DIMETHYLETHANOLAMINE; DEANOL; DMAE; DMEA; DIMETHYLAMINOETHANOL (CAS RN 108-01-0; ILS CODE L112)

Description of Search Strategy and Results (Search Package) for 1997 Report Update

Reason for Update

Recently, reproductive studies in mice have indicated that dimethylethanolamine (DMAE) is teratogenic. There is widespread occupational exposure to the free base and numerous nutritional supplements and cosmetics/topical pharmaceuticals are available as the public as DMAE salts and esters.

Search Strategy

DMAE in STN International Databases

Most of the original searches were done on November 10-29, 1996, in the databases BIOSIS, CA, CANCERLIT, Chemical Industry Notes, Chemical Safety News Base, EMBASE, IPA , HSDB, MEDLINE, PROMT, REGISTRY, RTECS, SANSS, TOXLINE, TOXLIT, and TSCATS on STN International. EMIC/EMICBACK was searched on December 18, 1996, and Chemical Economics Handbook was searched on October 8. MEDLINE was searched again in the period April 4-10, 1997, in addition to DIOGENES, Drug Info, and Federal Register Abstracts (closed file since 1993). Because of the possible lag time for database incorporation, the current searches covered the years 1995 to 2002. Full records of interest were printed May 10, 2002, from TOXLINE and EMIC queries using only the CAS RN. A printout of TOXLINE citations in order by title was compared with titles of results from the STN International searches. Both were compared to the reference list in the 1997 report and the documents acquired for that effort.

On May 13, 2002, a simultaneous search of MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, EMBASE, CABA, ESBIOBASE, BIOTECHNO, BIOSIS, IPA, TOXCENTER, and LIFESCI was done using as search terms the CAS RN (1,566 records) and several systematic chemical synonyms, acronyms, and trade names listed in the ChemIDplus record. The names with the most records (before duplicate removal) were deanol (1,205 records), dimethylethanolamine (917), dimethylaminoethanol (694), and DMAE (212). The acronym DMEA was not used. The automated duplicate removal process reduced the set of 2,934 records to 1,720. Limiting the results to publications between 1995 and 2002 gave 245 records. The numbers of records per database (numbers of records selected for printing in full in parentheses) were as follows:

MEDLINE	53 (16)	CABA	5 (1)	TOXCENTER	120 (29)
CANCERLIT	0	ESBIOBASE	2 (0)	LIFESCI	1 (1)
AGRICOLA	2 (0)	BIOTECHNO	0		
NIOSHTIC	1 (0)	BIOSIS	17 (6)		
EMBASE	44 (16)	IPA	0		

[All of these STN International databases have at least one record indexed by 108-01-0:

ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIPPR*, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL]

A search was conducted in CAPLUS sections that would include publications on industrial hygiene and pollution of environmental media. A few additional records were identified by use of the "role" term pollutant (POL) with the CAS RN. Seventy-three titles were examined, which were not limited to publications since 1995. A broader search was appropriate since the 1997 ILS report did not give air concentrations to which workers had been exposed and did not give concentrations found in environmental media.

A search was done in CAPLUS and Food Science and Technology Abstracts on May 30, 2002, to find substantiation for the claims that fish, particularly salmon and anchovies, are rich sources of DMAE (Max, 2002, attributed to "Nicholas Perricone MD, dermatologist, assistant clinical professor at Yale Medical School, and author of *The Wrinkle Cure* [Rodale Press, 2000])." The terms "fish or salmon or anchov?" were combined with the 4538 results from the search statement "108-01-1 OR DMAE OR dimethylethanolamine OR dimethylaminoethanol OR deanol" to give 11 records (all but one from CAPLUS). One fish record was found when phosphatidyl and phospho were prefixed to dimethylethanolamine. Among these results, a 1959 study reported less than 2 ppb in salmon roe and a 1995 study indicated that phosphatidyl-DMAE was present in fish oils. Further combination of the DMAE terms with "food? OR meat? OR beef OR mutton OR lamb OR chicken? OR poultry OR veal" found 95 records, which were mostly on food/beverage container coatings.

Specific DMAE Salts and Esters in STN International Databases

Several DMAE salts and esters were mentioned in the 245 DMAE search results examined. However, by May 24, 2002, it was apparent that the search was not comprehensive for each of the salts and esters. Literature on the esters meclofenoxate and centrophenoxine did not always mention DMAE. Full Registry records with up to 10 recent CA records were printed for several of the salts. Not all of the salts and esters said to be "pharmaceutical raw materials" (Kraeber GmbH. and Company, 2001) in the list below were identified in the Registry searches. RTECS records, if available, were retrieved. Finally a simultaneous search was done in MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, and LIFESCI. (CABA was inadvertently omitted.) For most of the salts, search terms included the CAS RN OR the anion name combined with dimethylaminoethanol, dimethylethanolamine, deanol, OR sometimes DMAE OR dimethylaminoethyl. Only dimethylaminoethyl OR deanol was combined with chlorophenoxyacetate in the searches for meclofenoxate and centrophenoxine. The use of synonyms and trade names was not exhaustive. The publication dates were not limited to the period 1995 to 2002. Most results were found in EMBASE, MEDLINE, BIOSIS, and

TOXCENTER. Numbers of CAPLUS/CAOLD/multiple biomedical database records are in brackets in the second column.

