due to its polarity (Brockmann et al., 1998). However, another study showed DMAE is among VOCs that outgas from new carpets (Stadler and Kennedy, 1996).

Conventional tertiary amine catalysts are emitted from polyurethane foams. In their effort to reduce VOCs, some automobile manufacturers intend to avoid conventional amine catalysts (Kometani et al., 2000). The TOSOH Corporation has developed reactive amine catalysts that have low emissions. Not only automobile manufacturers but also other end-users of polyurethane foam in bedding, furniture, and carpet backing are interested in the reactive amine catalysts, such as DMAE, for low VOC emissions. Replacing the non-reactive with reactive catalysts to produce flexible HR molding [high resiliency molding; definition in Dow (2001b)] reduced total VOC emissions from foam formulations made with toluene diisocyanate (TDI) by 50% and with methylenediphenylene diisocyanate (MDI) by 80% (Sikorski et al., 1999; and Keimling et al., 2000; both cited by Rothe et al., 2001). When DMAE was used to produce slabstock foam, no DMAE was found in the resulting volatile organic compounds (VOCs). In contrast, two non-reactive amines, TD39 and NP133, contributed about 20 and 50 ppm respectively to the VOCs (Rothe et al., 2001).

Amines were sampled evaporating from polyurethane foams applied in buildings. Air concentrations of reactants in the vicinity of freshly produced polyurethane foam insulation material were 4.0 mg MDI/m^3 and 6.7 mg DMAE/m^3. While concentrations of MDI in a closed

space fell to < 0.05 mg/m^3 after two months, concentrations of 4.0 mg DMAE/m^3 were found at the same time (Lidberg and Komina, 1984).

6.2 Environmental Persistence

IUCLID (1997) summarized environmental fate characteristics for DMAE:

- Photodegradation: DMAE underwent indirect photolysis in air with hydroxide ion as a sensitizer.
- Distribution: At 10 °C, DMAE was distributed 56% in water, 44% in air. At 20 °C, DMAE was distributed 39% in water and 61% in air.
- Biodegradation: In the presence of nonacclimated domestic sewage microorganisms at 25 °C, DMAE biodegraded rapidly after a lag period of about five days when subjected to the biochemical oxygen demand test, which simulates a river. DMAE (released in wastewater from washout to control emissions from water-based paint spray booths [Stemad et al., 1995]) was "readily biodegradable" by activated sludge in aerobic conditions. A concentration of 1,000 mg/L sludge, related to chemical oxygen demand, degraded 90% of DMAE after 13 days. No temperature was given. DMAE was "readily biodegradable" by domestic sewage, non-adapted, in aerobic conditions. At a concentration of 100 mg/L DMAE in 30 g/L sewage at 25 °C, 85% of the DMAE degraded after 20 days (4% after five days and 67% after 10 days). DMAE was "readily degradable" by industrial sewage in aerobic conditions. A concentration of 100 mg/L DMAE in 30 g/L sewage at 25 °C degraded with ammonia as an end product.

Polyurethane foam compositions are widely used for sealing and caulking. Such a foam is used in underground coalmines to seal ventilation equipment. The product KN-96 was used as a sealant in a coal mine at a rate of 1 kg/min with an air-exchange rate of 90 cubic meters per minute. Initial concentrations of about 56 mg DMAE/m^3 fell below the maximum permissible values within one hour (Putina et al., 1991). Russian coal mining use of polyurethane resins for "anchoring of coal mine faces by sand-filled [resin] compositions" led to release of emissions of diisocyanates, DMAE, triethylamine, and other toxic components as the resin polymerized in the holes. Workers using the materials were advised to wear respirators. No traces of the components were detectable by the following day (Sukhanov et al., 1987 [Russian]).

7.0 Human Exposure

7.1 Occupational Exposure

The total number of U.S. workers exposed to DMAE was 33,474, of which 5,559 were female (NIOSH, 1984). See **Table 1** for data on exposure by occupation and **Table 2** for data on exposure by industry.

Table 1. National Occupational Exposure Survey (NOES)[a]: By Occupation

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Assemblers	216	4995	2286
Automobile Mechanics	38	115	
Biological Technicians	21	686	300
Brickmasons and Stonemasons	12	108	
Carpenters	327	3435	
Chemical Technicians	119	953	259
Chemists, except Biochemists	17	1344	255
Clinical Laboratory Technologists and Technicians	26	59	33
Construction Laborers	5	1714	5
Electrical and Electronic Equipment Assemblers	31	31	
Electricians	17	487	6
Engineering Technicians, N.E.C.	19	190	57
Grinding, Abrading, Buffing, and Polishing Machine Operators	3	9	
Hand Molders and Shapers, except Jewelers	22	87	65
Janitors and Cleaners	97	737	
Laborers, except Construction Workers	146	1061	46
Machine Operators, not provided	27	128	
Machinists	33	295	
Managers and Administrators, N.E.C.	300	300	
Metal Plating Machine Operators	14	43	
Millwrights	3	16	
Miscellaneous Precision Workers, N.E.C.	3	494	
Miscellaneous Metal and Plastic Processing Machine Operators	22	1488	306
Miscellaneous Woodworking Machine Operators	7	62	7
Miscellaneous Machine Operators, N.E.C.	92	2172	154
Miscellaneous Material Moving Equipment Operators	50	101	
Mixing and Blending Machine Operators	88	1589	108
Painting and Paint Spraying Machine Operators	453	1824	64
Printing Machine Operators	240	2393	850
Separating, Filtering, and Clarifying Machine Operators	201	4125	524
Stock and Inventory Clerks	19	37	
Supervisors, Production Occupations	127	713	
Technicians, N.E.C.	3	6	
Therapists, N.E.C.	73	219	219
Unspecified Mechanics and Repairers	14	710	14
Welders and Cutters	21	751	
TOTAL	2906	33,474	5559

[a]NIOSH (1984)

Abbreviations: N.E.C. = not elsewhere classified.

Table 2. National Occupational Exposure Survey (NOES)[a]: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Auto Repair, Services, and Garages	300	899	
Business Services	65	2016	639
Chemicals and Allied Products	197	10,096	1343
Electric, Gas, and Sanitary Services	38	115	
Electrical and Electronic Equipment	91	5624	1985
Fabricated Metal Products	65	535	
Food and Kindred Products	26	724	
Furniture and Fixtures	65	520	260
General Building Contractors	12	2033	5
Health Services	99	284	252
Instruments and Related Products	28	85	
Lumber and Wood Products	88	2256	7
Machinery, except Electrical	171	571	
Miscellaneous Manufacturing Industries	28	107	79
Paper and Allied Products	33	131	
Petroleum and Coal Products	21	1233	85
Primary Metal Industries	48	1383	14
Printing and Publishing	136	1364	818
Rubber and Misc. Plastics Products	67	713	64
Special Trade Contractors	246	2216	
Transportation Equipment	13	568	7
TOTAL	1838	33,474	5559

[a]NIOSH (1984)

Workplace Air Concentrations

DMAE is widely used in waterborne coatings, which are often applied by spraying. Industrial workers may be adequately protected by engineering controls and personal protective equipment.

NIOSH-sponsored industrial hygiene surveys conducted at four polyurethane foam insulation manufacturing facilities in 1979 found DMAE concentrations ranging from 0.02 to 0.22 ppm in workplace air at one facility and "very low" concentrations at another facility (Herrick et al., 1980; Reisdorf and Haggerty, 1980a,b; Reisdorf and Carese, 1980).

Davies et al. (1997) (in Authoritative Review group) estimated that industrial DMAE exposure in the United Kingdom is controlled by process enclosure, local exhaust, or personal protection equipment to less than 2 ppm as an 8-hour time-weight average (TWA). Higher exposures of 2 to 4 ppm are possible during spray painting with water-based coatings. The magnitude of dermal exposure was estimated to be 0 to 0.1 $mg/cm^2/day$ with up to 1 $mg/cm^2/day$ for spent catalyst drumming in organic flocculants manufacture.

In a Swedish study of a polyurethane foam production plant, the level of DMAE was always below the detection limit of 0.1 mg/m^3 (Akesson et al., 1986). A United Kingdom study described personal dosimeters used to determine tertiary amine catalysts, including DMAE, at nine polyurethane factories. Workers each wore a short glass tube containing Chromosorb 102. Air was drawn through the tubes by a pump at a flow rate of 10 to 20 ml per minute (Bugler et al., 1992). The tubes were subsequently thermally desorbed directly onto a GC column. Hansen et al. (1984) tested air samples in a polyurethane foam factory for trimethylamine and DMAE using isotachophoresis. No air concentrations were given in the abstract.

Workers in flexible foam manufacturing in the United Kingdom were monitored for exposure to the tertiary aliphatic amines used as catalysts, including DMAE, in workplace air. Among the eight catalysts studied, DMAE and 1,4-diazabicyclo[2,2,2]octane triethylenediamine (DABCO) were the most common catalysts in the nine companies studied (Bugler et al., 1992).

A time-weighted threshold limit value (TLV) of 5 ppm was established for DMAE by Union Carbide as an internal exposure limit. The short-term exposure limit set was 25 ppm (IUCLID, 1997). DuPont (2002) regulates DMAE at 2.0 ppm as a company-based 8-hour TWA.

U.S. EPA ORD (1994) described the then-new commercial process vapor injection curing (VIC) for coating plastic, steel, aluminum, wood, and castings. In VIC, an amine catalyst such as DMAE is generated as a vapor and dispersed in an air stream channel in the spray gun and mixed with the urethane component as the streams leave the spray gun. VIC is a high-solids coating process that reduces release of VOCs (U.S. EPA ORD, 1994). The standard reaction between the isocyanate and polyester alcohols is accelerated in the VIC process so that curing is attained without baking (Moyer, 1994). The process is done in an enclosed chamber (Greene, 1994) so that worker exposure might be expected to be minimal, at least original coating done at the manufacturing plant.

Science Applications International Corporation (SAIC) (1997) examined the new coating processes used for automobile refinishing in auto body shops where polyurethane coatings have several advantages. Spray painting is done manually in such shops. By the mid-1990s, at least 65% of them used high-volume low-pressure (HVLP) spray guns. The painter may be exposed due to inadequate respirator protection. The polyurethane systems described in this survey did not use ethanolamine catalysts, and exposure to diisocyanates was the only concern.

Welsh et al. (2000) found that the material safety data sheets (MSDS) for certain controlled products used in Canadian workplaces did not disclose some of the hazardous ingredients, which were detected at concentrations requiring their disclosure. A synthetic lubricant with an MSDS

listing hydroxytoluene and sodium alkylbenzenesulfonate also contained two undisclosed chemicals, including 2.3% DMAE.

A United Kingdom study monitored exposure of workers in the polyurethane factories to airborne DMAE. Factors influencing concentration include the quality of DMAE, the vapor pressure relative to the maximum temperature reached by the foam, and blowing agents used to make softer foams at lower temperatures, such as methylene chloride or chlorofluorocarbons (CFCs) (Bugler et al., 1992).

The TWA values for worker exposure in polyether block plants and in hot cure molding plants were up to 60 ppb total amine burden, which is comprised of DABCO and DMAE. The range of DMAE was < 1 to 87 ppb in polyether slabstock production, 7 to 1,100 ppb in hot cure molding, and < 10 ppb in cold cure molding and in conversion and cold block handling (Bugler et al., 1992).

A United Kingdom study examined occupational exposure during DMAE production and its use in manufacturing polyurethane foams, flocculants, surface coatings and ion-exchange resins. Using the Estimation and Assessment of Substance Exposure (EASE) method, potential for skin exposure would be 0 to 0.1 $mg/cm^2/day$, and in the manufacture of organic flocculants, as high as 0.1 to 1 $mg/cm^2/day$ (Davies et al., 1997).

7.2 Nonoccupational Exposure

Consumer Products Other Than Dietary Supplements

Honegger and Honegger (1959) extracted salmon roe with ethanol followed by acidification and centrifugation of the extract. Unbound DMAE was present in the alcoholic extract, and bound DMAE was found in the precipitate. Concentrations in the roe, as determined by gas chromatography using analogs as standards, were 260 ng/kg for unbound DMAE and 1,662 ng/kg for bound DMAE. [Values given as milligamma per kilogram were converted based on the conversion 1 gamma = 10^{-6} g.] In these studies, human brain had unbound DMAE at 5.1 ng/kg and bound DMAE at 76.4 ng/kg.

Ishibashi et al. (1984) studied conditions under which dietary amines in mollusks (squid) might be nitrosated during cooking. At pH 2.0 in a buffer solution and 90 °C, DMAE formed a high concentration of *N*-nitrosomethylethanolamine.

Phosphatidyldimethylethanolamine is found in fish oils along with phosphatidylcholine, phosphatidylethanolamine, phosphatidylmethylethanolamine, and phosphatidylserine (Segawa et al., 1995).

Sealants, architectural coatings, coatings on furniture and cabinets, polyurethane foam cushions, and carpets may emit DMAE in homes, commercial buildings, and vehicles (Brockmann et al., 1998; Kometani et al, 2000; Rothe et al, 2001; CARB, 1999).

Pharmaceuticals

Riker Laboratories' prescription drug Deaner® (deanol *p*-acetamidobenzoate) was a U.S. prescription drug for more than 20 years until 1983 when it was withdrawn from the market. It was used to treat children with learning and behavior problems. However, evidence of efficacy was insufficient (Natural Medicines Comprehensive Database, 2002). In 1959, an Italian article described the use of Deaner® in 50 children (Fois et al., 1959). The brief review by CVS Pharmacy (undated) listed the indications for use of Deaner® while it was FDA-approved as possibly effective. *The Merck Index*, 13th edition, deanol monograph states that Riker's preparation was patented in 1957. *Remington's Practice of Pharmacy*, 1961 edition (Martin and Cook, 1961) listed Deaner® as an unofficial (i.e., not listed in the *U.S. Pharmacopoeia* or the *National Formulary*) psychomotor stimulant. Doses of up to 900 mg/day had not been associated with any serious side effects. Oral doses for children with behavior problems were 75 mg/day to start with 75- to 150-mg/day maintenance doses. Twenty-five years ago, the suggested average daily dose of deanol for adults with Huntington's chorea was 1.0 to 1.5 g (3.7 to 5.6 mmol) (De Silva, 1977).

DMAE may be an impurity or a metabolite of ditilin (succinylcholine chloride; http://physchem.ox.ac.uk/MSDS/SU/suxamethonium_chloride.html) (Arzamastsev et al., 1999). Karaisz and Snow (2001) found DMAE among hydrolysis and thermal degradation products of diphenhydramine, which is available as Benadryl® (the hydrochloride salt) and several generic over-the-counter antihistamines as well as a component of the antinausea drug dimenhydrinate. DMAE is a metabolite of the local anesthetic tetracaine hydrochloride along with 4-butylbenzoic acid (Hansen, 1970), which is not used in the United States.

The anti-inflammatory, analgesic composition Diclofenac-deanol is apparently available in dosages of 75 mg diclofenac and 15 mg deanol (Gerot Pharmazeutica, undated).

Dietary Supplements

A large number of dietary supplements contain DMAE. The predominant form, when specified, is DMAE bitartrate. Typical adult doses of DMAE in dietary supplements range from 100 to 500 mg/day, based on an ILS analysis of retrievals from this Google search: DMAE synonyms and "mg".

Sources from an Internet Google search about unspecified DMAE listed doses of 400 mg/day, 600 mg/day, and up to 600 mg three times per day. Two products contained DMAE

cyclohexylcarboxylate fumarate, and one contained 100 mg DMAE *p*-acetamidobenzoate, equivalent to 33 mg DMAE. Many of these products were formulations with other dietary supplements such as *Gingko biloba*. SmartBodyz Nutrition (2002) offers a DMAE-*Gingko biloba* supplement with 100 mg per tablet. Lee-Benner (undated) markets a product, Perfect Mind I, which contains 100 mg DMAE bitartrate per tablet but also contains choline bitrate, vitamin B-5, phosphatidyl choline, and RNA.

The Natural Medicines Comprehensive Database (2002) stated that the typical starting dose for DMAE is 100 mg/day, with a gradual increase to 500 mg/day. Clinical studies have used 300 to 2,000 mg/day.

Pediatric doses of DMAE in several sources from the Internet range from about 16 to 40 mg/day (Brain Child Nutritionals, undated-a; Good4all.net, 2002; VitaBoy, undated; and The Mineral Connection, 2002). Formulations with DMAE intended for attention deficit disorder (ADD) include Pay Attention™ ADD brain formula by Smart Nutrition (undated). Gugliotta (2000) in a *Washington Post* article listed other DMAE products targeted for children for treatment of ADD and attention deficit hyperactivity disorder (ADHD). DMAE bitartrate is the key ingredient of Focus Child by Source Naturals, which is now called Attentive Child (Suzannes.com, undated). Introduced in 1999, Focus Child became one of the company's top ten sellers within a year (a feat in a company that offers more than 400 products). Another product named by Gugliotta (2000) was Pedi-Active A.D.D. Other DMAE supplements offered for children included chewable tablets and bars containing fruit and chocolate. En Garde Health Products (1997) markets a buffered aqueous solution of DMAE. Typical doses are 10 drops (25 mg) daily for children and up to 20 drops (50 mg) twice daily for adults. An approximate 2-month supply is equivalent to 2.3 oz. (70 mL; 200 drops). Brain Child Nutritionals (undated-a, undated-b) offers Spectrum Support I with 100 mg DMAE bitartrate (37.6 mg DMAE) per liquid ounce. BIAM (1999) markets a dietary supplement with DMAE hemisuccinate for adults with a suggested daily dose of 200 to 600 mg. The Web site mentions a supplement for children, no longer marketed, which had a suggested daily dose of 50 to 100 mg per day.

8.0 Regulatory Status

FDA CFSAN (2002) compiled a list of "Everything Added to Food in the United States." Regulations applicable to DMAE in 21 CFR were 173.20, 175.105, and 175.300. Regulations are detailed in **Table 3**:

Table 3. Federal Regulations Relevant to Dimethylethanolamine and Selected Salts and Esters

	Regulation	Effect of Regulation/Other Comments
EPA	40 CFR 60. Subpart YYY – Standards of Performance for Volatile Organic Compound (VOC) Emissions from Synthetic Organic Chemical Manufacturing Industry (SOCMI) Wastewater.	Standards that regulate emissions for VOCs emitted from wastewater generated by SOCMI and are limited to emission points in wastewater collection and treatment systems (U.S. EPA, undated-a).
	40 CFR 63. National Emission Standards For Hazardous Air Pollutants For Source Categories.	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the Clean Air Act (U.S. EPA, 1994).
	40 CFR 63.100ff. Subpart F-National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry.	Chemical manufacturing process units that manufacture DMAE or mixtures containing the compound are regulated under this subpart when produced at a plant site that is a major source as defined in section 112(a) of the Clean Air Act (U.S. EPA, 1994).
FDA	21 CFR 173. Secondary Direct Food Additives Permitted in Food for Human Consumption. Subpart A-Polymer Substances and Polymer Adjuvants for Food Treatment.	173.20 (Ion-Exchange Membranes). This part regulates membranes produced by reacting a polyethylene-styrene compound with DMAE for food processing applications (U.S. FDA, 2001a).
	21 CFR 175. Indirect Food Additives: Adhesives and Components of Coatings.	§175.105 (Adhesives) regulates polyurethane resins produced by reacting *m*-tetramethylxylene diisocyanate with dimethylethanolamine for the purpose of packaging, holding, or transporting food (U.S. FDA, 2002). §175.300 (Resinous and Polymeric Coatings) This part states that DMAE may be used as an optional adjuvant substance limited to no more than 2 wt. % based on polymer solids in the coating emulsion (U.S. FDA, 2001b).