DMAE aceglumate; DMAE acetylglutamate (a salt) (3342-61-8)	[13/5/47]
DMAE *p*-acetamidobenzoate (an ester) (2811-31-6)	[5/3/combined with salt]
DMAE *p*-acetamidobenzoate; Deaner; DNZ-2 (a salt) (3685-74-3**)** [Failed to use this CAS RN in the search.]	[21/5/78]
DMAE bitartrate; DMAE tartrate (5988-51-2)	[4/0/9]
DMAE *p*-chlorophenoxyacetate; Meclofenoxate; Meclophenoxate; Cerebon (an ester) (51-68-3)	[245/19/962]
DMAE *p*-chlorophenoxyacetate; Centrophenoxine; Meclofenoxate hydrochloride; Lucidril (an ester & a salt) (3685-84-5) [Some of the databases use this CAS RN for meclofenoxate itself.]	[266/4/1037]
DMAE dihydrogen phosphate; DMAE monophosphate; P-DMEA; Demanyl phosphate (6909-62-2)	[33/13/35]
DMAE 1-hydrogen glutamate	
DMAE orotate (1446-06-6)	[6/4/3]
DMAE pyroglutamate (pidolate)	

Because of the frequent interchangeability of the names meclofenoxate and centrophenoxine in the biomedical literature, their answer sets were combined to give 1,905 records before duplicate removal and 1,146 after. The record distribution was: 466 from MEDLINE, 4 from CANCERLIT, 3 each from AGRICOLA and NIOSHTIC, 449 from EMBASE, 13 from IPA, 140 from BIOSIS, 57 from TOXCENTER, and 1 from LIFESCI. To avoid retrieval of records already seen in the earlier May 2002 dimethylethanolamine search, records with 108-01-0 OR the most important names used in that search were eliminated (the answer set was reduced by only about 70). The records of 18 reviews were examined. The remaining answer set of 1,056 records was reduced to 134 records by combination with the terms "toxic? OR adverse? OR aggressive? OR weight(3A)(loss OR lost)." [In this search statement, "?" is a truncation symbol and "3A" specifies that the word weight is within three words in either direction of the word loss or lost.] Several records were printed in full after examination of the list of record titles. Many of these were added to the search package.

Combination of all the sets for the other salts gave 228 records before duplicate removal, which reduced to only 41 after the earlier search terms were omitted and duplicates were removed. The 41 records provided few additional records for this search package.

Internet Searches

Other information was sought in trade literature available on the Internet using the Google and Scius search engines and the U.S. EPA OPPT Inventory Update Rule database. General searches using the search engines found the 1997 OECD SIDS (Organization for Economic Cooperation and Development Screening Information Data Set) report and IUCLID (1997).

Google search engine Internet searches using the names and acronyms in the title of this search summary were combined with several keywords to try to find a small subset of commercial products sold as dietary supplements. The keywords and the numbers of "hits" are indicated below.

memory	7,300	skin	7,150
brain	4,950	dermal	117
Alzheimers	3,460	topical	855
mental	3,410		
aging	3,400	mg	8,990
mind	2,780	dose	2,420
Alzheimer	1,630		
cognitive	1,320	"how to order"	543
dementia	729	"credit card"	284
dementias	65	(printed summaries for 175; 45 on DMAE not relevant)	

Combinations with CVS Pharmacy, Eckerd, and General Nutrition Center identified few products. Combination with "mg" retrieved about 80 hits, about half of which identified the form as DMAE bitartrate.

PubMed searches were conducted on May 17 to determine if other developmental or reproductive toxicity studies had been overlooked. (Nothing was found in the DART database.) Terms used included pregnan*, gestat*, foetus/fetus, foetal/fetal, fetotox*/foetotox*, placenta*, transplacenta*, embryo*, and neonat*. [The asterisk is a truncation symbol.]

Search Results

The database records are grouped by each subject code with a colored sheet separating the groups rather than file folders. To facilitate location of the full records, the groups will be in the order of the subject code. Subgroups within a discussion may not always be physically separated in the groups of records. Records within a group are simply in alphabetical order by first author surname. Although the major search was limited to sources published from1995 to 2002, the ancillary searches found older records that may be needed to augment or clarify information in the 1997 ILS report.

Authoritative Reviews (Subject Code 05)

Advis. Comm. Haz. Subt. (1995) may be only an announcement. The committee gave its opinion on five draft U.K. reviews prepared under phase 2 and 3 of the SIDS program.

Davies et al. (1997) is a 56-page risk assessment by the U.K. Health and Safety Executive. The report covers occupational exposure, acute toxicity, 90-day studies, sensitivity, and reproductive toxicity.

HSE (1997) reviewed several asthmagenic compounds, including DMAE.

The IUCLID Data Sheet on DMAE (IUCLID, 1997) is an annex to OECD SIDS (1997). This review summarizes older published literature and several unpublished studies by ICI Chemicals and Polymers, Ltd. Topics include photodegradation; biodegradation; acute, 11-day, and 90-day inhalation toxicity studies in rats; a 90-day feeding study in rats; other acute toxicity studies including corrosivity/irritation experiments; the murine local lymph node screening assay for sensitization; a developmental toxicity/teratogenicity study in which pregnant rats were exposed on gestation days 6 to 15 to DMAE at concentrations up to 100 ppm in the air; and genotoxicity studies in *Salmonella typhimurium* and the CHO/HGPRT assay. A list of 52 references is provided. The 1997 ILS report cited 12 of them.

OECD SIDS (1997) summarizes studies, but does not give references.

Other Reviews (Subject Code 11)

Carson and Markowitz (1996) reviewed deanol and other drugs used in psychiatry (only 2 pages).

The approximately one-page review with 11 references in the *PDR for Nutritional Supplements* (Hendler and Rorvik, 2001) mainly pointed out that many of the claims for the beneficial effects of DMAE and its salts are unfounded.

Koch and Masche (2000) [German] reviewed “Stimulants from herbal medicine” (4 pp.). Several trade name products are indexed.

The Life Extension Foundation (1999) uncritically reviewed some published and unpublished studies in which DMAE and DMAE *p*-chlorophenoxyacetate (meclofenoxate) or its hydrochloride (centrophenoxine) were tested for their effect on the lifespan of various mouse strains. Since the 1997 ILS report did not include chronic studies, abstracts of publications in which DMAE synonyms were coupled with the words lifespan OR longevity were sought May 21, 2000, in PUBMED, TOXLINE, and the Internet.

The Life Extension Foundation (undated) review provided a collection of published-article abstracts on tests with rats and mice using centrophenoxime.

McGrath and Soares (2000) and Soares and McGrath (1999) reviewed clinical studies using deanol for tardive dyskinesia. Deanol was not effective and caused an excess of side effects.