Several warning letters from FDA were located on the FDA Web site. For example, Messa (1999) signed an FDA warning letter to En Garde Health Products, Inc. Its Super Oxy DMAE PABA was "offered with anti-pain claims," which would require a New Drug Application (NDA). This product was listed among others as violating the Federal Food, Drug, and Cosmetic Act as products not intended for ingestion, which does not meet the definition of a "dietary supplement" as defined in Section 201(ff)(2)(A)(I) of the Act. Directions with the product "instruct the user to either hold the product under the tongue or in the mouth for 30 seconds to 1 minute before swallowing." The accompanying literature touted the advantages of sublingual use. A pure deanol product offered for treatment of chronic pain and ADHD was another product whose therapeutic claims would require NDA submission. [The warning about sublingual and buccal use does not seem to have been especially effective. En Garde Health Products still offers a "pure Deanol" product (which is a flavored aqueous solution with phosphoric acid), whose advertisement found on the Internet on May 17, 2002, advised the user to "(h)old the drops in the mouth for at least 30 seconds to start the digestive process."

Another warning letter to the maker of SuperBrain Brain Cognitive Formula™ mentioned that the product is mislabeled "to be used in the cure, mitigation, treatment or prevention of disease or to affect the structure or function of the body," and thus falls under Section 201(g) of the Federal Food, Drug, and Cosmetic Act. The FDA stated that the drug documentation makes claims in the absence of substantial scientific evidence, violating Section 502(a). The letter called the supplement a new drug within Section 201(p). In addition, the label failed "to include adequate directions for use for the conditions for which they are offered" as is required in 21 CFR 201.115 (Davis, 1994). A June 17, 2002, Internet search indicates Zygon International no longer carries nutritional supplements.

The State of Oregon (1997) has recognized deanol (brand name example DNZ-2 [DMAE as deanol *p*-acetamidobenzoate 250 mg (83 mg of elemental DMAE)]) as a Therapeutic Class 11 medication that psychiatrists and other mental health practitioners may prescribe for the treatment of mental disorders "without authorization from a fully capitated health plan or the Office of Medical Assistance Programs."

In 1992, DMAE was placed on the U.S. EPA's Master Testing List due to its inclusion in the OECD SIDS voluntary testing program.(U.S. EPA, undated-b). DMAE was included in the Organization for Economic Co-operation and Development (OECD) investigation of high production volume (HPV) chemicals to identify possible data gaps in assessing potential risks to human health and the environment. Based on the screening information data set (SIDS) initial assessment report (SIAR) developed by the OECD, DMAE was characterized as "presently of low priority for further work" (OECD, 1997). The OECD SIAR concluded that DMAE was "of

low risk for human health based on existing control measures." No additional toxicity studies were recommended.

The National Collegiate Athletic Association (2001) includes meclofenoxate on its list of banned drugs under stimulants.

9.0 Toxicology Data

9.1 General Toxicology

9.1.1 Human Data

Pfeiffer et al. (1959; cited by Beard and Noe, 1981) reported that 10 to 20 mg (0.042-0.084 mmol) of DMAE tartrate administered orally to humans, produced mild mental stimulation. At 20 mg/day (0.084 mmol), there was a gradual increase in muscle tone and perhaps an increased frequency of convulsions in susceptible individuals. Larger doses (not specified) produced insomnia, muscle tenseness, and spontaneous muscle twitches.

DMAE is available as a liquid or as deanol bitartrate. The most common form of supplementation is as deanol bitartrate, 100 mg per day (Hendler and Rorvik, 2001b). Recommended doses of centrophenoxine begin with 100 mg/day (0.340 mmol/day) and gradually increase to 500 mg/day (1.700 mmol/day) (Life Extension Vitamin Supplies, Inc., undated; cited by Quackwatch, 2002). In a non-scientific study, Zs-Nagy (2002) reported that he and several colleagues have been self-medicating with centrophenoxine (500 mg/day; 1.700 mmol/day) since 1976 with no apparent evidence of adverse effects. The FDA has approved a human study of DMAE (salt form not provided), recommending daily dose of 200 mg (2.20 mmol) (LifeExtension Foundation, 1999). Doses used in clinical studies have ranged from 300 to 2000 mg/day (3.30 to 22.20 mmol/day) (Re, 1974; George et al. 1981; Penovich et al., 1978; cited by Quackwatch, 2002). Gosselin et al. (1976) reported that doses of DMAE as high as 1200 mg/day (13.46 mmol/day) produced no serious side effects. A single 2500-mg (27.80-mmol) dose taken in a suicide attempt had no adverse effect. Information regarding how the free base of DMAE was administered was not found.

DMAE supplementation is contraindicated during pregnancy and lactation (Quackwatch, 2002; Hendler and Rorvik, 2001b). It is also contraindicated for treatment of people with symptoms of schizophrenia and clonic-tonic seizure disorders (Osol and Hoover, 1975; cited by Quackwatch, 2002). The principal contraindication to the use of DMAE cited by Gosselin et al. (1976) was grand mal epilepsy. DMAE also antagonizes the depressant effects of barbiturates.

<u>Adverse Effects</u>

A large number of adverse health effects were associated with DMAE in the FDA's Special Nutritionals Adverse Event Monitoring System (SN/AEMS) Web Report (FDA CFSAN, 1998), a voluntary reporting system. Complaints associated with several DMAE-containing products

included cardiovascular, neurological, and/or psychological effects. Specific attribution of adverse effects to DMAE is unlikely, as many of these products also contained *Ephedra vulgaris* alkaloids and other *Ephedra* spp. *Ephedra* alkaloids cause similar cardiovascular and neurological effects reported for DMAE (FDA, 1999). Similar adverse effects have been reported to support the FDA SN/AEMS by Ott and Owens (1998), Osol and Hoover (1975), and Haug and Holzgraefe (1991); and by Casey (1979), de Montigny et al. (1979), Fisman et al. (1981), and Sergio (1988) (all cited by Quackwatch, 2002).

DMAE, thought to be a precursor for acetylcholine, has been tested for its efficacy in treating a variety of diseases possibly related to deficiencies of acetylcholine, including tardive dyskinesia, Alzheimer's disease, amnesic disorders, age-related cognitive impairment, and Tourette's syndrome, with mixed results (Hendler and Rorvik, 2001b). Treatment with DMAE for tardive dyskinesia, a side effect of neuroleptic medications, was associated with serious cholinergic side effects: nasal and oral secretions, dyspnea, and respiratory failure (Mehta et al., 1976; Nesse and Carroll, 1976). DMAE was used in the treatment of one patient for a low-frequency action tremor. This treatment was successful for ten years, until side effects of increasing neck pain and orofacial and respiratory dyskinesia occurred. Treatment was discontinued, and it was concluded that the dyskinesia could be attributed to the effects of DMAE (Haug and Holzgraefe, 1991). A meta-analysis of randomized controlled trials indicated that DMAE was no more effective than placebo in the treatment of tardive dyskinesia. Rather, there was a significantly increased risk of adverse events associated with the DMAE treatment (McGrath and Soares, 2000; Soares and McGrath, 1999).

Clinical trials to determine the efficacy of DMAE in treating cognitive dysfunction have, overall, resulted in negative findings. Normal or minimally impaired nondemented elders (eleven subjects) showed no benefit after 21 days of treatment with 900 mg DMAE (10.0 mmol) per day (Marsh and Linnoila, 1979). Likewise, DMAE failed to improve cognitive function in patients suffering from Alzheimer's disease in both a double-blind, placebo-controlled trial (27 patients, dose and duration not provided) and an open-label trial (14 patients, 1.8 grams/day, duration not indicated) (Fisman et al., 1981; Ferris et al., 1977; both cited by Ott and Owen, 1998).

Treatment with a mixture of DMAE (as DMAE orotate, dose not provided) and vitamins and minerals successfully modified mental impairments of sixty volunteers (30 females, 30 males, age ranging from 40 to 65) self-reporting poor concentration and efficiency during mental exercise in a double-blind, placebo-controlled study (Dimpfel et al., 1996). Comparisons of the before and after DMAE-treatment recordings showed statistically significant changes towards decreased theta power during rest and increased absolute theta power induced by mental exercise, specifically in the frontotemporal cortex during both memory and symbol recognition tests. Similar results were observed in a randomized, parallel, placebo-control, double-blind study of 43 patients (40 to 65 years old) with poor concentration and thinking problems. Increased absolute

spectral EEG power in the delta and theta frequency bands, mainly in the front-temporal cortex, were observed (Schober et al., 1994).

In a double-blind clinical trial examining the effects of centrophenoxine, an ester of DMAE, in 50 patients (25 males and 25 females) suffering from organic psychosyndrome (phase DSM III, Category 1, ICD No. 229), improvements were observed in 47.6% receiving the drug versus only 28% observed in placebo-treated patients. Patients, all greater than 60 years of age, were dosed with Helfergin 500 tablets (two tablets, twice a day, after breakfast and lunch) containing 500 mg centrophenoxine-HCL (verum) for a total dose of two grams per day, for eight weeks, or with an identical looking placebo. Six types of evaluations, including observations by a medical doctor and psychologist, memory and performance tests, daily activity observations, and a self-rating evaluation were used to evaluate changes in performance (Pék et al, 1989).

Statistical analysis for the study was made difficult due to the small numbers of individuals per treatment group and heterogeneity in the performance of the tested groups. Criteria for effectiveness of centrophenoxine were based on intra-individual improvements in at least four of the six psychometric and behavioral tests (Pék et al., 1989). Both the percentage of patients demonstrating improvements and the average percent improvement per patient were higher in the treatment than placebo group (average of 21.2% and 9% per patient, respectively). Of the seven patients in the placebo group demonstrating improvements, only two were described by medical doctors to have improved in health status, relative to nine out of ten patients in the treatment group (Pék et al., 1989).

Negative effects were also recorded for this study. Worsening mental status was observed in one placebo-treated patient (85 years old) and five treatment patients (average age of 79.4 years). Also, three patients in the treatment group were removed from the study due to health-related issues. All three patients died within three weeks of being removed from the study. Autopsy results suggested that the deaths were not treatment-related. Three female placebo-treated patients died within six weeks of completion of the trial, with similar autopsy finds as those recorded for the deaths observed in the treatment group (Pék et al., 1989).

In one occupational study in the manufacture of polyurethane foam insulation for refrigerators, adverse effects included disorders of the upper respiratory tract and nervous system, along with significant changes in the immune status of workers exposed to a mixture of DMAE, ethylenediamine, propylene oxide, and 4,4´-methylenediphenyl diisocyanate (Pokrovskaya et al., 1986). A spray painter developed severe respiratory symptoms, which seemed to be related to occupational exposure to a specific type of spray paint containing DMAE. Follow-on skin tests with DMAE (undiluted, and 1:10 and 1:100 dilutions in saline) in three human volunteers produced wheal and flare responses at the high dose. This was interpreted as an irritant response, and not a sign of immunotoxicity (Vallieres et al., 1977). Despite one clear case for

occupational asthma form DMAE exposure, it fails to meet the current criteria for classification as a respiratory sensitizer (Davies et al., 1997).

Holmen et al. (1988) failed to demonstrate mutagenic effects as demonstrated by chromosomal aberrations, sister chromatid exchanges, or micronuclei in cultured lymphocytes from peripheral blood or mutagenic activity and thioether concentrations in the urine of workers exposed to a mixture of chemicals, including DMAE.

Using a method to classify the risks associated with occupational exposures to neurotoxic chemicals obtained from four national computer-based registers, Simonsen and Lund (1992) categorized DMAE as having small risk of damaging the nervous system under normal work conditions.

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

DMAE is absorbed (either from the small intestine after oral dosing or from the bloodstream after injections), and rapidly transported to the liver where much of it is metabolized (Groth et al., 1958; cited by Zahniser, 1977; Hendler and Rorvik, 2001b). Approximately 280 nmol (25.2 µg) DMAE/gram plasma was observed in male mice about ten minutes after receiving 300 mg (3.30 mmol) DMAE/kg, intraperitoneally (Zahniser et al., 1977). Dormard et al. (1975a; cited by Zahniser, 1977) dosed pigs and rats with cyprodenate maleate, the cyclohexylpropionic acid ester of DMAE, and found that it, too, was well absorbed from the digestive tract and distributed to tissues and organs. Approximately 2.41, 1.30, and 0.20% of an administered dose of 30 mg/kg (0.13 mmol/kg) (with 100 µCi) of ^{14}C-cyprodenate was found in the liver, brain and plasma, respectively, five minutes after intravenous dosing in male rats Similarly, centrophenoxine was well absorbed after oral administration. After transport to the liver, a portion of centrophenoxine is converted to its constituent moieties, DMAE and *p*-chlorophenoxyacetic acid (PCPA), while the unmetabolized form was transported throughout the body by the circulatory system.

Daily oral exposures of chinchilla rabbits to DMAE (as deanol acetamidobenzoate) or DMAE (1.8 or 4.5 nmol [0.48 µg deanol acetamidobenzoate or 0.40µg DMAE], respectively, duration not provided) resulted in plasma concentrations of 6 to 7 µM (1.6 to 1.9 µg/mL) deanol acetamidobenzoate or 12 to 18 µM (1.1 to 1.6 µg/mL) DMAE. The drug could not be detected in the plasma 36 hours after the end of the treatment period. Concentrations in the cerebrospinal fluid were similar to measurements in the plasma. In psychiatric patients orally medicated with either 1.9 or 3.8 mmol (170 mg or 340 mg) Deaner® for one week, plasma concentrations of Deaner® were 0.25 and 0.52 µM (0.022 and 0.047 µg/mL), respectively (Ceder and Schuberth, 1977).

Dormard et al. (1975b) showed that DMAE was metabolized through the phospholipid cycle to produce phosphoryldimethylethanolamine and glycerophosphatidylcholine. Male Wistar rats

(150 grams) were dosed with either [^{14}C]DMAE (11mg/kg [120 mmol/kg]) body weight or [^{14}C]cyprodenate (30 mg/kg), each containing total radioactivity of 100 μCi, intravenously. Blood, brain, and kidneys were collected at 6, 15, and 60 minutes after dosing. Urine was collected for four and 24 hours. Plasma levels of radiolabeled DMAE at 6 minutes post-dosing represented 0.16% and 0.2% of administered DMAE and cyprodenate, respectively. DMAE was oxidized rapidly to the *N*-oxide of DMAE. Although the *N*-oxide represented the primary urinary metabolite, only 13.5 % of the administered dose was eliminated by the 24 hour time point, which suggested that most of the DMAE was routed toward phospholipid biosynthetic pathways.

In humans, 33% of an injected 1 g (10 mmol) dose of DMAE was excreted unchanged (Williams, 1959; cited by Beard and Noe, 1981). It was suggested that the remaining dose may have been demethylated to ethanolamine and entered into normal metabolic pathways.

Several enzymatic studies have been performed to demonstrate the presence of choline acetyltransferase or phosphatidylethanolamine *N*-methyltransferase in an effort to identify acetylcholine or choline in body tissues. Bishop et al. (1976) identified DMAE acetate in both bull and human spermatozoa. DMAE propionate was only identified in bull spermatozoa. Both acetylcholine and choline acetyltransferase were found in bull and human spermatozoa samples, suggesting *in situ* synthesis of acetylcholine.

Yang et al. (1988) used the existence of phosphatidylethanolamine *N*-methyltransferase in rat mammary tissue as supporting evidence for *de novo* synthesis of choline in breast tissue. Their results suggested that at least two distinct enzyme activities were involved, one catalyzing the methylation of phosphatidylethanolamine to phosphatidyl-*N*-methylethanolamine and the other catalyzing the further methylation of phosphatidyl-*N*-methylethanolamine to form phosphatidyl-*N,N*-dimethylethanolamine. When exogenous phosphatidyl-DMAE was added to homogenates of rat mammary tissue, twice as much phosphatidylcholine was produced from lactating rats as from non-lactating rat tissue. Similar activities were identified in homogenates of mammary tissue from non-lactating humans, supporting the hypothesis that some choline found in breast milk could be synthesized *de novo* in the mammary gland.

The most significant results reported in Jope and Jenden (1979) as a result of DMAE treatment was an increase in the concentration of choline in both the plasma and the brain of treated rats, although the mechanism for this phenomenon was unknown. Since it was known that DMAE inhibits the influx of choline to the brain across the blood brain barrier (Cornford et al., 1978; cited by Jope and Jenden, 1979), it was possible that DMAE also inhibited the efflux of choline from the brain, resulting in an accumulation in the brain.

Differential penetration of the blood-brain barrier by several DMAE derivatives has been noted.

Miyazaki et al. (1976) found that radiolabeled DMAE *p*-chlorophenoxyacetate was found in higher concentrations in the brain than radiolabeled DMAE after intravenous treatment of mice. Higher levels of DMAE were found in the brain after dosing with centrophenoxine than with DMAE, possibly due to improved penetration of the blood-brain barrier by the esterified form of DMAE (South, undated). Similarly, Dormard et al. (1975a) reported that, relative to radiolabeled DMAE, radiolabeled cyprodenate maleate was more rapidly absorbed and accumulated to a large extent in the brain.

Biochemical analysis of brains from mice (strain not provided) treated intravenously with [^{14}C]DMAE or its *p*-chlorophenoxyacetate derivative (doses not provided) yielded phosphoryl-DMAE and phosphatidyl-DMAE, the apparent end-metabolite of DMAE in the brain. Although acid-soluble and lipid cholines were also found in treated brains, the authors hypothesized that methylation of DMAE and its ester probably occurred in other organs, based on the relative incorporation rates of labeled methyl groups in choline in the brain and liver (Miyazaki et al., 1976). In a study using DMAE *p*-chlorophenoxyacetic acid, Wood and Peloquin (1982) found that treatment of rats (dose and route not provided) resulted in increase levels of choline in the central nervous system of rats. These increased levels were accompanied by elevated steady state levels for acetylcholine within the hippocampus. DMAE was only about half as effective as DMAE *p*-chlorophenoxyacetate in increasing levels of choline in rat brains. The observed changes in choline levels were primarily extraneuronal. No consistent alterations in acetylcholine turnover were measured. Pedata et al. (1977) reported that DMAE (Deaner®) did not affect acetylcholine brain concentrations in rats, cause behavioral changes, or antagonize the effect of HC-3 [2,2´-(4,4´-biphenylene)bis(2-hydroxy-4,4-dimethylmorpholinium)], an inhibitor of high-affinity transport of deuterated choline into cholinergic nerve endings, on striatal acetylcholine. Danysz et al. (1967b), on the other hand, reported a dose-dependant increase in acetylcholine levels in the brains, with peaks at 11 (higher doses) and 14 days (lower doses) of mice (strain and sex not provided) dosed with DMAE (175 to 350 mg/kg; 1.95 to 3.90 mmol/kg).

It is unclear to what extent DMAE is methylated and substituted into acetylcholine. Early reports indicated that the DMAE that crossed the blood-brain barrier was methylated to form choline and then incorporated into acetylcholine (Goldberg and Silbergeld, 1974; Haubrich et al., 1975; both cited by Jope and Jenden, 1979; De Silva, 1977; Millington et al., 1978; cited by HSDB, 1996). Other studies fail to support this pathway (Ansell and Spanner, 1975; Freeman and Jenden, 1976; cited by Jope and Jenden, 1979). Jope and Jenden confirmed previous reports, through both *in vivo* and *in vitro* studies, that DMAE was not methylated to from choline in brain tissues. Neither acute (*in vitro*) nor chronic (*in vivo*) treatments with [$^{2}H_{6}$]DMAE had the capacity to alter levels of acetylcholine in the brain tissues. Treatment with HC-3, effectively reducing the concentration of acetylcholine in the brain, did not promote acetylcholine synthesis from DMAE in the rat brain. Although DMAE uptake, which is

diffusion-dependant, was unaffected by HC-3, acetylcholine levels dropped dramatically, failing to support the contention that DMAE can supplement the synthesis of acetylcholine.

Ansell and Spanner (1979; cited by Schlenk, 1990) observed that [^{14}C]DMAE injected intracerebrally in rats (strain not provided) disappeared rapidly. Concentrations of phospho-DMAE reached maximal levels within one-to two-hours post-treatment, while phosphatidylethanolamine increased continuously throughout the seven-hour observation period. Similarly, when [^{14}C]DMAE was injected intraperitoneally, the brain content of phosphatidylethanolamine also increased throughout the seven-hour observation period, resulting in levels that were 10- to 40-fold higher than those of phosphodimethylethanolamine. Data regarding brain acetylcholine levels were not discussed.

Zahniser et al. (1977) determined that the levels of endogenous DMAE in whole brains of rats or mice was less than 1 nmol (0.09 µg) per gram brain tissue (wet weight) compared to 57 or 1.9 nmole (5.1 or 0.17 µg) per gram brain tissue for humans and pigs, respectively (Honegger and Honegger, 1959; cited by Zahniser et al., 1977). There is little evidence that significant levels of DMAE cross the blood-brain barrier. No more than 0.2% of the total recovered dose of DMAE was found in the brains of mice (Swiss-Webster, either sex), 30 minutes after dosing, even after dosing with 3000 mg DMAE/kg (33.40 mmol/kg) body weight intraperitoneally. While overall concentrations of DMAE in the brain did increase (up to 990.7 nmol DMAE/gram tissue) in mice receiving increasing doses (33.3 to 3000 mg /kg body weight; 0.370 to 33.40 mmol/kg) of DMAE, no significant increases in whole brain tissue levels of acetylcholine or choline, indicating that DMAE administered acutely to rodents was not directly incorporated into brain acetylcholine (Zahniser et al., 1977).

In kainic acid-lesioned rats (strain not provided), DMAE (dose not provided) was converted to a substance that cross-reacted in the radioenzymatic assay for acetylcholine (London et al., 1978; cited by Schlenk, 1990). In a study conducted by Haubrich et al. (1981; cited by HSDB, 1996), administration of DMAE to mice increased both the concentration and rate of turnover of free choline in blood and kidneys (dose, route of administration, and mouse species and age were not provided).

Concentrations of DMAE, choline, and acetylcholine were measured in the cortex and striatum of pregnant rats maintained on choline-deficient, choline-deficient supplemented with 0.8% choline, choline-deficient plus 1% *N*-methylaminoethanol, or choline-deficient supplemented with DMAE, beginning on day six of pregnancy through fifteen days postpartum. Neither choline or acetylcholine levels in the cortex and striatum of animals fed the choline-deficient plus choline nor *N*-methylaminoethanol varied significantly from animals fed the choline-deficient diets alone. While the choline content could not be measured accurately in the presence of a tenfold excess of DMAE relative to choline, acetylcholine levels in the cortical and striatal regions were similar to

levels found in the same regions of brains dissected from rats fed the choline-deficient diet. On the other hand, DMAE was found in the brains of both the *N*-methylaminoethanol- and DMAE-supplemented diets. Brain concentrations of DMAE were approximately 30-fold higher in the DMAE-treated rats than in the *N*-methylaminoethanol-treated animals. The authors concluded that the presence of *N*-methylaminoethanol or DMAE, both precursors in the biosynthesis of choline, did not stimulate the endogenous synthesis of either choline or acetylcholine in adult rats maintained on choline-deficient diets (Zahniser, 1978).

In fetal rat brain aggregating cell cultures exposed to varying concentrations of [^{3}H]DMAE for 72 hours, 95%, and 5% of the radioactivity was associated with phosphatidyl-DMAE and phosphatidylcholine, respectively. The rate of formation of radioactive products was concentration dependant up to 4 mM [^{3}H]DMAE, the highest concentration tested. The authors calculated an apparent half-life of 24 hours (Dainous and Kanfer, 1988).

9.1.2.1 Choline

Choline, or trimethylaminoethanol, may be formed by methylation of DMAE (South, undated). Choline has recently been recognized as an essential nutrient. *De novo* synthesis of choline typically involves conversion of phosphatidylethanolamine to phosphatidylcholine. Although small amounts may be synthesized, choline must be supplemented through the diet to maintain adequate physiological concentrations for optimal health. **Figure 1** shows the interrelationships of intracellular pathways of choline and methionine.

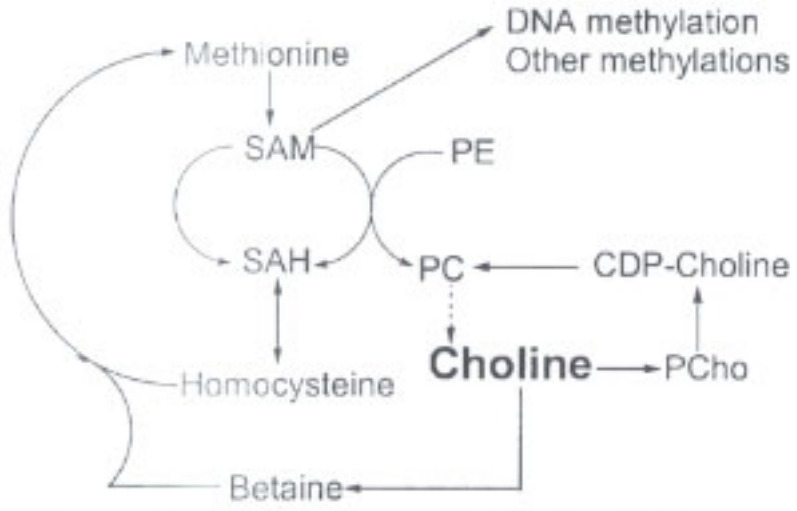


Fig. 1. Schematic representation of the interrelationship between the intracellular pathways for the utilization of choline and methionine. Choline is utilized in PC (phosphatidylcholine) biosynthesis or oxidized to betaine, which serves as the methyl donor in the conversion of homocysteine to methionine. In this manner, the generation of methionine from homocysteine intersects choline and 1-carbon metabolic pathways. Methionine, as SAM is also an important precursor for the conversion of phosphatidylethanolamine to phosphatidylcholine, a pathway that is most active in liver. The contribution of tetrahydrofolate in the regeneration of methionine in cells is not shown in this

metabolic scheme. Abbreviations: CDP-choline = cytidinediphosphocholine; PC = phosphatidylcholine; PCho = phosphocholine; PE = phosphatidylethanolamine; SAH = S-adenosylhomocysteine; SAM = S-adenosylmethionine (Taken from Lehman-McKeeman et al., 2002)

Most of the body's choline is found as a component of phospholipids. Choline-containing phospholipids, especially phosphatidylcholine and sphingomyelin, are structural components of cell membranes. These two phospholipids are also precursors for the intracellular messenger molecules diacylglycerol and ceramide. Choline is metabolized to form two other cell signaling molecules, platelet activating factor (PAF) and sphingophosphorylcholine. Phosphatidylcholine is a required component of very low-density lipoproteins (VLDL) particles, necessary for the transportation of cholesterol and fat from the liver to other sites in the body. Betaine, a metabolite of choline, participates in methyl-group transfer. Finally, choline is a precursor for the neurotransmitter, acetylcholine (Oregon State University, 2000). As a possible precursor of choline, DMAE has been studied as a potential modulator of many of the above-mentioned biological processes.

9.1.3 Acute Exposures

The acute toxicity values for DMAE are presented in **Table 4**.

In general, inhalation exposures to 1668 ppm (6134 mg/m^3) and above resulted in irritation to the mucous membranes of the eyes and upper respiratory tract and incoordination (Davies et al., 1997). In male and female Wistar rats exposed to 1668, 2408, or 3311 ppm (6134, 8856, or 12,180 mg/m^3; 68.22, 98.49, or 135.5 mmol/m^3) DMAE for four hours and observed for fourteen days, 5/10 low-dose, 7/10 mid-dose, and 8/10 high-dose rats died one to twelve days after exposure (Klonne et al., 1987). Rats from all exposure groups exhibited blepharospasms and lacrimation; excessive salivation; ocular, oral, and nasal discharge and encrustation; respiratory difficulties; decreased motor activity; coordination loss, and swelling and bleeding of extremities (feet and nose) from excessive preening (high-dose only); and a substantial body-weight loss. Discolored lungs, liver, kidneys, and spleen were observed in rats that died and in two high-dose survivors. Survivors in the low- and mid-dose groups did not have exposure-related macroscopic lesions at the end of the 14-day observation period (Klonne et al., 1987; Ballantyne and Leung, 1996).

Stadler and Kennedy (1996) studied the sensory irritation potential of DMAE in mice exposed (head-only) to DMAE in the air. Exposed animals exhibited a 50% decrease in respiration rate (RD_{50}) between 100 and 1,000 ppm (368 and 3678 mg/m^3; 4.09 and 40.90 mmol/m^3). The authors concluded that DMAE concentrations from carpets would not induce human respiratory irritation.

In rats (strain and age not provided) administered a single oral dose of 1.0, 1.41, or 2.0 mL/kg (890, 1250, or 1800 mg/kg; 10, 13.9, or 20.0 mmol/kg) DMAE and observed for 14 days, signs

Table 4. Acute Toxicity Values for Dimethylethanolamine and Selected Salts and Esters

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
Inh.	Mouse (sex and strain n.p.)	3250 mg DMAE /m^3 (36.14 mmol/m^3; 883.7 ppm)	Giglena Truda I Professional´nye Zabolevaniya (1970; cited by RTECS, 1996)
	Rat (M and F, Wistar)	1641 ppm DMAE (4 hr exposure) (6035 mg/m^3; 67.12 mmol/m^3)	Klonne et al. (1987); API (2000)
	Rat (sex and strain n.p.)	6.5 mg DMAE/L (0.07 mmol/L; 70 mmol/m^3)	OECD SIDS (1997)
p.o.	Mouse (sex and strain n.p.)	1750 mg DMAE *p*-chlorophenoxyacetate hydrochloride/kg (5.948 mmol/kg)	C. R. Seances Soc. Biol. Fil. (1959; cited by RTECS, 2002e)
	Mouse (sex and strain n.p.)	1750 mg DMAE *p*-chlorophenoxyacetate/kg (6.790 mmol/kg)	Thuillier (1960)
	Mouse (strain and sex n.p.)	3100 mg DMAE tartrate/kg (13.00 mmol/kg)	Pfeiffer (1959; cited by LifeExtension Foundation, 1999)
	Mouse (sex and strain n.p.)	3918 mg DMAE *p*-acetamidobenzoate/kg (14.60 mmol/kg)	Usdin and Efron (1972; cited by RTECS, 2002b)
	Rat (sex and strain n.p.)	865 mg DMAE *p*-chlorophenoxyacetate hydrochloride/kg (2.94 mmol/kg)	Khim. Sel'skom Khozyaistve (1978; cited by RTECS, 2002e)
	Rat (sex and strain n.p.)	2600 mg DMAE *p*-chlorophenoxyacetate/kg (10.10 mmol/kg)	Usdin and Efron (1972; cited by RTECS, 2002d)
	Rat (F, strain n.p.)	1.36 mL DMAE (1210 mg; 13.50 mmol)	Union Carbide (1986a)
	Rat (sex and strain n.p.)	1420 to 2340 mg DMAE/kg (15.79 to 26.02 mmol/kg)	API (2000)
	Rat (M, strain n.p.)	1.75 mL DMAE (1550 mg; 17.2 mmol)	Union Carbide (1986a)
	Rat (sex and strain n.p.)	1803 mg DMAE/kg (20.05 mmol/kg)	IUCLID (1997)
	Rat (sex and strain n.p.)	2000 mg DMAE /kg (22.20 mmol/kg)	Schmidt et al. (1974; cited by RTECS, 1996 and IUCLID, 1997)
	Rat (M; Sprague-Dawley)	2083 mg DMAE/kg (23.17 mmol/kg)	Ballantyne and Leung (1996)

Table 4. Acute Toxicity Values for Dimethylethanolamine and Selected Salts and Esters

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
p.o. (cont.)	Rat (sex and strain n.p.)	2130 mg DMAE/kg (23.69 mmol/kg)	BASF AG (unpublished; cited by IUCLID, 1997)
	Rat (sex and strain n.p.)	2340 mg DMAE/kg (26.02 mmol/kg)	Smyth et al. (1951; cited by Beard and Noe, 1981)
	Rat (M, Sprague-Dawley)	6000 mg DMAE/kg (67.31 mmol/kg)	Hartung and Cornish (1968)
Dermal	Rabbit (sex and strain n.p.)	1.37 mL DMAE /kg (1210 mg/kg; 13.5 mmol/kg)	Smyth et al. [1951; cited by IUCLID (1997); OECD SIDS (1997); RTECS, (1996)]
	Rabbit (sex and strain n.p.)	1215 mg DMAE/kg (13.51 mmol/kg)	API (2000)
	Rabbit (M; New Zealand White)	1219 mg DMAE/kg (13.56 mmol/kg)	Ballantyne and Leung (1996)
	Rabbit (sex and strain n.p.)	3135 mg DMAE/kg (34.86 mmol/kg)	IUCLID (1997); OECD SIDS (1997)
s.c.	Mouse (sex and strain n.p.)	1560 mg DMAE *p*-chlorophenoxyacetate hydrochloride/kg (5.30 mmol/kg)	Drugs in Japan (Ethical Drugs) (1982; cited by RTECS, 2002e)
	Mouse (sex and strain n.p.)	961 mg DMAE /kg (10.7 mmol/kg)	Naunyn-Schmiedeberg's Archiv für Exper. Pathol. Pharmakol. (1955; cited by RTECS, 1996)
	Mouse (sex and strain n.p.)	3250 mg DMAE aceglumate/kg (11.70 mmol/kg)	Therapie (1961; cited by RTECS, 2002a)
	Mouse (sex and strain n.p.)	2380 mg DMAE hydrochloride/kg (19.00 mmol/kg)	Arch. Int. Pharmacodyn. Ther. (1957; cited by RTECS, 2002f)
	Rabbit (sex and strain n.p.)	1370 mg DMAE /kg (15.20 mmol/kg)	Smyth et al. (1951; cited by Beard and Noe, 1981)
	Rabbit (M, strain n.p.)	1.87 mL DMAE /kg (1660 mg/kg; 18.5 mmol/kg)	Union Carbide (1986a)
	Rabbit (F, strain n.p.)	2.14 mL DMAE /kg (1900 mg/kg; 21.1 mmol/kg)	
i.p.	Mouse (sex and strain n.p.)	104 mg DMAE acetate/kg (0.793 mmol/kg)	Int. J. Neuropharmacol (1969; cited by RTECS, 2002c)

Table 4. Acute Toxicity Values for Dimethylethanolamine and Selected Salts and Esters

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
i.p. (cont.)	Mouse (sex and strain n.p.)	660 mg DMAE *p*-chlorophenoxyacetate hydrochloride/kg (2.20 mmol/kg)	Drugs in Japan (Ethical Drugs) (1982; cited by RTECS, 2002e)
	Mouse (sex and strain n.p.)	572 mg DMAE *p*-chlorophenoxyacetate/kg (2.22 mmol/kg).	Tarakhovskii et al. (1966)
	Mouse (sex and strain n.p.)	234 mg DMAE /kg (2.60 mmol/kg)	J. Pharmacol. Exp. Ther. (1948; cited by RTECS, 1996)
	Mouse (sex and strain n.p.)	758 mg DMAE *p*-chlorophenoxyacetate/kg (2.94 mmol/kg)	Farmakol. Toksikolog. (Moscow) (1975; cited by RTECS, 2002d)
	Mouse (sex and strain n.p.)	845 mg DMAE *p*-chlorophenoxyacetate/kg (3.28 mmol/kg)	Thuillier (1960)
	Mouse (sex and strain n.p.)	1020 mg DMAE *p*-acetamidobenzoate/kg (3.801 mmol/kg)	Usdin and Efron (1972; cited by RTECS, 2002b)
	Mouse (sex and strain n.p.)	1150 mg DMAE phenylacetate/kg (5.550 mmol/kg)	Jpn. J. Pharmacol. (1955; cited by RTECS, 2002g)
	Mouse (M and F combined, Swiss-Webster)	1074 mg DMAE/kg (11.94 mmol/kg)	Leung and Ballantyne (1997)
	Rat (sex and strain n.p.)	142 mg DMAE/kg (1.58 mmol/kg)	BASF AG (1969; cited by IUCLID, 1997)
	Rat (sex and strain n.p.)	800 mg DMAE *p*-acetamidobenzoate/kg (2.98 mmol/kg)	Usdin and Efron (1972; cited by RTECS, 2002b)
	Rat (sex and strain n.p.)	3100 mg DMAE aceglumate/kg (11.14 mmol/kg)	Ind. Med. Surgery (1951; cited by RTECS, 2002b)
	Rat (M, Sprague-Dawley)	1080 mg DMAE/kg (12.01 mmol/kg)	Hartung and Cornish (1968)
i.v.	Mouse (sex and strain n.p.)	330 mg DMAE *p*-chlorophenoxyacetate hydrochloride/kg (1.10 mmol/kg)	French Medicament Patent Document, undated; cited by RTECS, 2002e)
	Mouse (sex and strain n.p.)	330 mg DMAE *p*-chlorophenoxyacetate/kg (1.30 mmol/kg)	Thuillier (1960)
	Mouse (sex and strain n.p.)	1020 mg DMAE hydrochloride/kg (8.120 mmol/kg)	Archives Int. Pharmacodynamie Therapie (1957; cited by RTECS, 2002f)

Table 4. Acute Toxicity Values for Dimethylethanolamine and Selected Salts and Esters

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
i.v. (cont.)	Rabbit (sex and strain n.p.)	150 mg DMAE *p*-chlorophenoxyacetate/kg (0.580 mmol/kg)	Usdin and Efron (1972; cited by RTECS, 2002d)
		LD_{Lo} Value	
i.p.	Guinea pig (sex and strain n.p.)	450 mg DMAE /kg (5.00 mmol/kg)	Proc. Soc. Exp. Biol. Med. (1954; cited by RTECS, 1996)
i.v.	Rabbit (sex and strain n.p.)	150 mg DMAE *p*-chlorophenoxyacetate hydrochloride/kg (0.510 mmol/kg)	C. R. Seances Soc. Biol. Fil. (1959; cited by RTECS, 2002e)

Abbreviations: DMAE = dimethylethanolamine; F = female; Inh. = inhalation; L = liter; LD (C)χ = dose (concentration) lethal to χ% of test animals; LD_{Lo} = lowest lethal dose; M = male; n.p. = not provided; p.o. = *per os*; ppm = parts per million

of toxicity were observed with the two higher doses (Union Carbide, 1986a). Toxic effects included sluggishness, discharge around the eyes and nose, kyphosis (abnormal bending of the spine), and prostration. Symptoms abated at between two and five days. Signs of toxicity from LD_{50} studies included sluggishness, lacrimation, chromodacryorrhea, diarrhea, kyphosis, and prostration. Necropsy results in animals that died disclosed distended stomachs containing blood with dark red or purple discolorations of the glandular portion. Blood was also found in the intestines. Lung showed a dark red mottling. No unusual gross pathological findings were noted in animals that survived the full 14-day observation period (Ballantyne and Leung, 1996). In rabbits that died, death occurred in one day or less. Necropsy revealed mottled and red lungs, dark fluid in stomach and intestine, and reddened stomach.