The Medline record for the review by Mode et al. (1984) on statistical tests of significance in survivorship studies indexes meclofenoxate, but the only laboratory animal indexed was *Drosophila melanogaster*. Schneider and Reed (1985) also reviewed anti-aging studies.

The Natural Medicine Comprehensive Database (2002) published a 4-p. critical review on DMAE on May 12, 2002, with 29 references. CVS Pharmacy (undated) provided a less rigorous review, but has a good description of the uses of DMAE in children as does Gugliotta (2000).

Nikolov and Nikolova (1987) [Spanish] included meclofenoxate in a review of adverse drug reactions.

Schneider and Reed (1985) reviewed studies of life extension using antioxidants, etc. DMAE and Gerovital G3 were indexed in the MEDLINE record (no abstract) for this article published in the *New England Journal of Medicine*.

An uncritical review on centrophenoxine (Lucidril) by South (undated) was found on the web site of International Antiaging Systems. Adverse effects are discussed on page 6 of the review as the result of too much acetylcholine.

Zs-Nagy (2002) reviewed the beneficial effects of centrophenoxine and of the analog BCE-001 and the mechanism of action of DMAE (67 references; published in the Proc. NYAS).

Chemical Identification (Subject Code 13a)

The CAS RN, synonyms and trade names, molecular formula, and molecular structure of DMAE are copied from the Registry file record:

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L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   108-01-0  REGISTRY
CN   Ethanol, 2-(dimethylamino)- (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   (2-Hydroxyethyl)dimethylamine
CN   (Dimethylamino)ethanol
CN   (N,N-Dimethylamino)ethanol
CN   β-(Dimethylamino)ethanol
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CN   β-Dimethylaminoethyl alcohol
CN   β-Hydroxyethyldimethylamine
CN   2-(Dimethylamino)ethanol
CN   2-(Dimethylamino)ethyl alcohol
CN   2-(N,N-Dimethylamino)ethanol
CN   Amietol M 21
CN   Bimanol
CN   Dabco DMEA
CN   Deanol
CN   Dimethol
CN   Dimethyl(2-hydroxyethyl)amine
CN   Dimethyl(hydroxyethyl)amine
CN   Dimethylethanolamine
CN   Dimethylmonoethanolamine
CN   DMAE
CN   DMEA
CN   Kalpur P
CN   Liparon
CN   N,N-Dimethyl(2-hydroxyethyl)amine
CN   N,N-Dimethyl-β-hydroxyethylamine
CN   N,N-Dimethyl-2-aminoethanol
CN   N,N-Dimethyl-N-(β-hydroxyethyl)amine
CN   N,N-Dimethylethanolamine
CN   N-(2-Hydroxyethyl)-N,N-dimethylamine
CN   N-(2-Hydroxyethyl)dimethylamine
CN   Norcholine
CN   PC CAT DMEA
CN   Propamine A
CN   Rexolin
CN   Texacat DME
CN   Thancat DME
FS   3D CONCORD
DR   116134-09-9
MF   C4 H11 N O
CI   COM
...
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Recent trade literature mentioned two other trade names: JEFFCAT DMEA (Huntsman Corporation) and Desmorapid DMEA (API, 2000). Note that many of the producers use DMEA as the acronym rather than DMAE.

The report should also contain identification and properties information for some of the common salts used in nutritional supplements and/or pharmaceuticals from other countries such as those listed in the search description on pages 2-3.

Chemical-Physical Properties (Subject Code 13b)

The data in the 1997 ILS report may need to be augmented. The writer will check the following references.

The Registry record provides several calculated property values.

IUCLID (1997) gave property data from nine sources (four not publicly available).

Extensive physical-chemical property data, including chemical reactivity, may be found in product data literature by Dow (2001), Huntsman Corp. (1997) [not copied in this package], and BASF (1997) [not copied in this package], etc. The literature by Huntsman Corp. provided an extensive discussion of DMAE industrial uses, properties, and requirements for storage and handling. DMAE should be stored under an inert gas such as nitrogen to minimize reactions with air and atmospheric moisture (Huntsman Corp., 1997). DMAE is stable for about one year if stored in unopened original containers (BASF, 1997).

Analytical Methods (13c)

Analytical methods may be compiled from some of the studies grouped under occupational exposure and environmental releases. If necessary, we will do a search of the analytical section of CAPLUS.

Because of their polarity, amines may present analytical difficulties (e.g., Brockman et al., 1998, in Group 04).

API (2000) listed two industrial sampling and analytical methods for DMAE determination using trapping resins.

Brzezinka et al. (1999) described off-line coupling of thin layer chromatography (TLC) and electron-impact mass spectrometry (EIMS) for routine forensic and toxicological analysis. Meclofenoxate was one of the 493 drugs and metabolites for which the method was suitable.

Eigendorf (1988) [German] reported on an HPLC (high performance liquid chromatography) method suitable for 88 drugs, including meclofenoxate. Eigendorf et al. (1989, 1990) [German] used reversed-phase HPLC to determine 93 drugs, including meclofenoxate.

Hansen et al. (1984) used isotachophoreisis to determine DMAE in air from polyurethane foam production. [Abstract is with Group 02, occupational exposure.]

Hudson et al. (1995) reported that capillary zone electrophoresis could be used in forensic drug analysis. Deanol acetamidobenzoate (3635-74-3) was among the more than 400 drugs indexed in the database record.

Musumarra et al. (1985) identified drugs, including meclofenoxate, by principal components analysis of standardized TLC data in different eluent systems.

Plantard-Neau et al. (1978) used TLC to determine 37 psychotropic drugs, including meclofenoxate, in urine.

Sollenberg and Hansen (1987) compared the isotachophoretic system for determining aliphatic amines and ethanolamines, including DMAE, in workplace air with gas chromatographic (GC) and HPLC methods.

Stan'kov et al. (2000) reported on the determination of amino alcohols 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.