A single oral dose of 10 mg DMAE/kg (0.10 mmol/kg) in dogs resulted in muscular tremors (Davies et al., 1997).

DMAE was classified as corrosive by several groups (BASF AG, 1969, 1982; Potokar et al., 1985; all cited by IUCLID, 1997). Potokar et al. (1985, cited by IUCLID, 1997) noted that DMAE was corrosive after one hour with either occlusive or semi-occlusive dressings. Application of 445 mg (4.95 mmol) DMAE to open skin of rabbits (strain and age not provided) produced mild irritation (Union Carbide, 1971; cited by RTECS, 1996). No other details were given. Application of 0.5 mL (400 mg; 5 mmol) DMAE for four hours to occluded skin of three male and three female rabbits (strain and age not provided) produced severe erythema, edema, and necrosis in all animals following a 14-day observation period (Union Carbide, 1986a). Scabs appeared on all rabbits; ulceration and erythema on about half. In a follow-up study in rabbits (sex and strain not provided), one-hour and three-minute time-points for occluded contact with

0.5 mL (400 mg; 5 mmol) DMAE were assessed. After one hour of contact with DMAE, all six rabbits demonstrated moderate erythema and edema, with full-thickness necrosis. Three of the animals progressed to ulceration. Ecchymosis was noted for one rabbit. Scabs developed on three of the animals. The severe irritation persisted through the second day of observation, when the animals were sacrificed. Although no irritation was observed in four test animals, minor erythema, superficial necrosis, and ecchymosis was observed in one of six rabbits after three-minute occluded contact with DMAE. Two of the animals experienced desquamation and alopecia, developing scabs, which persisted for the full 14-day observation period (Union Carbide, 1990; Ballantyne and Leung, 1996).

Ballantyne and Leung (1996) ranked DMAE as having moderate acute percutaneous lethal toxicity in New Zealand White rabbits. Signs of toxicity included sluggishness, unsteady gait, emaciation, and prostration. Moderate to sever erythema and edema with ecchymoses, necrosis, and ulceration were observed after the application of DMAE in a 24-hour occlusion test and persisted to the end of the observation period (14 days), along with the development of local desquamation, alopecia, and scarring. Dark red mottled lungs, dark red livers, and mottled kidneys were observed upon necropsy of animals that died. Some of the survivors also showed evidence of red mottled lungs and dark red livers at necropsy.

In rabbits (strain and age not provided) administered a single subcutaneous (s.c.) dose of 1.0, 2.0, or 4.0 mL/kg (890, 1800, or 3500 mg/kg; 10, 20, or 40 mmol/kg) DMAE and observed for 14 days, signs of toxicity were observed with the two higher doses (Union Carbide, 1986a). Toxic effects included erythema, edema, necrosis, ulceration, and scabs in dosed skin, as well as salivation, sluggishness, labored breathing, emaciation, and prostration. Most deaths occurred on day one. Gross pathological examination revealed red and mottled lungs, mottled livers, red tracheas, and subcutaneous redness.

DMAE was moderately to severely irritating in the Draize Test (Texaco Data Sheet, undated; Smyth et al., 1951; BASF AG, 1990; all cited by IUCLID, 1997). Application of 0.75 mg (0.0083 mmol) DMAE to the eyes of rabbits (strain and age not provided) produced severe irritation (Smyth et al., 1951; cited by RTECS, 1996). Application of 0.005 mL (4 mg; 0.05 mmol) DMAE to the eyes of male and female rabbits (strain and age not provided) produced moderate to severe corneal injury, iritis, and severe conjunctival irritation (with necrosis) in all animals (Union Carbide, 1986a). Corneal damage occurred within one hour of treatment, becoming moderately to severely opaque and affecting 75% of the cornea. By the seventh day of observation, all corneas were severely opaque over the whole surface. The effects persisted to the end of the observation period, or 14 days. Necrotic areas in the conjunctivae and nictitating membrane (four hours post application), corneal neovascularization (seven days), and corneal ulceration (14 days) were also observed. The iris could not be inspected due to marked keratitis

(Ballantyne and Leung, 1996). Other signs detected included pinpoint pupils, exophthalmos (bulging), irregular corneal shape, and vascularization (incidences not provided).

DMAE (as centrophenoxine) was tested for its effects on spinal reflexes. While 20 mg/kg (0.070 mmol/kg) given intraperitoneally to mice (sex and strain not provide) had little effect on the transmission of impulses along the spinal cord synapses, 50 mg/kg (0.170 mmol/kg) demonstrated a considerable change in spinal reflexes, specifically in the inhibition of polysynaptic reflexes. Higher doses (400 to 600 mg/kg [1.40 to 2.04 mmol/kg] intraperitoneally) resulted in ataxia, reduced mobility, inhibition, and mortality in some treated mice. Similar doses in rats resulted in limited mobility and an inhibited state (Tarakhovskii et al., 1966). Danysz et al. (1967a) found that intravenous administration of DMAE (175 to 350 mg/kg; 1.95 to 3.90 mmol/kg) resulted in dose-dependant psychoanaleptic effects (as demonstrated by spontaneous running in mice) and an influence on conditioned reflexes in rats.

DMAE appears to exert a central vasomotor stimulant effect. Intracerebroventricular (ICV) administration of DMAE (0.1 to 2.0 mg; 1.0 to 20 µmol) resulted in potentiation of the carotid occlusion response (all doses) resulting in an increase in blood pressure in dogs (higher doses) (Dhawan et al, 1967). This effect was not abolished by atropine sulfate (ICV). Danysz et al. (1967a), however, found that intravenous administration of DMAE (3 to 40 mg/kg; 0.03 to 0.40 mmol/kg) to cats induced a transient hypotension.

Al-Zuhair et al. (1998) investigated the effects of meclofenoxate on the heart rate and blood pressure of old (24-month-old male rats, strain not provided) and compared the results to those obtained from four-month-old rats. The mean basal heart rate for the young versus old rats was 285 ± 11.83 and 320 ± 13.28, respectively. Blood pressures were 80 - 90 mmHg for the four-month old rats relative to 110 - 120 mmHg for the 24-month-old rats. With meclofenoxate treatment (10 to 40 mg/kg body weight; 0.040 to 0.16 mmol/kg), a significant dose-dependent reduction in both blood pressure (up to 49.7 ± 0.39 mmHg reduction) and heart rate (up to 71 ± 4.5% reduction) was observed in the old rats at the 40 mg/kg (0.16 mmol/kg) dose level.

9.1.4 Short-term Exposures

Selected studies described in this section are presented in **Table 5**.

Among male and female F344 rats exposed to 98, 288, or 586 ppm (360, 1060, or 2160 mg/m^3; 4.0, 11.8, or 24.0 mmol/m^3) DMAE for six hours/day, five days/week for nine exposures during an eleven-day period, all high-dose rats died between days four through eight, and four of fifteen mid-dose males died on days eight through twelve (Klonne et al., 1987). Signs of respiratory distress, ocular and nasal irritation, and corneal opacity were observed in the mid- and high-dose rats. All mid-dose rats had conjunctivitis and corneal opacity. The mean body weights, and some organ weights, were significantly depressed in low- and mid-dose rats. The principal

Table 5. Short-term Toxicity Studies of Dimethylethanolamine and Selected Salts and Esters

Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rabbit, New Zealand White; ≤ 20-wk-old, 5-10 rabbits/sex per group in control and exposed groups	DMAE, purity n.p.	Dermal: HD = 2.0 mL/kg/day (1800 mg/kg/day; 20 mmol/kg/day); MD and LD were not specified. Rabbits received 9 dermal applications (5 d, 6-h applications, followed by 2 non-treatment days, plus 4 d, 6-h applications) over 11 d; rabbits were sacrificed 1 d after the final treatment.	DMAE caused severe skin irritation. No mention was made of reaction of controls. There were no treatment-related microscopic findings in regions other than treated skin.	Hermansky et al. (1995)
Rat, F344, approx. 8-wk-old, 10 M, 10 F per group, both exposed and control groups	DMAE, ≥ 99% pure	Inh.: 98, 288, or 586 ppm (360, 1060, or 2160 mg/m^3; 4.0, 11.8, or 24.0 mmol/m^3), 6 h/d, 5 d/wk for 9 exposures during an 11-d exposure period (no exposure on days 5 and 6); animals sacrificed when moribund or on the morning after the last exposure.	All HD rats died before the end of the study and were not evaluated; 4/15 MD males died 8-12 days after initiation of exposure (MD F were not mentioned). Signs of respiratory distress, ocular and nasal irritation, and corneal opacity were observed in MD and HD rats. No exposure-related neurobehavioral effects were detected. The principal histologic lesions were detected in the upper respiratory tract of LD and MD rats and in the eyes of the MD group. Most of the serum chemistry, hematology, and urinalysis values for the MD group were significantly different from control values.	Klonne et al. (1987)
Rat, Wistar, 24- and 4-mo-old, 8 animals per group	Meclofenoxate, purity n.p.	Oral: 100 mg/kg (0.390 mmol/kg) b.w., 1/d; X 4 wk	One group of 24-mo-old rats was treated with meclofenoxate. Two groups of rats (one 24-mo-old and one 4-mo-old) were untreated. MDA, phospholipids, superoxide dismutase, GSH, and PrSHs were measured in plasma, brain, heart, and liver. MDA and GSH were significantly higher in all 4 tissues; PrSHs were significantly higher in serum, brain, and heart; phospholipids significantly elevated in the brain and heart; and SOD significantly elevated in the brain and liver of old versus young rats. Treatment with meclofenoxate resulted in values for these 5 parameters intermediate between the old and young rats, and frequently the value with treatment was significantly different from the untreated aged rats.	Al-Zuhair et al. (1998)

Abbreviations: d = day(s); F = female; GSH = glutathione; h = hour(s)(ly); HD = high dose; Inh. = inhalation; LD = low dose; M = male; MD = mid dose; MDA = malondialdehyde; mo = month(s)(ly); n.p. = not provided; ppm = parts per million; PrSHs = protein thiols; SOD = superoxide dismutase; wk = week(s)(ly)

histologic lesions were detected in the upper respiratory tract of low-dose and mid-dose rats, and in the eyes (ranging from corneal edema to ulcerative keratitis) of mid-dose rats. A large variety of nasal tissue histopathologic conditions was observed in low- and mid-dose rats.

In a study to investigate the modulations by centrophenoxine in combination with some natural products on age-related oxidative changes, 24-month-old male Wistar rats were dosed orally with 100 mg/kg body weight (0.640 mmol/kg) once a day for four weeks. Plasma, liver, and brains of these animals were collected at the end of the study and malondialdehyde (MDA), phospholipid content, superoxide dismutase activity (SOD), glutathione (GSH), and protein thiol (PrSHs) levels were measured and compared to those of untreated 4- and 24-month-old rat tissues. Significant differences in the levels of these parameters were observed when comparing tissue levels from untreated young and old rats. Typically, treatment of the 24-month-old rats with centrophenoxine resulted in tissue levels of MDA, phospholipid content, SOD, GSH, and PrSHs that were intermediate to the two untreated groups. These levels, however, were often significantly different from the untreated old rats but not significantly different from the younger group of animals, suggesting a reversal in age-related effects (Al-Zuhair et al., 1998).

Male and female New Zealand White rabbits treated dermally with DMAE developed severe skin irritation (Hermansky et al., 1995). The highest dose administered was 2.0 mL/kg/day (1800 mg/kg/day; 20 mmol/kg/day). Two lower doses were also administered, but information on these doses was not provided. All rabbits received nine applications on shaved dorsal skin over eleven days. Microscopic examination revealed no treatment-related effects in regions other than treated skin.

Voronina et al. (1987a,b) [Russian] reported that long-term administration [details not provided in the abstracts] of centrophenoxine and Cleregil (DMAE aceglumate) increased the "emotional reactivity" and aggressiveness in rats. Spontaneous aggressiveness and "still greater enhancement of emotional reactivity" occurred after withdrawal of the drugs. Garibova et al. (1984) reported that prolonged intraperitoneal injections of Cleregil (150 mg/kg) induced "manifestations of aggressiveness, fear and anxiety." The rats "developed a dissociated state in which the reflex [learning in a T-maze] manifested itself only after [Cleregil] injection and did not occur without it." Withdrawal of either centrophenoxine or Cleregil produced an "even greater enhancement of emotional reactivity and appearance of spontaneous aggressiveness" (Voronina et al., 1987b). Meszaros and Gajewska (1972) reported increased aggressiveness in mice associated with several forms of DMAE. In this report, the authors stated that several pharmacological properties of centrophenoxine may be attributed to the *p*-chlorophenoxyacetic acid (PCPA) moiety. Low doses of PCPA or centrophenoxine increased aggressiveness in mice, whereas high doses decreased aggressiveness. DMAE increased aggressiveness at high doses and decreased aggressiveness at low doses. The effects of centrophenoxine and PCPA were more similar to each other than with DMAE.

A similar dissociated phenomenon was reported for the manifestation of antiamnestic and antihypoxic effects observed with centrophenoxine and Cleregil in mice (Voronina et al., 1987a). The antihypoxic effects were noted only at high doses of centrophenoxine. Tonibral administered subcutaneously (60 mg/kg/day [0.40 mmol/kg/day], daily for three to ten days) increased the survival in rats subjected to barochamber simulation of 12-km altitudes. Tonibral also accelerated adaptation to high altitude (Zurdinov et al., 1986).

9.1.5 Subchronic and Chronic Exposures

Selected studies described in this section are presented in **Table 6.**

Male and female F344 rats were exposed to 8, 24, or 76 ppm (30, 88, or 280 mg/m^3; 0.3, 0.98, or 3.1 mmol/m^3) DMAE for six hours/day, five days/week for thirteen weeks (Klonne et al., 1987). Half of the rats were killed after at least two days of exposure during the fourteenth week of the study. The remaining rats were killed after five weeks of recovery. In mid- and high-dose rats, corneal opacity occurred at the end of the daily exposures, beginning approximately at exposure week two to three. This opacity regressed during unexposed nighttime periods. In the high-dose group there was also an increase of audible respiration. Histopathologic examination revealed changes in nasal tissue in high-dose rats, and to a much lesser degree, in mid-dose rats. Nasal conditions included rhinitis, squamous metaplasia, degeneration of respiratory epithelium, atrophy of olfactory epithelium, and microcysts in respiratory epithelium. Nasal lesions were limited to the anterior nasal cavity and the incidence and severity of these lesions decreased by the end of the recovery period.

Chronic exposures (duration not provided) of mice (details not provided) to emissions from freshly foamed polyurethane insulation produced disturbances in blood composition including increased leukocyte count and decrease in erythrocytes and hemoglobin content. DMAE was recorded at about 6.7 mg/m^3 (0.075 mmol/m^3) in the vicinity of freshly foamed polyurethane insulation. In closed containers, the concentration decreased to about 4 mg/m^3 (0.04 mmol/m^3) after two months. 4,4′-Methylenediphenyldiisocyanate was also detected (4.0 mg/m^3) in the emissions from polyurethane foam insulation (Lidberg and Komina, 1984).

Smyth et al. (1951) reported a NOAEL and LOAEL of 180 and 890 mg (2.00 and 10.0 mmol/kg) DMAE/kg, respectively, from a 90-day feeding study. Thuillier (1960), on the other hand, failed to observe any toxic effects in the rat after long-term exposures (details not provided). A decrease in plasma triglyceride and cholesterol was observed in rats receiving 10 mg/kg (0.10 mmol/kg) per day DMAE orotate for six months, without any signs of fatty acid infiltration of the liver. The authors speculate that there was an inhibition of free fatty acid mobilization from adipose tissue (Pinelli and Colombo, 1973). Lukoshko et al. (1997) reported that a four-month

Table 6. Subchronic and Chronic Toxicity Studies of Dimethylaminoethanol and Selected Salts and Esters

Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Mouse, Swiss Webster albino, 8.6-mo-old, 32 and 31 animals/exposed and control group, respectively, M	DMAE *p*-chlorophenoxyacetate, purity n.p.	Oral: 0.3 g DMAE *p*-chlorophenoxyacetate/L drinking water; averaging 20 mg (0.20 mmol) DMAE/kg b.w./d. Animals dosed from 8.6- to 18.2-mo of age. Exposures were suspended from 18.2- to 22.2-mo of age and continued from 22.2 mo to end of experiment. Controls received normal drinking water.	Nine mo after start of study, 2 animals/group were sacrificed for histochemical determination of lipofuscin pigment in brain and myocardial tissues. Both treated and untreated brains were heavily pigmented relative to young animals. Significant differences in fluorescent pigment density were found between the control and treated group in myocardial tissues, with treated animals having less pigment. Mean, median, and maximum survival times were 12.39, 12.3, 24.3, and 9.73, 9.5, 17.4 mo from start of trial for treated and control groups, respectively. At 4.7 mo from start of trial, the treated group was on average slightly heavier (47.8 g) than the control group (45.1 g). By 13.8 mo from the start of trail, the treatment group was significantly lighter (40.6) than control animals (45.5 g).	Hochschild (1973a)
Mouse, A/J, 604- to 674-d-old (avg. 21 mo.), 57 exposed and controls, M	DMAE acetamidobenzoate, purity n.p	Oral: 86 µg DMAE/mL drinking water; averaging 7 mg (80 µmol) DMAE/kg/d. Treated animals were maintained on DMAE acetamidobenzoate for the remainder of their lives. Controls received normal drinking water.	Mean, median, and maximum survival times for treated and control groups were 85.1, 51, 372, and 56.9, 39, 273 d from start of trial, respectively. Prior to the beginning of trial, average body weights for the two groups were not significantly different. At 109 d from start of trial, the treated group was on average slightly heavier (26.7 g) than the control group (23.4 g). There were insufficient control animals for comparisons later in the experiment.	Hochschild (1973b)
Rat, F344, approx. 9-wk-old, 20 M, 20 F per group, exposed and control groups	DMAE, ≥ 99% pure	Inh: 8, 24, or 76 ppm (30, 88, or 280 mg/m^3; 0.3, 0.98, or 3.1 mmol/m^3), 6 h/d, 5 d/wk, 13 wk. One-half of all rats per group were sacrificed after a minimum of 2 exposures in the 14th wk of study. Remaining animals were sacrificed after 5 wk of recovery.	In MD and HD rats, corneal opacity occurred at the end of the daily exposures, beginning ~ 2-3 wk after initiation of exposure. The opacity regressed during non-exposed periods. In the HD group there was also audible respiration. There were no exposure-related effects on the gross appearance of organs. Histopathology of nasal tissues revealed rhinitis; squamous metaplasia; degeneration of respiratory epithelium; atrophy of olfactory epithelium; and microcysts in respiratory epithelium. The incidence and severity of these lesions were decreased at the end of the recovery period.	Klonne et al. (1987)

Table 6. Subchronic and Chronic Toxicity Studies of Dimethylaminoethanol and Selected Salts and Esters

Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, strain, age, number, and sex n.p.	DMAE, purity n.p.	Oral: dietary exposure (450 to 890 mg/kg/d; 5.00 to 10.0 mmol/kg), 90-d exposure.	Highest dose levels resulted in increased liver and kidney weights; otherwise no microsomal changes were observed in the liver, kidney, spleen, or testes.	Smyth et al. (1951; cited by Davies et al., 1997)

Abbreviations: avg. = average; b.w. = body weight; d = day(s); DMAE = dimethylaminoethanol; F = female; h = hour(s)(ly); HD = high-dose; M = male; MD = mid-dose; mo = month(s)(ly); ppm = parts per million; wk = week(s)(ly);

continuous inhalation exposure of rats to high concentrations of DMAE (2.76 mg/m^3; 0.031 mmol/m^3) resulted in a disturbance in the "dynamic equilibrium between processes of inhibition and excitation" with "prevalence for excitation. "

Hochschild (1973a, b, c) investigated the ability of DMAE (as DMAE *p*-chlorophenoxyacetate or DMAE acetamidobenzoate) to extend the life of adult mice (male Swiss Webster, female C57BL/6J, or male A/J). *p*-Chlorophenoxyacetate was used in the Swiss Webster and C57BL/6J and the A/J mice were dosed with the acetamidobenzoate form of DMAE. Mean survival, reported as percent over control values (from the start of the trial), were 27.3, 5.9 and 49.5 for the Swiss Webster, C57BL/6J, and A/J mice, respectively. Maximum survival (percent over controls) was 39.7% and 36.3% for the Swiss Webster and AJ mice, respectively. The only other parameter noted was body-weight changes. Typically, the treated animals gained more weight early in the trial, but weighed slightly less than control animals by the end of the study.

9.1.6 Synergistic/Antagonistic Effects

Theoretically, concomitant use might decrease the effect of drugs with anticholinergic activity, due to the potential cholinergic activity of DMAE (Cited by Quackwatch, 2002).

Several studies report interactive biological effects, either potentiation or antagonism, caused by derivatives of DMAE, possibly due to improved penetration into tissues. DMAE (175 to 350 mg/kg [1.95 to 3.90 mmol/kg], subcutaneously) was reported to potentiate the central action of cardiazol, strychnine, morphine, chlorpromazine, evipan, and phenobarbital in rats. Treatment with DMAE for seven to fourteen days increased levels of chlorpromazine in the brains of rat, relative to treatment with chlorpromazine alone (Danysz et al., 1967b). Rowell and Chiou (1976) reported that a synthetic ester of DMAE, *N,N*-DMAE chloroacetate, inhibited choline acetyltransferase in a reversible and uncompetitive fashion.

DMAE bitartrate (100 to 500 mg/kg; 0.300 to 1.5 mmol/kg, intraperitoneally), administered simultaneously with paracetamol (acetaminophen), protected rats and mice from the hepatotoxic effects of the latter. Mixed function oxidases that metabolize paracetamol were inhibited, and elimination of free paracetamol and its glucuronide was enhanced (Siegers and Yones, 1979).

DMAE *p*-chlorophenoxyacetate, given one hour prior to pentetrazole (route not provided) reduced the threshold for pentetrazole-induced generalized tonic-clonic crisis (species not provided) (Thuillier, 1960). Chicks injected intraperitoneally with Small doses of DMAE *p*-acetamidobenzoate (Deaner®, 2 mg/kg; 0.02 mmol/kg) 15 minutes before intraperitoneal injection of tremorine potentiated the tremorine-induced tremor response. Large doses of DMAE (Deaner®, 200 mg/kg; 2.00 mmol/kg) given two hours prior to tremorine suppressed the tremor response completely (Bowman and Osuide, 1968).

Al-Zuhair et al. (1998) investigated the interactive effects of meclofenoxate (100mg/kg [0.400 mmol/kg] orally, daily) with an extract of ginkgo biloba (EGb 761) (daily oral dose of 150 mg/kg) or zinc sulfate (daily oral dose of 10.5 mg/kg) for four weeks, in 24-month-old male Wistar rats. At the end of the treatment period, animals were sacrificed and the liver, heart, brain, and plasma were collected for determination of MDA, phospholipid content, SOD, GSH, and PrSHs levels. Comparisons were made between 24-month-old rats untreated, or treated with meclofenoxate alone and in combination with either EGb 761 or zinc sulfate. The combination of meclofenoxate and EGb 761 resulted in levels that were significantly different from the meclofenoxate-treated group, but not significantly different from the 4-month-old rats for the brain (MDA, SOD, GSH, PrSHs, and phospholipids) and the heart (MDA, GSH, PrSHs, and phospholipids). In many cases, the parameters were lower with the combined treatment than found in the four-month-old animals. With the meclofenoxate plus zinc sulfate, statistically different levels relative to the meclofenoxate only treatment, were reported only for brain levels of GSH. MDA (plasma, brain, and heart), SOD (brain), GSH (blood, brain, and heart), and PrSHs (serum and brain) levels were statistically different from the untreated 24-month-old rats, only.

Abood et al. (1988) and Abood (1989) synthesized and tested a number of aromatic, cycloalkyl, and heterocyclic carbamic acid, thiocarbamic acid, and carboxylic acid esters of di- and trialkylaminoalkyl and heterocyclic amino alcohols for their pharmacology and receptor binding characteristics at the nicotine receptor in the rat brain, and for their ability to induce seizures and prostration and antagonize nicotine-induced seizures and prostration. Nine DMAE derivatives were listed as synthesized and tested. Abood et al. (1988) found that tertiary amino derivatives were effective; however, they were considerably less potent than the quaternary amino derivatives in antagonizing the effects of nicotine.

Meclofenoxate (100 mg/kg [0.400 mmol/kg] for ten days) "alleviated learning and memory disability" of three-month-old rats with fetal alcohol syndrome. The authors suggested the usefulness of meclofenoxate for prophylactic treatment of fetal alcohol syndrome-related disturbances (Vaglenova and Vesselinov Petkov, 2001).

9.2 Reproductive and Teratological Effects

Selected **s**tudies described in this section are presented in **Table 7.**

No histopathological changes in the gonads were observed after repeated exposure to DMAE in a 90-day inhalation study in rats (no further details provided) (Davies et al., 1997).

Information described by Leung et al. (1996b) and IUCLID (1997) appear to represent the same study. DMAE via inhalation induced maternal toxicity at all tested exposure levels (10, 30, and 100 ppm; 40, 110, and 370 mg/m^3; 0.41, 1.20, and 4.10 mmol/m^3), as demonstrated by changes in body weight gain in the mid- and high-dose groups and ocular changes in the mid- and low-dose

Table 7. Reproductive and Developmental Effects of Dimethylethanolamine and Selected Salts and Esters

Species, Strain, Age, Number, and Sex	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, Fischer 344, 25/exposure group, pregnant F	DMAE, purity n.p.	Inh: 0, 10, 30, and 100 ppm (0, 40, 110, and 370 mg/m^3; 0, 0.41, 1.20, and 4.10 mmol/m^3) DMAE on GD 6 through 15. Animals sacrificed on GD 21.	Mean analytical values for exposure were 0.1, 10.4. 29.8, and 100 ppm. Maternal toxicity was observed at all dose groups in the form of reduced body weight gain and ocular changes. Reduced weight gain in the high-dose animals persisted after cessation of exposure. Ocular changes, more profound at the 30 ppm exposure level, were and minimal and transient in the low-dose group. Maternal body weights were reduced in the high-dose group at sacrifice. No treatment-related changes in gravid uterine weight, body weight corrected for gravid uterine weight, or absolute or relative liver weight. No treatment related effects were observed in pre- or post-implantation loss, sex ratio, individual malformations, malformations by category, or total malformations. Fetal body weights per litter (for M and F, but not for total) were increased at 100-ppm relative to controls. One fetal variation, split (bipartite) cervical centrum, was elevated at the 100 ppm exposure level; however, the incidence of fetal variation did not indicate a consistent pattern suggesting fetotoxicity. NOAELs for maternal toxicity and teratogenicity were estimated at 10 ppm and 100 ppm, respectively.	Union Carbide (1986b; cited by IUCLID, 1997); Leung et al. (1996b)

Abbreviations: d = day(s); DMAE = dimethylethanolamine; F = female; GD = gestation day; Inh. = inhalation; M = male; NOAEL = no-observed-adverse-effect-level; n.p. = not provided; ppm = parts per million

groups. While the changes in weight gain persisted after exposures were halted, resulting in a reduction in body weights in the high-dose group at the termination of the study, the weight gain changes in the mid-dose group were transient, occurring only during exposures. Ocular changes, consisting of darkened, cloudy, and hazy eyes, corneal vascularization, and fixed and dilated pupils, were found primarily in the mid- and high-dose groups, although transient changes were also observed in the low-dose group. Although these studies appear to be the same, Leung et al. (1996b) reported sporadic, inconsistent alterations in gestational parameters including significant decreases in viable implants per litter, percentage live fetuses/litter, and litter size in rats exposed to 10 ppm (40mg/m^3; 41 mmol/m^3) and a significant decrease in the percentage of male fetuses in rats exposed to 30 ppm (110 mg/m^3; 1.20 mmol/m^3), while IUCLID (1997) reported no treatment-related effects on any reproductive parameters including pre- and postimplantation losses or sex ratio changes. Inhaled DMAE induced variations in six skeletal parameters in the fetuses of pregnant Fischer 344 rats exposed to 10 (40 mg/m^3; 0.41 mmol/m^3) to 100 ppm (370 mg/m^3; 4.10 mmol/m^3) DMAE on gestation days 6 to 15. Skeletal variations included decreased incidences of poorly ossified cervical centrum 6, bilobed thoracic centrum 9, bilobed sternebrae 5, unossified proximal phalanges of the forelimb, and increased incidences of split cervical centra 1, 2, 3, and/or 4 and bilobed thoracic centrum 1. However, a consistent pattern was lacking, resulting in a NOAEL for embryofetal toxicity and teratogenicity of 100 ppm (370 mg/m^3; 4.10 mmol/m^3) or greater. A NOAEL for maternal toxicity was estimated at 10 ppm (40 mg/m^3; 0.41 mmol/m^3). The study may have been performed at Research Triangle Institute. Tyl et al. (1987) published an abstract with a similar title in *The Toxicologist*.

Gramette et al. (1986) dosed pregnant rats with DMAE beginning on gestation day 12 and continued to dose the offspring through postnatal day 10. DMAE diminished behavioral decrements (motor activity in the pups; striatal dopamine release in adults) induced by postnatal hypoxia.

Fujiwara et al. (1968) investigated the changes in lung phospholipids in immature, transitional, and term lambs and found a predominance on dipalmityl phosphatidylcholine in term lambs, whereas negligible amounts of alveolar phosphatidylcholine were obtained from immature lamb fetuses and lung washing lacked surface activity. Phosphatidyldimethylethanolamine was recovered from the lung washings of transitional and term lamb fetuses.

Neumann and Seyfarth (1982) conducted a five-generation study in which each generation of rats or only the first and fifth generations were exposed *in utero* to centrophenoxine on gestation days 11 to 14 (during embryogenesis). Treating Wistar dams with meclofenoxate prenatally resulted in significant increases in weight of the offspring. The increase in embryo weights did not continue into postnatal life. Continuous treatment through several generations increased fertility and an overall increase in the number of offspring (Neumann, 1985).

Benesova et al. (1980 abstr.) and Peterka et al. (1980) reported that meclofenoxate was

cardiotoxic to chicken embryos.

9.3 Carcinogenicity

The study described in this section is presented in **Table 8**.

There was no statistically significant increase, or morphological difference, in the incidence of neoplasms in any organ in female C3H/HeN mice given drinking water with 10 mM (900 µg/mL) DMAE for 105 weeks, or in female C3H/HeJ(+) mice given 15 mM (1300 µg/mL) DMAE for 123 weeks (Stenbäck et al., 1988). No changes in the structure, appearance, or microscopic morphology of various organs were observed. Treatment with DMAE did not affect survival, initial body weight gain, or mature body weight of either strain of mouse.

9.4 Initiation/Promotion Studies

No studies identified as initiation/promotion studies were located.

9.5 Anticarcinogenicity

Brophy and Sladek (1978 abstr.) and Kanzawa et al. (1972) reported that centrophenoxine potentiated the antitumor activity of chlorambucil *in vivo*. Centrophenoxine was indexed in a database record investigating antineoplastic effects, but it was not specifically mentioned in the abstract (Von Metzler and Nitsch, 1986).

Fontaine et al. (1987) reported that enrichment of tumorigenic LM cell cultures with choline or DMAE enhanced the antineoplastic action of 5-fluorouracil by threefold.

9.6 Genotoxicity

Studies described in this section are presented in **Table 9**.

Four studies (Murray and Cummins, 1979; Zeiger et al., 1987; and Union Carbide, 1987; cited by IUCLID, 1997; Leung and Ballantyne, 1997) were identified that used the *Salmonella typhimurium* assay. Tester strains TA98, TA100, TA1535, TA1537, and TA1538 were all tested, both in the presence and absence of a metabolic activation system. DMAE, ranging from 0.37 to 995 µmol (0.033 to 89.5 mg)/plate failed to demonstrate any mutagenic response. DMAE also failed to induce any sex-linked recessive lethal mutations in the *Drosophila melanogaster* (7200 or 8100 ppm; 80.10 or 90.10 mmol/L) (Foureman et al., 1994).

The genotoxicity of DMAE was investigated in several mammalian systems, both *in vitro* and *in vivo*. *In vitro* assays included sister chromatid exchange (Union Carbide, 1988; cited by IUCLID, 1997; Leung and Ballantyne, 1997) and hypoxanthine-guanine phosphoribosyl transferase forward gene mutation test (HGPT) (Leung and Ballantyne, 1997), both in Chinese hamster ovary cells. All of the *in vitro* assays failed to demonstrate genotoxicity within the dose ranges

Table 8. Carcinogenicity of Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
mouse (C3H/HeN and C3H/HeJ(+); age n.p.)[1]	exposed: 60F C3H/HeN; 50F C3H/HeJ(+) controls: 60F C3H/HeN; 50F C3H/HeJ(+)	DMAE, purity n.p.	10 mM (900 μg/mL)(group 2) or 15 mM (1300 μg/mL) (group 4) in drinking water	105 wk (groups 1 and 2) or 123 wk (groups 3 and 4); mice were allowed to die of natural causes or were sacrificed when moribund	Treatment with DMAE did not affect survival or the initial body weight gain or mature body weight of either strain of mouse. No macroscopic or microscopic pathological changes were apparent; only the extent of lipofuscin (brown pigmented lipid-containing granules representing residues of lysosomal digestion) appeared less distinct in the livers of mice in groups receiving 10 or 15 mM DMAE.	Stenbäck et al. (1988)

Abbreviations: DMAE = Dimethylethanolamine; F = female; n.p. = not provided; wk = week(s)(ly)

[1] C3H/HeN mice carry a dominantly expressed germinal mammary tumor provirus, Mtv-1; C3H/HeJ(+) mice also carry the exogenous milk-transmitted mammary tumor virus

Table 9. Genotoxicity of Dimethylethanolamine and Selected Salts and Esters

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Endpoint Response	Comments	Reference
Prokaryotic Systems							
Salmonella typhimurium strain TA100	*his* reverse gene mutations	-	DMAE, purity n.p.	100 µL/plate (995 µmol/plate; 89.5 mg/ plate)	Negative	No other experimental details were given.	Murray and Cummins (1979)
S. typhimurium strains TA1535, TA1537, TA98, and TA100	*his* reverse gene mutations	-/+	DMAE, purity n.p.	33 to 10,000 µg/plate (0.37 to 100.00 µmol/plate)	Negative	The pre-incubation method was used with and without 10% rat or hamster liver S9.	Zeiger et al. (1987)
S. typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100	his reverse gene mutation	-/+	DMAE, purity n.p.	Concentrations n.p.	Negative	DMAE did not produce positive or dose-dependent mutagenic responses in any of the bacterial strains tested, with or without metabolic activation.	Union Carbide (1987; cited by IUCLID, 1997)
S. typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100	his reverse gene mutation	-/+	DMAE, 99.9% pure	0.01 to 10 mg/plate (0.11 to 110 µmol/plate)	Negative	Test included activation-independent positive controls (4-nitrophenylenediamine, sodium azide, and 9-aminoacridine) and activation-dependent control (2-aminoanthracene).	Leung and Ballantyne (1997)
Lower Eukaryotic Systems							
Drosophila melanogaster strains Canton-S males and *Basc* females	sex-linked recessive lethal mutations	+	DMAE, purity n.p.	7200 ppm (units as reported by authors) (7200 mg/L; 80.10 mmol/L) for a 3-day feeding exposure or 8100 ppm (8100 mg/L; 90.10 mmol/L) via injection.	Negative	No increase in sex-linked recessive lethals was observed.	Foureman et al. (1994)

Table 9. Genotoxicity of Dimethylethanolamine (cont.)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Endpoint Response	Comments	Reference
Mammalian Systems *In Vitro*							
CHO cells	SCE	-/+	DMAE, purity n.p.	0.1 to 0.3 mg/mL (1.1 to 3..3 µmol/mL)	Negative	Lowest concentration producing cell toxicity with metabolic activation was >3 mg/mL; without metabolic activation, 1 mg/mL. DMAE failed to produce clastogenic effects	Union Carbide (1988; cited by IUCLID, 1997)
CHO cells	SCE	-/+	DMAE, 99.9% pure	0.1 to 1.5 mg/mL (1.1 to 16.7 µmol/mL)	Negative	Positive controls consisted of ethyl methanesulfonate and dimethylnitrosamine. DMAE did not produce any statistically significant increase above control values.	Leung and Ballantyne (1997)
CHO cells	HGPRT forward gene mutation test	-/+	DMAE, 99.9% pure	0.1 to 2.0 mg/mL (1.1 to 22.2 µmol/mL)	Negative	Positive controls consisted of ethyl methanesulfonate and dimethylnitrosamine. DMAE induced some increases (2- to 3-times greater than concurrent controls) in mutation rates; however, increases were not dose-related and not repeatable. DMAE was not judged to be positive in this assay.	Leung and Ballantyne (1997)

Table 9. Genotoxicity of Dimethylethanolamine (cont.)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Endpoint Response	Comments	Reference
Mammalian Systems *In Vivo*							
Mouse, Swiss-Webster, adult M, F	Micronucleus test	n.a.	DMAE, 99.9% pure	i.p.: 270 to 860 mg/kg (3.00 to 9.60 mmol/kg)	Negative	Doses represent approximately 25%, 50%, and 80% of the LD_{50}. Triethylenemelamine was used as a positive control agent. No significant differences in polychromatic erythrocyte to normochromatic erythrocyte ratios were observer, nor were any significant increases in the incidence of micronucleated polychromatic erythrocyte observed at any dose level or sampling time.	Leung and Ballantyne (1997)

Abbreviations: CHO = Chinese hamster ovary; HGPRT = hypoxanthine-guanine phosphoribosyl transferase; n.a. = not available; n.p. = not provided; SCE = sister chromatid exchange

of 0.1 to 0.3 mg (1.0 to 3.3 µmol)/mL. A single *in vivo* test (micronucleus assay) for clastogenic potential of DMAE in Swiss-Webster mice was identified. No significant increases in the incidence of micronucleated polychromatic erythrocytes were observed at DMAE dose levels ranging from 270 to 860 mg/kg body weight (3.00 to 9.60 mmol/kg) (Leung and Ballantyne, 1997).

9.7 Cogenotoxicity

No studies related to the cogenotoxicity of DMAE or selected salts or esters were identified.