Stein (1987) [German] reported that alkylammonium ions could be introduced by thermospray into a mass spectrometer, omitting chromatographic separation. The technique was faster than conventional GC-electron impact mass spectrometry (MS). It is not clear from the indexing of the CAPLUS record what ammonium form or fragment of DMAE was measured.

Meclofenoxate and its degradation products were determined by HPLC by Yang and Thyrion (1998).

Commercial Availability

Producers (01a)

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 Petrochemical Corp., ICI Americas, and Union Carbide.

Suppliers (01b)

Bulk suppliers (producers boldfaced) listed in *Chemcyclopedia 2002* were Ashland Distribution Company; **Dow Chemical Co.;** Mallinkrodt Laboratory Chemicals, Division of Mallinkrodt, Baker; Quaker City Chemicals, and **Union Carbide**. 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, ISOtanks 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 Corporation** (1997) 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* for the acrylate and methacrylate esters and the hydrochloride salt (13242-44-9). ATOFINA (2000) offers DMAE and other ethanolamines for ultraviolet-cured coating systems.

Various tactics were tried to identify the numerous dietary supplements commercially available that contain DMAE. In a Google Internet search, combination with "mg" retrieved about 80 hits, about half of which 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 in the Google summary contained DMAE or its salt(s) in amounts from 15 to 250 mg. Seventeen products in this unspecified-form group used amounts of 100 mg. Daily doses mentioned in this group were 400 mg/day, up to 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*.

The Natural Medicine Comprehensive Database (2002) review on DMAE lists a number of other salts. This source stated that the typical starting dose is 100 mg/day, with a gradual increase to 500 mg/day. Clinical studies have used 300 to 2,000 mg/day. [This information might also be used in a discussion of nonoccupational exposure.]

Production Processes (01d)

DMAE preparation from equimolar amounts of ethylene oxide and dimethylamine was first described in 1904 (The Merck Index, 2001), which is the basis for the statement on production processes in the 1997 ILS report. According to the Condensed Kirk-Othmer, the method is used industrially. ILS should acquire the appropriate chapter from the 4th edition of the *Kirk-Othmer Encyclopedia of Chemical Technology* for better information.

Production and Import Volumes (01c)

The U.S. EPA OPPT High Production Volume Chemicals List published in 1997 indicated annual production in the range 8,890,482 to 11,938,890 lb (4,032 to 5,414 metric tons).

Uses (01f)

Industrial

Trade literature from Dow (undated, 2001, 2002) described a wide range of DMAE applications in more detail than in the 1997 ILS report. Vopak Canada (2001) gives a list of DMAE uses, many of which were included in the ILS 1997 report.

DMAE is one of at least 60 amine compounds used to manufacture polyurethane and polyisocyanurate foams. Polyurethane formulations require about 0.1 to 5.0% amine catalyst (API, 2000). API (2000) lists 27 other amine catalysts used in polyurethane manufacture. The di-DMAE ether, that is, bis(2-dimethylaminoethyl) ether, CASRN 3033-62-3, may be the most widely used amine catalyst in polyurethane manufacture (it is first in the unalphabetized list; DMAE is ninth).

DMAE is used for solubilization of water-insoluble resin components for water-based coatings (ATOFINA, 2000). Solubilization is achieved by reaction of DMAE with the resins (Huntsman Corp., 1997). A recent French study of about 30 water-based paint formulations available to vehicle manufacturers all contained glycol ethers, *N*-methylpyrrolidone [...pyrrolidinone], and alkanolamines (DMAE was mentioned as an example) (Jargot et al., 1999). 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.

DMAE bitartrate was part of an aqueous cathodic coating composition to which maleic acid was added to reduce discoloration by metal ions (Lucas, 1983; Patent Assignee PPG Industries, Inc., USA).

Several publications have studied use of DMAE as a corrosion inhibitor in steel-reinforced concrete (CCIA, undated). Commercial formulations for such use are described in FHWA DOT (2000).

DMAE is used to produce acrylate and methacrylate monomers. Their polymers are used as antistatic agents, electrically conducting materials, flocculants, and "paper auxiliaries" (Huntsman Corp., 1997).

Vapor-phase DMAE is used to catalyze polyurethane-based inks (Huntsman Corp., 1997) as well as coatings (see VIC process below).

Kandasamy et al. (2000) of Procter and Gamble Co., USA, reported the use of DMAE hydrochloride in the manufacture of detergent compositions.

Pharmaceuticals and Dietary Supplements (See also Nonoccupational Exposure)

DMAE was one of the drugs in a Warner-Lambert Company USA World patent (Cade et al., 1997) for an encapsulation process for solid dosage forms.

In 1959, an Italian article described the use of Deaner in 50 children (Fois et al., 1959).

Use of DMAE bitartrate as a geriatric drug was reported by Friederichs (1971).

DMAE aceglumate and DMAE acetamidobenzoate were drugs in a World patent assigned to Alza Corporation, USA (Hamel et al., 1998) for "ascending-dose pharmaceutical dosage forms containing polymers." Other drugs included amphetamines and pseudoephedrine.

DMAE orotate (1446-06-6) was mentioned in a European patent application (Ismail, 1985; Patent Assignee was Federal Republic of Germany]) for vitamin E-containing drugs with vasodilators for skin protection and treatment.

DMAE was indexed in the CAPLUS record for a World patent on "compositions for rapid transdermal delivery of pharmaceutically active agents" assigned to Transdermal Technologies, Inc., USA (Kirby and Pettersson, 2000). 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.

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., USA (Morozowich and Gao, 1999).

The Natural Medicine Comprehensive Database (2002) review summarized the purported usefulness of DMAE in dietary supplements and indicated which treatments might be effective.

Perricone (2001) is a U.S. patent for alkanolamine compositions for treatment of topical scars. DMAE at 0.1 to 10 weight percent was "particularly preferred." [This patent was awarded to a physician unaffiliated with a pharmaceutical company.] Perricone (1997) patented compositions containing DMAE for treating skin damage and aging.

Meclofenoxate was in formulations in a German patent for "transdermal or transmucosal dosage forms containing nicotine for smoking cessation" (Theobald and Frick, 2001; Patent Assignee LTS Lohmann Therapie-Systeme A.-G., Germany).