9.8 Antigenotoxicity

No studies related to the antigenotoxicity of DMAE or selected salts or esters were identified.

9.9 Immunotoxicity

DMAE was unable to covalently derivatize protein in an *in vitro* assay (Gauggel et al., 1993). It is thought that the ability to covalently derivatize protein enables some low-molecular-weight chemicals (LMWC) to induce allergic antibody-mediated responses that may cause asthma in people occupationally exposed to LMWC. In an unpublished ICI report (undated; cited by IUCLID, 1997), the ability of DMAE to act as a skin sensitizer was tested in the murine local lymph node assay at 0, 3, 10, and 30% w/v (0, 33, 110, and 330 mmol/L). The test resulted in test:control ratios of 0, 1.93, 2.13, and 14.50 respectively. Typically, ratios greater than 3 are indicative of potential sensitizers; therefore, based on this test, DMAE was classified as a potential skin sensitizer. Human experiences with DMAE under normal handling precautions have not supported this result. Similarly, DMAE, evaluated in the guinea pig maximation procedure, was without any clear evidence of skin sensitization (Leung and Blaszcak, 1998).

9.10 Other Data

<u>Nervous System Effects</u>

Several derivatives of DMAE have been synthesized and tested for their ability to modulate nervous system activity. *N*-Demethylated carbachol [also known as 2-(dimethylamino)ethyl carbamate] was recommended as a potentially useful ocular hypotensive agent based on its lack of acute toxicity in rabbits and dogs, ability to penetrate ocular tissues effectively, and ability to lower intraocular pressure of glaucomatous beagles (Chiou et al., 1980). Trzeciakowski and Chiou (1978) synthesized and tested 2-(dimethylamino)ethyl carbamate for cholinergic activity, *in vitro* and *in vivo*, finding that it was an effective stimulant, active at both muscarinic and nicotinic sites. Succinylcholine iodide [bis(2-(dimethylamino)ethyl)succinate dimethiodide], has curariform activity equal in intensity to that of *d*-tubocurarine chloride, as demonstrated by strong neuromuscular blocking action in cats, rabbits, and mice, though shorter in duration (Phillips, 1949; Castillo and Beer, 1950). Szabo (1989) isolated a macromolecule from adrenal gland and spleen with similar, though weaker, effects as acetylcholine. The author speculated that this macromolecule contained, preformed, the active agents, adrenaline and DMAE acetate.

Cellular Effects

The potential of DMAE to induce DNA synthesis *in vitro* has been investigated. NIH 3T3 clone-7 fibroblasts were treated with 0.1, 0.25, 0.5, or 1 mM (9.0, 22.0, 45.0, or 90.0 µg/mL) DMAE for 17 hours, with the addition of [methyl-^{3}H]thymidine for the last hour (Kiss and Crilly, 1996). DNA-associated ^{3}H-activity was measured; 0.5 and 1 mM (45.0 and 90.0 µg/mL) DMAE enhanced DNA synthesis 12- and 33-fold, respectively. When insulin (500 nM) was added to DMAE-supplement media, it was shown to greatly enhance the modest (15- to 20-fold) mitogenic effect of insulin. The mitogenic effects of insulin and DMAE were inhibited by both 100 nM wortmannin (55-60% inhibition) and 0.5 mM 8-bromo cyclic AMP (~90% inhibition), but not by the protein kinase C inhibitor GF 109203X (data not given).

In a related study (Kiss et al., 1996), NIH 3T3 clone-7 fibroblasts were treated with the protein kinase C inhibitor GF 109203X, followed by DMAE (0.1, 0.25, 0.5, 1, or 2 mM; 9.0, 22.0, 45.0, 90.0 µg/mL, or 180 µg/mL) for 17 hours (Kiss et al., 1996). DMAE at a dose of 1 mM (90.0 µg/mL) enhanced insulin-induced DNA synthesis ~ 8.4-fold. Detectable (~ 2-fold) enhancement of DNA synthesis occurred with 0.1 mM (9.0 µg/mL) DMAE alone, while maximal enhancement of DNA synthesis occurred with 1 mM (90.0 µg/mL) DMAE.

Malewicz et al. (1998) studied the potentiation of the stimulatory effects of insulin on DNA synthesis by DMAE *in vitro*. In NIH 3T3 cells overexpressing the Drosophila ethanolamine kinase, ethanolamine (50 to 200 µM) inhibited the mitogenic response induced by DMAE in the presence of insulin, supporting the hypothesis that phosphorylated and non-phosphorylated ethanolamines are negative and positive regulators of insulin-induced mitogenesis, respectively.

The mechanism by which apoptosis was prevented in docosahexaenoic acid-supplemented OLN 93 cells was investigated (Brand et al., 2001). OLN 93, a clonal line of oligodendroglia origin naturally low in docosahexaenoic acid, was made highly susceptible to oxidative stress when supplemented with docosahexaenoic acid, ultimately resulting in a high proportion of cell death by apoptosis (47% within 24 hours). Co-supplementation with 50 µM or 1 mM (4.5 or 90 µg/mL) DMAE reduced cell death from 48% to 6% (3 days) or 20% (20 hours). Exposures to 0.5 mM H_2O_2 (ten minutes) resulted in a rapid phosphorylation of extracellular signal regulated protein kinase 1 (ERK1). Whereas the phosphorylation of ERK1 in the docosahexaenoic acid-supplemented cells was persistent and accompanied by translocation to the nucleus where ERK1 could interact with transcription factors, levels of activated ERK1 in DMAE-supplemented cells was localized to the cytosol and declined rapidly. Prevention of translocation of activated ERK1 to the nucleus was thought to protect the cell from apoptosis (Yavin et al., undated-a and undated-b). Further studies (Brand and Yavin, 2001; Yavin et al., undated-b) suggested that DMAE supplementation reduced the synthesis of ethanolamine phosphoglycerides, prevented

its externalization to the outer membrane leaflet, and thereby rescued the cells from apoptotic death.

Membrane Effects

The content of polyunsaturated phosphatidylcholines represents one parameter by which one can regulate membrane function. Several groups have investigated methods to modulate incorporation of phosphatidylcholine in membranes. Alvaro et al. (1989) were able to enrich the phosphatidylcholines content in hepatic membranes by infusing DMAE (0.3 mg (3.3µmol)/kg/min, intravenously) in bile fistulated rats for 15 hours. Along with a significant ($p<0.01$) enrichment in phosphatidylcholines, there was a significant ($p<0.01$) decrease in the hepatic concentration of triacylglycerols. The specific activity of hepatic phosphatidylcholine approximated that of phosphatidyldimethylethanolamine, suggesting that DMAE was methylated after its incorporation into phosphatidyldimethylethanolamine (Alvaro et al., 1989).

Kaiho and Mizuno (1985) found that DMAE, at concentrations ranging from 10 to 100 µg/mL (110 to 1110 µM), was capable of inhibiting dimethylsulfoxide-induced differentiation of Friend leukemia cells, possibly due to modifications in the phospholipid composition of the cell membrane.

Yasumiba et al. (2001) infused bile-duct cannulated Sprague-Dawley rats intravenously with DMAE (0.01 mg /min/100grams body weight; 10 µmol/min/100 grams body weight) for 15 hours. DMAE treatment resulted in an increase in biliary phospholipid secretion, increased canicular membrane fluidity, and decreased biliary phospholipid hydrophobicity, without a change in its transporter activity, suggesting that canalicular membrane fluidity facilitates the transporter activity and/or phospholipid molecular movement from the canalicular outer membrane into the bile.

DMAE concentrations higher than 0.0001 M (9.0 µg/mL) blocked ecto-ATPase activity (Rybal'chenko et al., 1991) [Russian].

Tadros and Tucker (2002) of Sandia Corp. were awarded a European patent for a formulation to neutralize chemical warfare and biological warfare agents. DMAE and triethanolamine may serve as the solubilizing compound of the invention. The solubilizing compound renders the agent susceptible to attack by the reactive compound(s) of the formulation that serve(s) to detoxify or kill the CW or BW agent. Examples of the oxidative and/or nucleophilic reactive compounds were peroxides, quaternary ammonium salts, and sodium hypochlorite.

Life Extension Studies

The LifeExtension Foundation has included large number of abstracts on their website pertaining to treatments that may extend the lifespan of humans. Studies on the effects of DMAE,

Deaner®, and centrophenoxine, with the focus on centrophenoxine, on age-related processes were found among the abstracts and short articles. According the LifeExtension Foundation, centrophenoxine was shown to be effective in the reduction of age-associated accumulation of pigmentation in neurons, muscles cells, and skin cells. It is also used to increase brain energy through increased uptake of glucose, essential for energy production (LifeExtension Foundation, 2002). Many of the abstracts have been interpreted as supporting the membrane hypothesis of aging. This hypothesis suggests that age-dependent changes in the body may be explained as inevitable plasma membrane alterations that result in the accumulation of dry mass in the intracellular space of cells. By this hypothesis, the plasma membrane plays a central role in mitotic regulation, cell differentiation, and senescence (Zs-Nagy, 1997). Below is a summarization of results from abstracts found at the LifeExtension Foundation site (LifeExtension Foundation, undated, 1999, 2000, 2002) not previously covered in this report.

Treatment of mice with centrophenoxine (11- to 12-month-old, dose and duration not provided) or female 17-month-old mice (0.1 mg/g [1.0 µmol/g], daily, 3 months) in general reduced the accumulation of lipofuscin pigments [brown pigment characteristic of ageing found in lysosomes (Porta, 2002)] in the brain, and specifically in the cerebral cortex and hippocampus. Centrophenoxine treatment of the 11- to 12-month-old mice for three months also resulted in improvements in memory and learning in a T-maze. In the 17-month-old mice, the lipofuscin granules also appeared less osmiophilic and demonstrated a greater preponderance of membranes and vacuoles (LifeExtension Foundation, undated).

Long-term studies in mice have resulted in conflicting results regarding life extension. Hochschild has published three studies (1973a, b, c) reporting mean increases in lifespan ranging from 5.9% (32.8 mg/kg DMAE; 365 mmol/kg) to 49.5% increase (7 mg/kg DMAE; 80 µmol/kg) when exposed through the drinking water (LifeExtension Foundation, 1999, 2000). Treatment of mice with meclofenoxate (100 mg [390 µmol]/kg, daily), which is about 33% DMAE, resulted in 40% of treated mice surviving to 30 months. Only 8% of the control group survived to the end of the experiment (personal communication from K. Nandy, LifeExtension Foundation, 1999). Meclofenoxate (0.25 and 0.50% [2500 and 5000 mg/kg feed]) in the diet actually decreased life expectancy of treated mice (personal communication from D. Harman, LifeExtension Foundation, 1999). Estimated daily doses were in the range of 83 and 166 mg (0.92 and 1.85 mmol)/kg DMAE for the 0.25% and 0.50% treatment groups, respectively (LifeExtension Foundation, 1999).

A wider variety of parameters was observed in the rats than in the mouse. Although doses vary, the most common dosing regime for these experiments was 100 mg/kg daily for six to eight weeks. Older rats (>12 month-old) were typically used in the treatment groups. For the most part, reversions to adult or more youthful conditions were reported in most of these studies. For example, decreased deposition of neuronal lipofuscin, reversal in the age-related shift towards

higher molecular weight membrane proteins, increased microviscosity and decreased cholesterol content of synaptosomes in the brain, and a lack of reduction in the rates of total and polyA sup+RNA synthesis observed in the older, untreated rats (LifeExtension Foundation, undated).

Centrophenoxine (daily, 80 and 120 mg [0.30 and 0.410 mmol]/kg, six weeks) increased the activity of SOD, glutathione peroxidase (GSH-PER), and GSSG-RED glutathione reductase (GSSG-RED) in the particulate fractions from the cerebrum, cerebellum, and brain stem from of rats aged six, nine, and twelve months. Only SOD and GSH-PER activity was increased in the soluble fractions. The author suggested that the reduction in lipofuscin was related to the increased activities of these antioxidant enzymes (LifeExtension Foundation, undated).

The trend towards an increase in molecular weight of membrane proteins was thought to be a result of increased cross-linking of membrane proteins as part of the aging process. Prevention by centrophenoxine was attributed to the free-radical scavenging properties of the DMAE moiety of centrophenoxine. Likewise, lateral diffusion coefficients of proteins were investigated. These coefficients typically decrease with age. Centrophenoxine resulted in an increase in lateral diffusion coefficients, but only in old (24- or 26-month-old) rats (LifeExtension Foundation, undated).

Centrophenoxine also induced some neurological changes in 12- to 24-month-old Wistar rats. Treatment resulted in an increase in multiple unit activity (action potentials derived simultaneously from a number of neurons in a given brain region) in the parietal cerebral cortex of rats. The normal age-related trend is toward a decrease in multiple unit activity (LifeExtension Foundation, undated).

On a subcellular level, centrophenoxine treatment caused a marked increase in the surface density of synaptic junctions. In older rats (27 months) daily treatments for six weeks was associated with an increase in the length of the synaptic junctions, while 18-month-old rats, treated tree times per week for five months failed to demonstrate the normal age-dependent reductions in numerical density of the synaptic junctions (LifeExtension Foundation, undated). On a histological level, the nucleolus of Purkinje neurons were found to be hyperactive, as demonstrated by budding and extrusions. Frank regeneration of the Nissl patches was observed along with increased α-esterase and decreased acid phosphatase activity in the cerebella of senile white rats treated with centrophenoxine for 60 days (LifeExtension Foundation, undated).

9.11 Toxicity of Complex Mixtures

The dermal and ocular toxicity of a chemical mixture containing 8% dimethylethanolamine, ~ 47% isobutyl alcohol, and 42% ethanol, 2-(dimethylamino,4-methylbenzenesulfonate) (salt) was evaluated in New Zealand albino rabbits (American Cyanamid, 1991). For the dermal study, the rabbits were administered 0.5 mL of the chemical mixture on one intact and one abraded site on

clipped dorsal skin (1.0 mL total dose/rabbit; skin was occluded) for four hours. Rabbits were evaluated for irritation at 1, 24, 48, and 72 h post-exposure. On a scale of 0 to 4 (Draize dermal scoring method), the chemical mixture scored a 0 for dermal irritation. For the ocular irritation study, each rabbit had 0.1 mL of the chemical mixture placed into the conjunctival sac of the left and right eyes. Twenty to 30 seconds post-exposure, the left eye was flushed with water; the right eye was not washed. Eyes were evaluated 1, 24, 48, and 72 hours, and 7 days post-exposure. Corneal opacity, iritis, and moderate to severe conjunctival irritation persisted through day 7 in washed and unwashed eyes.

9.12 DMAE and Choline

Choline, recently classified as an essential human nutrient, plays a critical role in the structural integrity of cell membranes as a precursor in the biosynthesis of the phospholipids, phosphatidylcholine, and sphingomyelin. Both phosphatidylcholine and sphingomyelin are precursors of the intracellular messenger molecules diacylglycerol and ceramide; therefore choline also plays a role in intracellular signaling. Platelet activating factor (PAF) and sphingophosphorylcholine, metabolites of choline, also have cell-signaling properties (Oregon State University, 2000; Hendler and Rorvik, 2001a). Perturbations in choline metabolism will affect a range of cellular structures and functions.

Absorption, Distribution, Metabolism, and Excretion

Naujokaitis et al. (1984) conducted a study on the ability of DMAE and some of its analogues to inhibit choline uptake in murine L1210 leukemia cells. DMAE (200 µM for 20 minutes) was found to be the most potent inhibitor of choline uptake.

Synergistic/Antagonistic Effects

Pretreatment of rats with Tonibral (80 mg/kg [0.50 mmol/kg], intraperitoneally) one hour prior to cooling (48 hours at -15° C) inhibited cold-induced decreases in epinephrine, norepinephrine, and dopamine in heart and other muscle tissues (Filatova et al., 1986). Haubrich et al. (1981) reported that DMAE acted as a choline oxidase inhibitor and markedly inhibited rates of oxidation and phosphorylation of intravenously administered [^{3}H-methyl]choline in the mouse kidney (strain not provided). Co-injection of 5 mM (450 µg/mL) DMAE and [^{14}C]choline via the renal artery of male Sprague-Dawley rats reduced renal medullary betaine accumulation by 80% relative to control values (Moeckel and Lien, 1997). In isolated perfused kidneys, DMAE (3.0 to 5.0 mM; 270 to 450 µg/mL) significantly decreased both the rate of [^{14}C]choline removal and the rate of [^{14}C]betaine addition to the perfusate. DMAE (5.0 mM; 450 µg/mL) significantly inhibited [^{14}C]betaine production in cortical, outer, and inner medullary regions of rat kidney in tissue slice experiments (Lohr and Acara, 1990). In the liver, however, DMAE only inhibited the rate of phosphorylation. Overall, DMAE treatment resulted in increased blood choline levels, possibly by inhibiting metabolism of choline in peripheral tissues (Haubrich et al., 1981).

Reproductive and Teratological Effects

Although able to synthesize choline from phosphatidylethanolamine, mammals do not synthesize enough to meet the needs of the body and require dietary supplementation, especially during pregnancy, lactation, and periods of rapid growth. Choline-deficient diets may result in growth retardation, renal dysfunction and hemorrhage, or bone abnormalities in animals (Zeisel, 2000).

In an oral feeding study, pregnant rats were either maintained on a choline deficient diet or a choline deficient diet supplemented with 0.8% choline chloride, 1% DMAE, or 1% monomethylethanolamine from gestation-day six through two weeks postpartum. Pregnancies progressed to term equally well for all treatment groups and litters of similar sizes were delivered. However, only 18/253 offspring of rats exposed to DMAE, survived for more than 36 hours after birth, whereas all offspring of control rats survived to 15 days (end of observation period). Pups born to dams fed the DMAE-supplemented diet demonstrated moderate degrees of glycogen and fatty infiltrations in their livers. Measurable amounts of DMAE (72.2 ± 12.7 nmol/g) were observed in the brains of pups from DMAE-supplemented dams. No DMAE was found in the brains of pups from choline-deficient diets or choline-supplemented diets. Levels of choline and acetylcholine in the brains were elevated 53% and 36% in pups from the DMAE-supplemented group, relative to the choline-deficient pup brains. Distributions of phosphatidyl choline (38.9%) and phosphatidyl aminoethanol (16.2%) from the brains of DMAE-supplemented pups were markedly lower than from pups derived from the choline-deficient (52.4% and 25.3%, respectively) or choline-supplement groups (52.4% and 22.7%, respectively) (Zahniser et al., 1978).

Fisher et al. (2001, 2002) reported that the DMAE-induced perturbations of choline uptake and metabolism caused neural tube defects and craniofacial hypoplasia in neurulating mouse embryos *in vitro*. Incubation of mouse embryos (harvested at gestation-day nine) for 26 hours in DMAE-containing medium (0, 250, 375, 500, or 750 µM; 0, 22.5, 33.7, 45.0, or 67.0 µg/mL) resulted in a statistically significant, dose-dependent increase in malformation rate and severity. Malformations included neural tube defects, caudal dysgenesis, craniofacial hypoplasia, and abnormal circulation. Average embryonic protein content was also reduced, significantly so in the 375 µM (33.7 µg/mL) and above DMAE treatment groups. Analysis of [^{14}C]choline uptake by the embryos and yolk sacs indicated that DMAE-treatment reduced choline uptake by 70% in the 375 µM group (33.7 µg/mL), relative to untreated control embryos. Staining with LysoTracker Red stain failed to demonstrate elevated cell death in embryos incubated with 375 µM (33.7 µg/mL) DMAE for up to 26 hours.

Follow-on studies to investigate the impact of choline metabolism and to identify mechanisms associated with growth and developmental abnormalities caused by DMAE were conducted in gastrulation/neurulation stage mouse embryos. DMAE (375 µM; 33.7 µg/mL) decreased the

incorporation of [^{14}C]choline into phosphocholine, phosphatidylcholine, and sphingomyelin to 25%, 35%, and 50% of control values, respectively. Labeled betaine was threefold higher in the DMAE-treated embryos than in the control embryos. Reduced phosphatidylethanolamine synthesis from [^{3}H]ethanolamine was noted in both treated embryos and yolk sac. DMAE treatment produced a 15% increase in embryonic ceramide, an important cell-signaling molecule (Fisher et al., 2002).

Buznikov et al. (2001) [Russian] reported that DMAE esters of polyenoic fatty acids inhibited the actions of choline esters of polyenoic fatty acids on sea urchin embryos and larvae. The choline esters blocked cell divisions, which led to "formation of one-cell multinuclear embryos." When choline esters were "added at the mid or late blastula stage," many extruded cells formed "extra-embryonic cell clusters near the animal pole of embryos or larvae."

Co-Carcinogenicity

LM fibroblasts (LM primary tumor cells derived from a subline of Earle's L cell, clone 929) were adapted to grow in chemically defined media without serum. When grown in DMAE-containing, serum-free medium, LM cells incorporated DMAE into membrane phospholipids (Kier and Schroeder, 1982). When the cells were injected into nude mice, the frequency of lung metastasis was 46% compared to frequencies of 74% and 68% for serum- and choline-fed cells, respectively. Choline-, DMAE-, and serum-cultured cells induced extensive, highly invasive metastases (Kier et al., 1988).

Other Data

Phosphatidylcholine, a component of the class of lipoproteins known as very low-density lipoproteins (VLDL), is important in the transport of fat and cholesterol from the liver to tissues that require them. Addition of DMAE or monomethylethanolamine to cultured hepatocytes isolated from choline-deficient rats resulted in the biosynthesis of phosphatidyldimethylethanolamine or phosphatidylmonomethylethanolamine in the place of phosphatidylcholine. Phosphatidyldimethylethanolamine corrected, to a limited extent, the choline-deficient reduction in VLDL secretion; however, phosphatidylmonomethylethanolamine inhibited VLDL secretion entirely. Supplementation of these cultured hepatocytes with ethanolamine failed to improve VLDL secretion. Overall, the results suggested that the choline head-group moiety of phosphatidylcholine is specifically required for normal VLDL secretion (Yao and Vance, 1989). Without VLDL secretion, fat and cholesterol accumulate in the liver, producing liver damage (Oregon State University, 2000).

Choline deficiency results in the depletion of intracellular methyl-folate and methionine with a simultaneous increase in intracellular *S*-adenosylhomocysteine and homocysteine concentrations (Zeisel, 2000). Elevated homocysteine levels are a significant risk factor of atherosclerosis and other cardiovascular and neurological disorders (Hendler and Rorvik, 2001a).

10.0 Structure-Activity Relationships

10.1 Di- and Triaminoethanols

Stenbäck et al. (1988) noted that di- and triaminoethanols, which are structurally related to DMAE and are found in cutting fluids, pesticides, and cosmetics, can give rise to *N*-nitrosodiethanolamine (NDELA) via nitrosation resulting from reaction with nitrite or nitrous oxide. The authors also noted that NDELA has been shown to be a potent carcinogen, producing mainly hepatocellular carcinomas in rats and epithelial neoplasms of the nasal cavity and trachea in hamsters. Based on these data, Stenbäck et al. (1988) suggested that "if [dimethylethanolamine] were similarly nitrosated, the resulting nitrosamine might be carcinogenic."

10.2 Ethanolamine [141-43-5]

Human Toxicity

Ethanolamine has had wide industrial use without reports of human injury. Undiluted ethanolamine applied on gauze to human skin resulted in marked redness after 90 minutes (Browning, 1953; cited by Beard and Noe, 1981).

Chemical Disposition, Metabolism, and Toxicokinetics

Ethanolamine is naturally found in mammals and is a normal constituent of urine (Luck and Wilcox, 1953; cited by Beard and Noe, 1981). A slight gender-dependent variation in excretion rates has been noted in humans, with a mean excretion rate of 0.492 mg/kg/day for women (n =11; range = 7.7 to 34.9 mg/kg/day) versus 0.162 mg/kg in men (number not provided; range = 4.8 to 22.9 mg/day). Excretion rates for cats, rats, and rabbits were 0.47, 1.46, and 1.0 mg/kg/day, respectively (Luck and Wilcox, 1953; cited by Beard and Noe, 1981).

[^{15}N]-Ethanolamine (40% of administered dose) was excreted in the urine of rabbits within 24 hours of administration as urea, suggesting it was deaminated. Ethanolamine is also methylated to choline and metabolized to form serine and glycine (Beard and Noe, 1981).

In the perfused hamster heart, it was shown that at low exogenous concentrations of ethanolamine ($\leq$ 0.1 μM) the conversion of phosphoethanolamine to cytidine diphosphate ethanolamine was the rate-limiting step; as concentrations increased ($\geq$ 0.4μM) phosphorylation of ethanolamine became rate limiting. It also appeared that newly imported (exogenous) ethanolamine was preferentially used over endogenous ethanolamine for the synthesis of phosphatidylethanolamine (McMaster et al., 1992).

Massarelli et al. (1988) demonstrated that both cultured rat and chick neurons were able to methylate ethanolamine phospholipids, free ethanolamine, or phosphorylethanolamine to form choline. In addition, the authors were able to demonstrate that the newly synthesized choline was used in the synthesis of acetylcholine, even in the presence of HC-3, an inhibitor of

transmembrane transport of choline, in the chick neurons.

Animal Toxicity

In a subchronic oral toxicity study (90-day), 1.28 g/kg resulted in lethality and microscopic pathological changes in rats. Changes in liver or kidney weight were observed at 0.64 g/kg while doses of 0.32 g/kg and lower were without effect (Smyth, 1956; cited by Beard and Noe, 1981). Treon et al. (1949; cited by Beard and Noe, 1981) reported an acute LD_{50} of 2.74 g/kg (species not given).

Early inhalation studies conducted by Treon et al. (1958; cited by Beard and Noe, 1981) reported exposing mice, rats, guinea pigs, rabbits, cats, and dogs to ethanolamine concentrations ranging from 0.26 to 2.47 mg/L. Guinea pigs appeared to be most susceptible to the toxic effects, with four of six succumbing to 0.58 mg/L for one hour. Sixty of 61 rats, rabbits, and mice survived exposures to 0.26 and 0.27 mg/L, seven hours/day, for five consecutive days; 25 of 26 survived 25 seven-hour exposures to 0.26 mg/L ethanolamine over a five-week period. Dogs and cats survived exposures to 2.47 mg/L, seven hours/day, for four consecutive days. The primary effects included respiratory tract irritation and some nonspecific degenerative changes in the liver and kidneys. Longer duration studies (up to 90 days) by Weeks (1958; cited by Beard and Noe, 1981) indicated that dogs, rats, and guinea pigs survived 90-day exposures to 12 to 25 ppm. Fractional mortality was reported in dogs at 100 ppm on days 24 to 30 and in rodents at 66 to 75 ppm. Skin irritation and lethargy was observed at five and twelve ppm. Ethanolamine applied directly to the eye (rabbit) resulted in severe damage (Carpenter and Smyth, 1946; cited by Beard and Noe, 1981).

Carcinogenicity

LM fibroblasts grown in the presence of ethanolamine resulted in fewer lung metastases in the nude mouse, possibly due to modifications of surface membrane components, relative to the metastases induced by trimethylethanolamine-supplemented serum (Kier and Schroeder, 1982). The metastases formed lung emboli without invasions into neighboring tissues.

Other Data

The addition of 1 or 2 mM ethanolamine to NIH 3T3 cells produced a slight (4.5- to 5-fold) increase in DNA synthesis. The combination of ethanolamine (1 mM) and insulin (500 nM) increased insulin-induced DNA synthesis by only 2.1-fold. The addition of choline (1 or 5 mM) enhanced even further the combined effects of ethanolamine and insulin. Inhibitors of protein kinase C (GF 109203X or staurosporine) enhanced the combined effect of ethanolamine and insulin, causing the authors to speculate that the signal transduction pathway induced by these chemicals is inhibited by protein kinase C (Kiss and Crilly, 1996; Kiss et al., 1996).

Ethanolamine, unlike monoethylethanolamine or dimethylethanolamine, failed to inhibit

dimethylsulfoxide-induced cell differentiation in Friend leukemia cells until concentrations of 100 µg/mL were reached. At that dose ethanolamine inhibited cell growth; therefore, any effects on cell differentiation was likely due to the inhibitory effects on cell growth (Kaiho and Mizuno, 1985).

Tumors derived from LM cells grown on ethanolamine-supplemented serum and injected into nude mice had significant reductions in the specific activity of ($Na^+ + K^+$)-ATPase (41.3 ± 3.6 nmol/minute per mg, $p<0.05$), NADH-dependent cytochrome-*c* reductase (299 ± 27 nmol/minute per mg, $p<0.025$), rotenone-insensitive NADH-dependent cytochrome-*c* reductase (276 ± 24 nmol/minute per mg, $p<0.025$), and rotenone-sensitive NADH-dependent cytochrome-*c* reductase (59 ± 6 nmol/minute per mg, $p<0.05$), relative to choline-supplemented serum. Significant changes were also observed in the fatty acid composition of plasma membranes, microsomes, and mitochondria, with significant increases in saturated fatty acids of 16 and 18 carbons in length in the microsomes and mitochondria, accompanied by significant reductions were found in the 18 carbon-length unsaturated fatty acids. Ethanolamine-supplemented serum produced a significant reduction in the ratio of unsaturated:saturated fatty acids (Kier et al., 1988).

10.3 Diethanolamine [111-42-2]

Human Toxicity

The National Toxicology Program (NTP) recently published a background document on diethanolamine supporting the 11th Report on Carcinogens on the Internet (http://ntp-server.niehs.nih.gov/newhomeroc/roc11/DEAPub.pdg). Studies investigating an association between diethanolamine exposures and increased cancer incidence *per se* were not identified. However, ethanolamines have been added to metalworking fluids (cutting fluids). Ethanolamines, primarily diethanolamine and triethanolamine, act as corrosion inhibitors in soluble, semisynthetic, and synthetic cutting fluids. They may also be added to adjust the pH of the cutting fluids. Diethanolamine has been documented at 1% to 4% levels in bulk machining fluids (Kenyon et al., 1993; cited by NTP, 2002).

The most consistent results from twelve human cancer studies was a small excess in stomach cancers, reported in a UAW/GM cohort (synthetic fluids), engine workers in Detroit (crankshaft workers exposed to synthetic fluids) and in Cleveland (grinding with semisynthetic fluids), and bearing manufacturing workers in Sweden and two sites in Connecticut (grinders exposed to soluble, synthetic, or water-based fluids). Synthetic metalworking fluids were also associated with weak to moderate risks for cancer of the liver (moderate), esophagus (moderate), pancreas (moderate), prostate (weak), larynx (weak), and hematopoietic system (leukemia, weak) (NTP, 2002).

Machining fluids represent a complex mixture, of which diethanolamine is only a single component. Other components may include biocides such as triazine, chlorinated compounds, metals, and sulfur compounds. In addition, nitrates may be added to the synthetic cutting fluids, potentially forming *N*-nitrosodiethanolamine (NTP, 1992). Therefore, attribution of increased cancer incidence specifically to diethanolamine is difficult (NTP, 2002).

The IARC Working Group concluded that there was inadequate evidence of carcinogenicity of diethanolamine in humans (IARC, 2000; cited by NTP, 2002).

Absorption, Disposition, and Excretion

Radiolabeled diethanolamine was found to be absorbed following intravenous, dermal, and oral administration to male F344 rats. Although the primary route of elimination was via the urine, this route accounted for only a fraction of the administered radioactivity. Most of the label was retained in tissues, primarily within the liver and kidneys. Dermal absorption of diethanolamine ranged from 3% (2.1 mg/kg) to approximately 16% (27.5 mg/kg). A doubling of the proportion of radiolabel associated with fecal elimination was observed after oral administration of diethanolamine, but still represented only about 2.5%. Some of the radiolabel found in the feces may have been unabsorbed material. Oral exposures for up to eight weeks suggested tissue accumulation of diethanolamine reached steady state concentrations at about four weeks. The elimination half-life was estimated at one week (NTP, 1992).

Similar, but less extensive, studies were performed with $B6C3F_1$ mice, with very similar results. Absorption of diethanolamine from mouse skin was significantly greater (about 60%) than observed with rats; however, larger doses were used in the mouse studies, making direct comparisons meaningless.

Animal Toxicity

Ranges for oral LD_{50}s for diethanolamine in rats have been reported at 780 to 1820 mg/kg (Beard and Noe, 1981; NTP, 1992). For mice, the LD_{50} for intraperitoneal and subcutaneous exposures was 2300 and 3553 mg/kg, respectively. Toxic symptoms included increased blood pressure, diuresis, salivation, and papillary dilation. Twenty mg/kg, administered over a 90-day period of time (species not provided) was the highest daily dose without adverse affects (Beard and Noe, 1981). Long-term (90 days) dietary exposures to 170 mg/kg resulted in uncharacterized microscopic lesions and death. At 90 mg/kg, alterations in liver weight occurred. Mild skin irritation was noted in rabbits at concentrations exceeding 5%; 50% concentrations produced severe ocular irritation (Beard and Noe, 1981; NTP, 1992). Undiluted and 40% diethanolamine produced severe eye burns. Dilution to 15% and 10% resulted in minor eye damage and redness, respectively, in the rabbit (Sutton, 1963; Carpenter and Smyth, 1946; both cited by Beard and Noe, 1981).

Diethanolamine administered either orally (single injection, 100 to 3200 mg/kg; Korsrud et al., 1973) or via inhalation (25 ppm, continuously, 216 hours; Hartung et al., 1970) to rats resulted in increased relative and absolute liver weights, respectively. The inhalation exposure was associated with elevated serum glutamic oxaloacetic transaminase (SGOT) activity. Oral exposures produced minimal parenchymal cell damage (200 to 1600 mg/kg) and large lipid droplets and focal cytoplasmic degeneration (1600 mg/kg) in hepatocytes. Hruban et al. (1965; cited by NTP, 1992) reported large vacuoles and fat droplets associated with hepatocytes along with ultrastructural changes in the endoplasmic reticulum and mitochondria from livers of rats treated for one to four days with 1000 mg/kg/day.

Renal changes included increased absolute (250 mg/kg, repeated intraperitoneal; 6 ppm, 8 hours per day, 13 weeks) (Hartung et al., 1970; cited by NTP, 1992) and relative tissue weights (100 to 3200 mg/kg, single oral), necrosis and cytoplasmic vacuolization of the renal tubular epithelium (Grice et al., 1971; cited by NTP, 1992), and increased blood urea nitrogen levels (25 ppm, 216 hours). Other toxic effects reported included depletion of zymogen granules and disruption of rough endoplasmic reticulum into vacuoles in pancreatic acinar cells and normocytic anemia without bone marrow depression or increased reticulocyte counts (NTP, 1992).

Lehman-McKeeman et al. (2002) tested the hypothesis that diethanolamine exposure would result in biochemical changes consistent with induced choline-deficiency in mice. Male B6C3F1 mice were exposed to diethanolamine, either through the diet (choline-devoid or control diet containing 0.25% choline) or dermally (0, 10, 20, 40, 80, or 160 mg/kg/day) for two or four weeks, respectively. After two weeks of exposure to diethanolamine in the diet, analysis of hepatic choline metabolites revealed a significant reduction in phosphocholine, glycerophosphocholine, choline, phosphatidylcholine, and *S*-adenosylmethionine. Phosphocholine was the most sensitive to the effects of diethanolamine, with a 75% reduction at the end of two weeks. *S*-adenosylmethionine was reduced by 20% relative to control animals. Despite the presence of biochemical changes in the hepatic choline metabolites, body weight gain and liver weights were unaffected. Changes in clinical parameters were restricted to total bile acids and serum triglycerides. The latter showed a 50% reduction (41 ± 12 mg/dL in the diethanolamine treated group versus 97 ± 12 mg/dL in the control group). Despite the biochemical evidence indicative of choline deficiency, there was no evidence of fatty livers in the treated animals.

Dermal application of diethanolamine (five day per week for four weeks) resulted in a dose dependent reduction in phosphocholine (significant at 20 mg/kg/day; 50% at 160 mg/kg/day), glycerophosphocholine (significant at 40 mg/kg/day; approximately 50% at 160 mg/kg/day), and choline. Phosphatidylcholine concentrations were reduced only at the highest concentration of diethanolamine. Unlike the dietary exposures, serum triglyceride levels were not altered with

dermal application. There was no evidence of fatty livers in the treated animals (Lehman-McKeeman and Gamsky, 1999).

Carcinogenicity

The National Toxicology Program (NTP, 1998) investigated the dermal carcinogenic potential of diethanolamine in male (0 to 64 mg/kg in ethanol) and female (0 to 32 mg/kg ethanol) F344/N rats and male and female $B6C3F_1$ mice (0 to 160 mg/kg in ethanol), dosed over a two-year period. Overall toxicity in the male rats became apparent at eight weeks in the 64 mg/kg dose group, as demonstrated by lower mean body weights relative to the vehicle control groups. Irritation at the site of application was the only clinical finding associated with dermal application of diethanolamine to rats. Pathological findings included minimal to mild nonneoplastic lesions in the epidermis at the site of applications (rats, both sexes). Incidences of acanthosis (64 mg/kg, male rats), hyperkeratosis (32 and 64 mg/kg, male rats; all dose groups, female rats), and exudates (64 mg/kg, male rats; all dose groups, female rats) were greater than incidences in control groups. Dosed female rats had an increased incidence and severity of nephropathy relative to vehicle control groups. It was concluded that there was no evidence of carcinogenic activity in male or female F344/N rats at these dose levels (NTP, 1998).

In the mice, survival of dosed females was significantly less that the vehicle control group. Body weight reductions relative to the vehicle control groups were observed in all female dose groups during the second year of the study. Reductions in the mean weight of male mice began in weeks 88 and 77 for dose groups 80 and 160 mg/kg, respectively (NTP, 1998).

A significant increase in the incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) was observed in all dosed groups of mice; hepatocellular carcinoma and hepatoblastoma were significantly higher in the 80 and 160 mg/kg male treatment groups relative to vehicle controls. Hepatocellular neoplasms were also significantly greater in the dosed female mice than in the vehicle control groups. The incidences of hepatocellular neoplasms in all dosed groups (males and females) exceeded the historical control range. Nonneoplastic changes observed in dosed mice included cytoplasmic alteration and syncytial alteration.

In the kidneys of treated mice, a positive trend was observed for renal tubule adenoma, but not for carcinoma and hyperplasia. Combining single and step kidney analyses revealed a dose-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma or carcinoma (combined), and an increase in the incidences of renal tubule adenoma in male mice. An increased incidence in thyroid gland follicular cell hyperplasia was found in dosed male and female mice relative to vehicle controls. As with the dosed rats, dose-related incidence of hyperkeratosis, acanthosis, and exudates were found at the site of application, with hyperkeratosis being significantly increased in the 80 and 160 mg/kg dose groups, relative to vehicle control groups. The NTP concluded that, based on increased incidences of liver

neoplasms (male and female mice) and renal tubule neoplasms (male mice), there was clear evidence for carcinogenic activity of diethanolamine in both male and female $B6C3F_1$ mice at the exposure levels used (NTP, 1998).