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.

Warrenbourg and Jaillard (1968) reported on clinical experimentation with demanyl (DMAE) phosphate in brain diseases.

Yavin and Brand (2001) of an Israeli company 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.

Cosmetics

Chabrier (1998, 2000) [no company affiliation] was issued French patents for cosmetic and dermatological compositions containing 5 to 20% meclofenoxate to prevent or repair "dermo-epidermal alterations."

DMAE hydrochloride (2498-25-1) was in a Japanese patent for anti-aging skin cosmetics containing biphenyl compounds (Hikima, 1998).

DMAE was also recommended for topical preparations for treatment or prevention of skin damage and aging. Acetylcholine precursors are described as firming muscles (Perricone, 1995).

DMAE was indexed in a European patent application for hair cosmetic compositions, including hair dyes (Tajima et al., 2002; Patent Assignee Kao Corp., Japan).

Environmental Releases, Occurrence, and Fate (04)

IUCLID (1997) summarized several environmental fate studies on biodegradation, photodegradation, and atmospheric reactions.

Seeber et al. (1998) sampled amines evaporating from polyurethane foams applied in buildings. Time-dependent concentration profiles were constructed using GC-MS and Fourier transform infrared spectrometry (FTIR). Air concentrations of reactants in the vicinity of freshly produced polyurethane foam insulation material were 4.0 mg MDI/m^3 (MDI = methylenediphenylene diisocyanate) 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).

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 VOCs from the wood glues, overlay materials such as PVC, and coatings. 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).

DMAE is among volatile organic carbon compounds (VOCs) that outgas from new carpets (Stadler and Kennedy, 1996 [filed with Group 03, Acute Toxicity].

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, but the potential for consumer exposure should be further explored.

Kometani et al. (2000) stated that conventional tertiary amine catalysts are emitted from polyurethane foams. In their effort to reduce VOCs, some automobile manufacturers intend to avoid conventional amine catalysts. TOSOH has developed reactive amine catalysts that have low emissions. Rothe et al. (2001) in "New catalysts for low VOC in flexible slabstock foam" stated that 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 for low VOC emissions. The abstracts are not explicit as to whether DMAE is considered reactive, but DMAE was grouped with the reactive amine catalysts in the indexing of the CA record.

Polyurethane foam compositions are widely used for sealing and caulking. Such a foam is used in underground coal mines to seal ventilation equipment. In a Russian publication, Putina et al. (1991), 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. 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).

Exposure Potential (02)

Occupational

The 1997 ILS report listed numerous occupations and industries that have potential DMAE exposure. However, no concentrations or biomarkers of exposure were provided. Most of the abstracts for these older publications did not give DMAE concentrations in air although several older publications were available that probably contain such information.

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 zero to 0.1 mg/cm^2/day with up to 1 mg/cm^2/day for spent catalyst drumming in organic flocculants manufacture.

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).

Akesson et al. (1986) measured relatively low levels of DMAE at a polyurethane foam production plant. Bugler et al. (1992) described personal dosimeters used to determine tertiary amine catalysts, including DMAE, at nine U.K. polyurethane factories. Hansen et al. (1982) tested air samples in a polyurethane foam factory for trimethylamine and DMAE using isotachophoresis. No air concentrations were given in the abstract.

A time-weighted "TLV" for DMAE was established at 5 ppm by Union Carbide as an internal exposure limit. The short-term exposure limit set was 25 ppm (IUCLID, 1997). DuPont (2001) gives exposure limits for DMAE as 3.0 ppm TWAE and 6.0 ppm STEV.

Simonsen and Lund (1992) evaluated Danish data on exposure to neurotoxic chemicals, including DMAE, in 69 industrial groups.

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 volatile organic compounds (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.

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. While the painter may be exposed due to inadequate respirator protection. The polyurethane systems described did not use ethanolamine catalysts, and exposure to diisocyanates was the only concern of the SAIC survey.

Welsh et al. (2000) found that the MSDS's for certain controlled products used in Canadian workplaces did not disclose some of the hazardous ingredients, which were detected at concentrations requiring their disclosure. Various analytical methods were used to determine the ingredients, apparently including DMAE, of three products used in coal mines and in aircraft maintenance.

Nonoccupational Exposure

Consumer Products Other Than Dietary Supplements

Several comments were found that salmon and some other fish are rich in DMAE (e.g., Max, 2002). Substantiation found in the scientific literature was meager:

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 nitrosomonoethanolamine.

Phosphatidyldimethylethanolamine is found in fish oils along with phosphatidylcholine, phosphatidylethanolamine, phosphatidylmethylethanolamine, and phosphatidylserine (Segawa et al., 1995) [Japanese]. The abstract is filed in Group 22.

According to publications in Group 04, sealants, architectural coatings, coatings on furniture and cabinets, polyurethane foam cushions, and carpets may emit DMAE 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. However, evidence of efficacy

was insufficient (Natural Medicines Comprehensive Database, 2002 [in Group 11). 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. It was contraindicated for patients with grand mal epilepsy. Oral doses for children with behavior problems were 75 mg/day to start with 75- to 150-mg/day maintenance doses.

DMAE may be an impurity or a metabolite of ethical pharmaceuticals such as ditilin (succinylcholine chloride; http://physchem.ox.ac.uk/MSDS/SU/suxamethonium_chloride.html) (Arzamastsev et al., 1999). Karaisz et al. (2001) found DMAE among hydrolysis and thermal degradation products of diphenhydramine. Diphenhydramine is available as Benadryl® (the hydrochloride salt) and several generic OTC antihistamines as well as a component of the antinausea drug dimenhydrinate [2-(benzhydryloxy)-*N,N*-dimethylethylamine compd. with 8-chlorotheophylline; Dramamine®]. DMAE is a metabolite of the local anesthetic tetracaine hydrochloride along with 4-butylbenzoic acid (Hansen, 1970 [German]). In our effort on local anesthetics, we concluded that tetracaine hydrochloride is not used in the United States.

DMAE may also be part of a drug salt form. A European product sold as Tratul® (not to be confused with a cimetidine product by Gador, which is also called Tratul [Merck Index, 2001]) as an anti-inflammatory, analgesic composition by an Austrian firm (Gerot Pharmazeutica, undated) is available in suppositories and vials [ampoules?; this was from a description in Italian] as diclofenac-deanol. The vials apparently contained 75 mg diclofenac and 15 mg deanol.

[Kabanov et al. (2000) of Supratek Pharma Inc. were issued a U.S. patent for compositions for administration of biological agents to the brain. DMAE was indexed in the TOXCENTER/CA abstract. However, this publication was dropped from consideration when examination of the actual patent found only "...dimethylaminoethanols (such as clofenciclan, cyprodenate, aminorex, and mazindol)...".]

Dietary Supplements

A large number of dietary supplements contain DMAE. See the Commercial Availability section above. Typical adult doses of DMAE in dietary supplements range from 100 to 500 mg/day. Formulations with DMAE intended for attention deficit disorder are still on the market. For example, see the product 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. Introduced in 1999, Focus Child become 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.

Regulations (24)

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."

Several other warning letters and notification letters to FDA from manufacturers were located on the FDA web site, but they have not yet been retrieved.

[Are there no other diisocyanates allowed with DMAE, etc., in 21 CFR Part 175 (see FDA, 1996, the final rule in the *Federal Register*) besides the *m*-tetramethylxylene diisocyanate mentioned in the 1997 ILS report?]

The State of Oregon (1997) recognizes 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."

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. The 1997 ILS report lacked information on 21 CFR 173.20 (U.S. FDA, 2001), which gives limits on extractables from an ion-exchange resin used in food processing.

Human Data (18)

The Natural Medicines Comprehensive Database (2002) compiled an extensive list of adverse effects of DMAE reported in the scientific literature (particular references were cited). DMAE side effects listed by the Washington Post Online (06-18-00) without attribution were constipation, hives, headache, drowsiness, insomnia, confusion, depression, elevated blood pressure, and mania. These may have been drawn from the FDA CFSAN (1998) report discussed below.

FDA CFSAN (1998) is a 285-page compilation of adverse effects associated with use of dietary supplements, infant formulas, and medical foods (The Special Nutritionals Adverse Event Monitoring System). Data collection began in 1993. Most of the reports for supplements containing DMAE were for products that also contained ma huang/ephedra, and the reported

CVS and CNS effects were typical of ephedrine toxicity [see FDA (1999) for a summary]. Three other cases of adverse events were associated with formulations containing other pharmacologically active ingredients. DMAE from Le Tan Products was associated with a person who suffered a tonic-clonic seizure and two mild strokes. The person was also taking ginseng from an unknown manufacturer.

Anonymous (1972) provided a review of the therapeutic use of meclofenoxate in humans and its adverse effects.

Bruce (1971) reported on adverse effects of meclofenoxate (Lucidril used to treat autism) in humans. There was no abstract, but the database record indexing suggests that meclofenoxate induced hyperkinesis.

Dimpfel et al. (1996) described a clinical trial with DMAE orotate in 60 elderly persons with cognitive deficits. EEG changes were monitored.

Dubska and Kumpel (1981) monitored the electrocardiogram curve during a clinical trial of meclofenoxate. Indexing of the EMBASE record includes the term "drug toxicity."
Gal et al. (1996) conducted a clinical trial with a mixture of ginseng extract and deanol, studying the effect on patients suffering from functional fatigue.

Jenkins and Graves (1965) warned that DMAE and other antidepressants have toxic synergies with anesthetics used in surgery.

Kaffarnik et al. (1972) followed carbohydrate balance and liver function during a clinical trial of centrophenoxine. Adverse effects in the indexing include induction of diabetes mellitus and glycosuria.

Life Extension Foundation (undated) contains abstracts for several clinical trials of centrofenoxime for treatment of dementias. [These are in Group 11.]

Marsh and Linnoila (1979) is one of the clinical trials in which no beneficial effect was observed in a clinical trial of deanol in elderly individuals with minimal cognitive decline.

Adverse effects observed in multicenter clinical trials of acetylcholinesterase inhibitors for treatment of Alzheimer's disease were discussed in a review by Ott and Owens (1998).

Pek et al. (1989) in Hungary described an 8-week double-blind clinical trial of centrophenoxine in 50 patients of average age 77 years with organic "psychosyndrome." Treated subjects received 2 g/day in tablets. Centrophenoxine, which was apparently harmless (no organ function tests mentioned in abstract), improved memory functions in 48% of the treated group compared to improvement of 28% in the placebo group.

Pokrovskaya et al. (1986) reported that workers exposed to DMAE, ethylenediamine, propylene oxide, methylene diisocyanate, and methylene chloride in a plant manufacturing polyurethane

foam for refrigerator insulation experienced upper respiratory tract and nervous system disorders and significant changes in immunity status.

Schmidt and Schlick (1979) [German] dosed ten older humans (mean age 64 years) for one year with centrophenoxine at the high level of 3 g/day. Body weight was slightly decreased, four patients had transient mild gastric pain. and five patients reported a "very small increase in jitteriness." No harmful effects were noted in bone marrow or in renal and hepatic function tests. Some beneficial effects on glucose tolerance and cardiopulmonary function were observed.

Schober et al. (1994) described a clinical trial of deanol orotate in 43 patients aged 40 to 65 years with poor concentration and thinking problems.

The Washington Post (06-18-00) listed side effects of DMAE without attribution.

ADME (12)

Recent Studies

Boiko et al. (1997) [Russian] reported on the pharmacokinetics of nootropic drugs, including DMAE (no abstract).

Zhang et al. (1998) studied the formation of dimethylamine from choline and its analogs. DMAE is indexed in the EMBASE record, but it is not mentioned in the abstract.

Older Studies

Studies cited by Schlenk (1990), which ILS cited in its 1997 report, are in boldface.