Lehman-McKeeman and Gamsky (2000) investigated whether cell transformation of Syrian hamster embryo (SHE) cells and the carcinogenicity associated with exposures to diethanolamine was mechanistically related to intracellular choline deficiency. SHE cells were exposed to diethanolamine, in the presence and absence of excess choline (30 mM). Diethanolamine (500 µg/mL) in the culture media resulted in a reduced incorporation of ^{33}P into phosphatidylcholine to 14 ± 2% relative to 43 ± 1% found in the unexposed SHE cells. Choline uptake by the SHE cells was inhibited in a concentration-dependent fashion in the presence of diethanolamine, with maximal inhibition (85%) occurring at 500 µg/mL diethanolamine. After a seven-day exposure to ^{14}C-diethanolamine, approximately 12% of the intracellular diethanolamine was associated the lipid fraction. Thin-layer chromatography of the lipid fraction confirmed that the ^{14}C-diethanolamine was incorporated into the phospholipids. Incubation of SHE cells in the presence of both diethanolamine and excess choline (30 mM) prevented the incorporation of diethanolamine into phospholipids.

Genotoxicity

Diethanolamine, tested in four strains of *Salmonella typhimurium*, in L5158Y mouse lymphoma cells, and in Chinese hamster ovary cells (with and without a metabolic activation system) failed to demonstrate any evidence of genotoxicity. It also failed to induce an increase in micronucleated normochromatic erythrocytes in the peripheral blood samples collected from male and female mice exposed to 80 to 1250 mg/kg diethanolamine, dermally for 13 weeks (NTP, 1998). In a single transformation study in SHE cells, diethanolamine tested positive after a seven-day exposure (Lehman-McKeeman and Gamsky, 2000).

Cellular Effects

A loss in cellular respiratory control was observed in hepatic mitochondria isolated from male Sprague-Dawley rats treated with diethanolamine in the drinking water (42, 160, or 490 mg/kg/day) for one, two, or three weeks, but not when exposed for 24 hours (Barbee and Hartung, 1979).

10.4 Monomethylethanolamine [109-83-1]

Animal Toxicity

Acute oral LD_{50} values for male and female rats were cited as 1908 and 1391 mg/kg, respectively, and not considered to be significantly different from each other. Lethality was associated with chromodacryorrhea, ataxia, and gastrointestinal hypermotility and diarrhea. Intraperitoneal LD_{50}s for the rat and mouse were 1330 and 125 mg/kg, respectively. Administered subcutaneously in the mouse, monomethylethanolamine resulted in a LD_{50} of 1802 mg/kg and

affected both the seizure threshold (producing comas) and respiration (RTECS, 1999a). The dermal LD_{50} in rabbits was 1070 µL/kg, producing somnolence, respiratory effects, and dermatitis. Ballantyne and Leung (1996) classified monomethylethanolamine as having moderate acute percutaneous toxicity, with LD_{50}s for male and female New Zealand White rabbits of 1880 and 1006 mg/kg, respectively. Toxic symptoms included sluggishness, unsteady gait, emaciation, and prostration. Moderate to severe erythema and edema with ecchymoses, necrosis, and ulceration occurred at the application site, progressing to desquamation, alopecia and scaring. Dark red mottled lungs, dark red livers, and mottled kidneys were found on necropsy of animals that died. Inhalation exposure of rats to a saturated atmosphere of monomethylethanolamine failed to induce lethality within six hours.

In irritancy studies, monomethylethanolamine produced a moderate to marked erythema and edema that was slowly resolving. Monomethylethanolamine was classified as skin corrosives, inducing full-thickness necrosis. Monomethylethanolamine also caused a severe hyperemia of the conjunctivae accompanied by edema and profuse discharge within one hour of application to the eye. Within one hour, up to 75% of the surface are of the cornea became severely opaque; 100% of the surface area was affected at seven days post-application. Necrotic areas in the conjunctivae and nictating membrane, corneal neovascularization, and corneal ulceration were also observed. The iris was not visible due to the marked keratitis (Ballantyne and Leung, 1996).

Applied to the skin of rabbits, monomethylethanolamine (470 mg) was classified as a mild irritant (Ballantyne and Leung, 1996; RTECS, 1999a).

Synergistic/Antagonistic Properties

In an *in vitro* hamster perfusion study, McMaster et al. (1992) found that the presence of 0.5 mM monomethylethanolamine in the perfusate significantly inhibited the uptake of radiolabeled-ethanolamine. Further analysis indicated that the radioactivity associated with the ethanolamine fraction was not significantly different; however, the radioactivity associated with the phosphoethanolamine and cytidine diphosphate ethanolamine were decreased to 33% and 63%, respectively, relative to control values. The authors suggest that monomethylethanolamine not only inhibited the uptake of ethanolamine, but also inhibited the activity of ethanolamine kinase.

Reproductive and Teratological Effects

No maternal or fetal toxicity was associated with maternal exposures to 150 ppm seven hours a day from gestation day seven through fifteen (Nelson et al., 1984).

Zahniser et al. (1978) reported a teratology study where pregnant dams were exposed to one of four diets (choline-deficient, choline deficient supplemented with 0.8% choline, choline-deficient supplemented with 1.0% monomethylethanolamine, or choline-deficient supplemented with1% DMAE) beginning on gestation day six through 15 days post-partum. Feed consumption was

fairly equal for all diets, except the monomethylethanolamine diet, where average daily intake (9.1 g) was less than half the average intake of the other diets (22.1 to 23.4 g/day). The decreased feed intake was reflected in the average daily weight gain (2.9 g) relative to 6.3 to 7.9 g average weight gains for the other treatment groups. Although all pregnancy progressed normally, with an average of 12 pups delivered per litter, the pups from the monomethylethanolamine group weighed significantly less (5.4 ± 0.28 g, $p < 0.05$) relative to the choline-deficient group (6.1 ± 0.2g). None of the 120 pups from the ten monomethylethanolamine-supplemented litters survived past 36 hours postpartum. Upon histopathological examination, pups from the monomethylethanolamine group showed a moderate degree of glycogen and fatty infiltrations in their livers.

Measurable (11.7 ± 1.8 nmol/g) amounts of DMAE were detected in the brains of monomethylethanolamine-exposed pups (one-day-old). DMAE was undetectable in the choline-deficient or choline-supplemented pups. Monomethylethanolamine-supplementation resulted in elevated levels of both choline (43%) and acetylcholine (27%) when compared to levels detected in the choline-deficient derived pups. However, when looking specifically at the cortical and striatal levels of acetylcholine, the monomethylethanolamine-treated group was not different from the choline-deficient pups. Significant differences were observed in the relative content of individual phospholipid in the brains. Sphingomyelin and phosphatidic acids were lower in the brains from pups on the choline-deficient diets. In the monomethylethanolamine-supplemented pups, phosphatidylcholine and phosphatidyl aminoethanol levels in the brain were significantly ($p<0.05$) lower relative to the choline-deficient-fed pups (Zahniser et al., 1978).

Carcinogenicity

LM fibroblasts grown in the presence of monomethylethanolamine resulted in fewer lung metastases (42%) in the nude mouse relative to the metastases induced by serum- or choline-supplemented serum (74% and 68%, respectively), possibly due to modifications of surface membrane components. Metastases from monomethylethanolamine-supplemented LM fibroblasts produced only embolus formation without invasion of local tissues (Kier and Schroeder, 1982; Kier et al., 1988).

Genotoxicity

Monomethylethanolamine was found to be nongenotoxic when tested in the presence and absence of a metabolic activation system in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and/or TA97 (Zeiger et al., 1987).

Immunotoxicity

In a study including four alkylalkanolamines (monomethylethanolamine, DMAE, *N*-methyldiethanolamine, and *N,N*-diethylethanolamine), only monomethylethanolamine demonstrated a positive response in the guinea pig maximation test, though the reaction was

weak and transient. Based on the Magnusson-Kligman Allergenicity Rating, monomethylethanolamine was classified as having a mild potential to produce skin sensitization in guinea pigs (Leung and Blaszcak, 1998).

Other Data

The addition of 1mM monomethylethanolamine to NIH 3T3 cells produced a ten-fold increase in DNA synthesis. The combination of monomethylethanolamine (1 mM) and insulin (500 nM) increased insulin-induced DNA synthesis by almost six-fold. Furthermore, the addition of choline (1 or 5 mM) further enhanced the combined effects of monomethylethanolamine and insulin without potentiating the mitogenic effects of monomethylethanolamine alone. Inhibitors of protein kinase C (GF 109203 X or staurosporine) enhanced the combined effect of monoethanolamine and insulin, causing the authors to speculate that the signal transduction pathway induced by these chemicals is inhibited by protein kinase C (Kiss and Crilly, 1996; Kiss et al., 1996).

Exposure of Friend leukemia cells to monomethylethanolamine at 10 µg/mL, either prior to or simultaneously with dimethylsulfoxide, inhibited dimethylsulfoxide-induced differentiation. Changes in the phospholipid composition suggest that inhibition of cell differentiation may be attributed to modification of phospholipid composition of the cell membrane (Kaiho and Mizuno, 1985).

In Kier et al. (1988), tumors derived from LM cells grown on monomethylethanolamine-supplemented serum and injected into nude mice had significant reductions in the specific activity of ($Na^+ + K^+$)-ATPase (42.9 ± 3.6 nmol/minute per mg, $p<0.05$), NADH-dependent cytochrome-*c* reductase (234 ± 15 nmol/minute per mg, $p<0.025$), rotenone-insensitive NADH-dependent cytochrome-*c* reductase (218 ± 17 nmol/minute per mg, $p<0.025$), and rotenone-sensitive NADH-dependent cytochrome-*c* reductase (53 ± 5 nmol/minute per mg, $p<0.05$), relative to choline-supplemented serum. Significant changes were also observed in the fatty acid composition of plasma membranes, microsomes, and mitochondria, with significant increases in saturated fatty acids of 16 and 18 carbons in length in the microsomes and mitochondria, accompanied by significant reductions were found in the 18 carbon-length unsaturated fatty acids. Monomethylethanolamine-supplemented serum produced a significant reduction in the ratios of unsaturated:saturated and long chain (>18 carbons):short chain (<18 carbons) fatty acids.

10.5 Methyldiethanolamine [105-59-9]

Chemical Disposition, Metabolism, and Toxicokinetics

Radiolabeled methyldiethanolamine was readily absorbed from dermal applications in the male and female rat (17 – 21% and 41 – 50% after 6 and 72 hours of contact, respectively).

Methyldiethanolamine was first sequestered in the skin then released to the blood stream where it was distributed uniformly to the major organs. The highest concentrations of radiolabel were found in the liver and kidneys. Nonlinear kinetic behavior following intravenous administration of 500 mg/kg suggests saturation of metabolism at high doses. Elimination is primarily through the urine, with an excretion half-life in excess of 30 hours after dermal application (Leung et al., 1996a).

Animal Toxicity

LD_{50}s for the rat (oral), mouse (intraperitoneal), and rabbit (dermal) were reported as 1945 mg/kg, 500 mg/kg, and 5990 µl/kg, respectively. Oral administration was accompanied by chromodacryorrhea, ataxia, and gastrointestinal tract hypermotility and diarrhea. Methyldiethanolamine was classified as mildly irritating to the skin (502 mg or 500 µL) and to the eyes (5 µL) of rabbits. In multiple dose studies, the lowest dose to induce adverse effects in rats was 9360 mg/kg, administered dermally on a daily basis for eleven days. Adverse effects included a change in food intake and weight gain and dermatitis. In a thirteen-week study, dermatitis was noted at a 1.6250E+04 mg/kg dose (as cited) (RTECS, 1999b).

In a series of acute toxicity tests of five alkylalkanolamines (monomethylethanolamine, DMAE, dimethylisopropanolamine, *t*-butyldiethanolamine, and methyldiethanolamine), methyldiethanolamine was found to be relatively less toxic. The oral LD_{50} for both male and female Sprague-Dawley rats was 1945 mg/kg. Signs of toxicity included sluggishness, lacrimation, chromodacryorrhea, diarrhea, kyphosis, and prostration. Necropsy of animals that died revealed distended stomachs containing blood and exhibiting dark red or purple discolorations of the glandular portion. Similarly, the intestines showed varying degrees of congestion and contained blood. Lungs showed dark red mottling (Ballantyne and Leung, 1996).

Dermal LD_{50}s for methyldiethanolamine were 10,244 and 11,336 mg/kg for male and female New Zealand White rabbits, respectively. The signs of toxicity were similar to those observed for oral toxicity and included sluggishness, unsteady gait, emaciation and prostration. Dermal effects included moderate to severe erythema and edema with ecchymoses, necrosis, and ulceration. These effects persisted and progressed to local desquamation, alopecia, and scarring by the end of the observation period at 14 days. Necropsy of animals that died revealed dark red mottled lungs, dark red livers, and mottled kidneys (Ballantyne and Leung, 1996). Six-hour exposures to saturated vapor did not produce any mortalities or significant signs of toxicity. Methyldiethanolamine was only mildly irritating in both the skin and eye tests. Application to the skin (four hours) produced only mild erythema and edema (lasting about two days) accompanied by a few scattered ecchymoses without necrosis. In the eye, only a slight to moderate conjunctival hyperemia and chemosis was observed and resolved itself within three days. A slight corneal opacity was observed at 24-hours post-treatment in one of six rabbits. A mild injection of the iris persisted for about three days (Ballantyne and Leung, 1996).

Several repeated-dose (short-term and subchronic) studies investigating local and systemic toxicity of dermally applied methyldiethanolamine in Fischer 344 rats were conducted. The two short-term studies exposed rats to 0, 100, 260, 500, 750, 1040, or 2080 mg/kg/day for nine days for six hours per day. The highest dose resulted in some changes in weight gain. Dose-related skin irritations occurred in both studies, along with an increase in adrenals gland weight. DMAE (260, 1040, and 2080 mg/kg/day) induced hematological (decreased hemoglobin concentration, hematocrit, and mean corpuscular hemoglobin; increased segmented neutrophils in females from the high-dose group) and clinical chemistry (increased glucose, urea nitrogen, sodium, and chloride in females) changes. Kidney weights were also increased, but without urinalysis or histological evidence of renal damage. In the second study, (100, 500, and 750 mg/kg/day) clinical chemistry results included significantly increased aspartate and alanine amino transferases and reductions for sorbitol dehydrogenase and calcium in high-dose males. In females, increased total protein and albumin, and decreased sorbitol dehydrogenase and inorganic phosphorus were noted. The subchronic study provided histopathological finding of acanthosis, hyperkeratosis, parakeratosis, dermatitis, dermal fibrosis, eschar, and ulceration (Werley et al., 1997).

Reproductive and Teratological Effects

Cutaneous exposure of CD rats to methyldiethanolamine (0, 250, 500, and 1000 mg/kg/day, gestation days six to fifteen, inclusive) failed to induce adverse effects on any gestational parameter or increase the incidence of malformations or variations (external, visceral, or skeletal by category or individually). No differences in maternal body weight, gestational weight gain, food consumption or liver, kidney, or gravid uterine weight were observed at any dose group. Maternal toxicity was apparent as anemia in dams at the 1000 mg/kg dose group. Severe skin irritation occurred at the 100 mg/kg/day, and included necrosis, ecchymoses, exfoliation, crusting, excoriation, erythema, and edema. The NOAELs for maternal toxicity and embryofetal toxicity and teratogenicity were estimated at 250 and at or above 1000 mg/kg/day, respectively (Leung and Ballantyne, 1998).

Genotoxicity

Methyldiethanolamine was nongenotoxic when tested in the presence and absence of a metabolic activation system in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and/or TA97 (Zeiger et al., 1987). Supporting this result, in a battery of genotoxicity assays including the *Salmonella*/microsome reverse gene mutation, CHO/HGPRT forward gene mutation, sister chromatid exchange (all with and without metabolic activation systems), and the *in vivo* micronucleus tests, methyldiethanolamine failed to induce mutations and was considered, overall, not to represent a genotoxic hazard (Leung and Ballantyne, 1997).

Immunotoxicity

Methyldiethanolamine failed to induce allergic contact dermatitis in the guinea pig maximization

test (Blaszcak, 1994; cited by Leung et al., 1996; Leung and Blaszcak, 1998).

11.0 Online Databases And Secondary References

11.1 Online Databases

Chemical Information System Files
SANSS (Structure and Nomenclature Search System)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files
158 DIOGENES
136 Federal Register Abstracts
229 Drug Information Fulltext

Internet Databases
Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

National Library of Medicine Databases
EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files
BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CEN (Chemical & Engineering News)
CIN (Chemical Industry Notes)
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE (Index Medicus)
PROMT (Predicasts Overview of Markets and Technology)
Registry File
RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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Appendix: Units and Abbreviations

°C = degrees Celsius
μg/L = microgram(s) per liter
μg/m^3 = microgram(s) per cubic meter
μg/mL = microgram(s) per milliliter
μM = micromolar
ACGIH = American Conference of Governmental Industrial Hygienists
ADD = attention deficit disorder
ADHD = attention deficit hyperactivity disorder
Ave. = average
bw = body weight
CFC = chlorofluorocarbon
CHO = Chinese hamster ovary cells
CNS = central nervous system
d = day(s)
EIMS = electron-impact mass spectrometry
EPA = Environmental Protection Agency
F = female(s)
FITR = Fourier transform infrared spectrophotometry
g = gram(s)
g/mL = gram(s) per milliliter
GC = gas chromatography
GC/MS = gas chromatography/mass spectrometry
GD = gestation day
GSH = glutathione
h = hour(s)(ly)
HD = high-dose
HGPRT = hypoxanthine-guanine phosphoribosyl transferase
HPLC = high-performance liquid chromatography
HSDB = Hazardous Substances Data Bank
HVLP = high-volume low-pressure
Inh. = inhalation
icv. = intracerebroventricular(ly)
i.p. = intraperitoneal(ly)
i.v. = intravenous(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC = liquid chromatography

LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
LD_{Lo} = lowest lethal dose
LD = low-dose
LOD = limit of detection
M = male(s)
MD = mid-dose
MDA = malondialdehyde
MDI = methylenediphenylene diisocyanate
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)(ly)
mol = mole(s)
mol. wt. = molecular weight
MSDS = material safety data sheet
n = number(s)
NIEHS = National Institute of Environmental Health Sciences
NIOSH = National Institute for Occupational Safety and Health
NOEL = no observable effect level
nm = nanometer(s)
n.p. = not provided
OSHA = Occupational Safety and Health Administration
OTC = over-the-counter
PEL = permissible exposure limit
ppb = parts per billion
ppm = parts per million
p.o. = peroral(ly), *per os*
PrSH = protein thiols
REL = relative exposure limit
s = second(s)
s.c. = subcutaneous(ly)
SCE = sister chromatid exchange
SHE = Syrian hamster embryo cells

SOD = superoxide dismutase
SPME = solid-phase microextraction
STEL = short-term exposure limit
TDI = toluene diisocyanate
TLC = thin-layer chromatography
TLV = threshold-limit value
TSCA = Toxic Substances Control Act
TWA = time-weighted average
USEPA = U.S. Environmental Protection Agency
VIC = vapor injection curing
VOC = volatile organic chemicals
wk = week(s)(ly)
yr = year(s)(ly)