Alvaro et al. (1989) reported that a significant increase in phosphatidylcholine (PC) was found in the liver of bile-fistula rats after intravenous infusion of DMAE with sodium taurocholate. Presumably, phosphatidyldimethylethanolamine was an intermediate.

Andriamampandry et al. (1992) described methylation of phosphodimethylethanolamine in the generation of phosphocholine in rat brain cytosol.

Ansell and Spanner (1980) studied DMAE metabolism in the brains of rats.

DMAE acid malate (Cerebrol) (94158-52-8) was readily absorbed by healthy adults. Peak plasma concentrations were attained after 30 minutes. Thirty-nine percent of the dose was eliminated in the urine within 48 hours (half-life = 3.5 hour; mean transit time = 5.75 hours). "The peak plasma level and area under the plasma concentration-time curve of [DMAE] were greater than those of" DMAE aceglumate (3342-61-8) (**Bismut et al., 1986**) [French].

Ceder and Schuberth (1977) reported on a GLC assay to identify DMAE acetamidobenzoate (Deaner) in rabbit and human blood after intake of therapeutic doses. Determination was by gas chromatography/flame ionization detection (GC/FID).

Dainous and Kanfer (1988) studied the phosphorylation of monomethylethanolamine and DMAE in fetal rat brain aggregating cell cultures.

The 1997 ILS report included data from **Dormand et al. (1975a)** as cited by Schlenk (1990), but did not include Dormand et al. (1975b). The latter studied the metabolism of a ^{14}C-labeled DMAE and a DMAE salt in rats and pigs and identified the phospholipid intermediates and labeled choline.

Drouva et al. (1986) reported that the formation of phosphatidyl DMAE in ovariectomized rats was enhanced by treatment with 17β-estradiol.

Phosphatidyldimethylethanolamine was found in the lung washings of transitional and term lamb fetuses in a study correlating increases in phosphatidylcholine concentrations in fetal alveoli with the appearance of surfactant during development (Fujiwara et al., 1968 [UCLA]).

Jope and Jenden (1979) reported that tritium-labeled DMAE metabolism in the brain of rats after intraperitoneal or oral administration led to an increase in choline in plasma and brain without altering the concentration of brain acetylcholine.

Massarelli et al. (1988) studied differences in choline synthesis in cultured rat and chick neurons, using DMAE as a source in some experiments. Compare Andriamampandry et al. (1992).

Miyazaki et al. (1976) compared metabolism of DMAE and its salt with *p*-chlorophenoxyacetic acid (meclofenoxate) in the brain and liver of mice after intravenous dosing.

Yang et al. (1988) reported that rat mammary tissue has an enzyme that catalyzes the methylation of phosphatidyl-DMAE to form phosphatidylcholine.

Zahniser et al. (1977) used a GC assay to determine DMAE in the tissue of mice after administration by a route not specified in the abstract. Free endogenous DMAE was not found in the tissues of control rats and mice. Only massive doses of DMAE *p*-acetamidobenzoate (Deaner) gave any elevations of acetylcholine in rat brain, indicating that DMAE is not an immediate precursor of acetylcholine in the CNS.

Zeisel et al. (1989) of Boston University studied the potential of choline and its analogs for nitrosamine formation *in vivo*. Although trimethylamine and trimethylamine *N*-oxide were formed in small amounts by intestinal bacteria in rats, the amount of dimethylamine formed from DMAE were minimal in comparison.

Acute Toxicity (03)

API (2000) listed oral LD_{50}s for rats as a range from 1,420 to 2,340 mg/kg.

Ballantyne and Leung (1996) of Union Carbide reported on acute studies in rats and rabbits. These are probably the same studies in the TSCA test submissions, but should be cited as well.

Claims for toning muscles may be based on the studies of Danysz et al. (1967a), who reported on acute nervous system effects in cats, mice, and rats in a Polish dissertation. Prolonged administration in progressively increasing doses increased muscle tone in rats.

Experiments conducted by Dhawan et al. (1967) in dogs indicated that "like acetylcholine, deanol [administers as Deaner] exerts a central vasomotor stimulant effect. However, deanol probably does not act through acetylcholine but has a direct stimulant action on the vasomotor center."

Funk (1994) reported that meclofenoxate induced hypoglycemia as an adverse effect in rats. Thuillier et al. (1963) reported the induction of hypoglycemia in rabbits by centrophenoxine.

Haubrich et al. (1981) of Merck, Sharpe, and Dohme Research Laboratories studied the effect of DMAE on choline concentrations of choline in organs and blood of mice and concluded that DMAE increased choline blood concentrations by inhibiting choline metabolism in peripheral tissues.

IUCLID (1997) cited numerous acute toxicity studies, most of which were not cited in the 1997 ILS report.

Levin et al. (1995) of Duke University Medical Center reported on the effect of brief dosing of rats with DMAE II to improve memory performance. DMAE II is DMAE cyclohexyl carboxylate fumarate. See also Petkov et al. (2000).

Loew et al. (1974) [German] published a 7-page article on the toxicity of meclofenoxate orotate (27166-15-0).

RTECS (2001) records for DMAE aceglumate; DMAE *p*-acetamidobenzoate (salt; Deaner); DMAE *p*-chlorophenoxyacetate (ester; meclofenoxate) and its hydrochloride salt (centrophenoxine) provided only LD_{50} data for rats, mice, and rabbits.

Smyth et al. (1951) reported an oral LD_{50} in rats of 2,340 mg/kg, which was not altered by administration in food.

The sensory irritation potential of DMAE in mice was studied by Stadler and Kennedy (1996). Mice exposed head-only to DMAE in the air exhibited a 50% decrease in respiration rate (RD_{50}) between 100 and 1,000 ppm. The authors concluded that DMAE concentrations from carpets would not induce human respiratory irritation.

Tarakhovskii et al. (1966) [Ukrainian] reported on acute toxicity studies of centrophenoxine in rats, cats, and mice. Centrophenoxine inhibited spinal reflexes at low intraabdominal doses.

Thuillier (1960) determined intravenous LD_{50}s in mice and rabbits for meclofenoxate. "The drug had no appreciable toxic effect in a chronic experiment with rats" [no details in the abstract].

Short-Term and Subchronic Toxicity (06a)

Without specification of duration, so-called chronic studies are placed in the subchronic group. Although studies to extend the lifespan of rodents (mentioned in the reviews discussion) may be contradictory, they may offer information about effects of long-term administration or the lack of adverse effects. Several are included with the subchronic and chronic studies.

The 1997 ILS report cited 11-day and 13-week rat studies with DMAE reported by Klonne et al. (1987).

Aged rats treated for 4 weeks with meclofenoxate at 100 mg/kg bw or meclofenoxate plus *Ginkgo biloba* and zinc showed improvement in age-associated oxidative changes (Al-Zuhair et al., 1998).

A study in which treatment of rats with DMAE for 7 to 14 days increased brain concentrations of co-administered chlopromazine (Danysz et al., 1967b) was excluded from the 1997 report as were studies of the effect of centrophenoxine (DMAE *p*-chlorophenoxyacetate ester hydrochloride) in male Swiss-Webster mice (Hochschild, 1973a) and female C57BL/6J mice (Hochschild, 1973b) [see next section] and the effect of the *p*-acetamidobenzoate ester [CAS RN assigned by CAS for the TOXLIT record indexing] on senile male A/J mice (Hochschild, 1973c).

DMAE dihydrogen phosphate (Panclar) was among drugs studied for their "pharmacological modulation of group behavior and biorhythms" during chronic experiments. Species, dosing, and duration were not given in the abstract of this Russian study by Grechko et al. (1998) of the Military Medicine Academy of St. Petersburg.

IUCLID (1997) cited a 90-day feeding study in rats by Smyth et al. (1951).

Lidberg and Komina (1984) [Russian] exposed mice "chronically" (probably at least 2 months) to emissions from foamed polyurethane insulation, which included methylenediphenylene diisocyanate (MDI). The abstract is in the environmental releases group (Group 04).

Life Extension Foundation (undated) provided abstracts for centrophenoxine studies in humans and laboratory animals. The duration of studies in rats ranged from 3 to 21 weeks (5 months). Abstracts of two 90-day studies in mice were included. [The abstract is with Group 11.]

Chronic administration (duration not indicated in the abstract) of DMAE in the drinking water of rats did not increase brain concentrations of acetylcholine, but the treatment prolonged CNS depression induced by pentobarbital or ethanol (Pepeu et al., 1960 [Yale Univ.]).

Voronina et al. (1987a) [Russian] reported that centrophenoxine and cleregil had pronounced antiamnestic activity in mice. Centrophenoxine required high doses to exert an antihypoxic activity on mice subjected to hypobaric hypoxia. "Dissociation" was observed in the manifestation of antiamnestic and antihypoxic effects. [This statement appears to be ambiguous, but see "dissociated state" in the next paragraph.]

Voronina et al. (1987b) [Russian] reported that long-term administration [no details in abstract] of centrophenoxine and cleregil (DMAE aceglumate) increased "emotional reactivity" and aggressiveness in rats. Spontaneous aggressiveness and "still greater enhancement of emotional reactivity" occurred after withdrawal of the drugs. One of the researchers (Garibova) co-authored an earlier publication (Garibova et al., 1984), which reported that prolonged intraperitoneal injections of Cleregil at a dose of 150 mg/kg induced "manifestations of aggressiveness, fear and anxiety." The rats "developed a dissociated state where the reflex [learning in a T-maze] manifested itself only after [Cleregil] injection and did not occur without it." Meszaros and Gajewska (1972) reported increased aggressiveness in mice associated with 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. Although DMAE also prolonged barbiturate sleeping time and increased the pain threshold, its effects were weaker than those of PCPA and centrophenoxine and "differed significantly."

Chronic Toxicity (Greater Than 90 Days) (06b)

Hochshild (1973b) dosed female C57BL/6J mice from about 10 months of age to the end of life. The modest increase in lifespan (5.9%) was "not quite significant." Negligible weight changes occurred up to 19 months but by 25 months, the "treated groups averaged somewhat lighter in weight" than controls.

Lukoshko et al. (1997) [Ukrainian] reported on the CNS effects observed in rats during 4-month continuous inhalation exposure to DMAE.

DMAE orotate fed to rats at a dose of 10 mg/kg/day for 6 months lowered plasma triglycerides and cholesterol (Pinelli and Colombo, 1973) [Italian].

Antagonisms and Synergisms (22)

Effects on cell proliferation

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."

Brand and Yavin (2001) reported that DMAE "reduced EPG [ethanolamine phosphoglyceride, which acts as a signaling molecule] synthesis...[and translocation] and rescued cells [in an oligodendroglia-like cell line] from apoptotic death" due to oxidative stress. The publication by Brand and Yavin (2000) described another experiment that showed that "*N*-methyl bases of ethanolamine prevent apoptotic cell death induced by oxidative stress in cells of oligodendroglia

origin." In additional experiments, Brand et al. (2001) focused on the mechanism of the protective effects of DMAE.

Malewicz et al. (1998) studied the *in vitro* DMAE potentiation of the stimulatory effects of insulin on DNA synthesis/cell proliferation and DMAE's protection against cell death.

Other Antagonisms/Synergisms

Small doses of Deaner (2 mg/kg) injected i.p. in chicks 15 minutes before i.p. injection of tremorine potentiated the tremorine-induced tremor response. Large doses of Deaner (200 mg/kg) given two hours before tremorine injection suppressed the tremor response completely (Bowman and Osuide, 1968).

Dobre et al. (1994) reported that DMAE and Gerovital H3 showed protective and curative effects on carbon tetrachloride-induced liver damage in rats.

The study by Haubrich et al. (1981), which was mentioned as cited by Schlenk (1990) in the 1997 ILS report, but not in connection with antagonisms, found that DMAE inhibited choline phosphorylation. [Many of the studies on the effects of DMAE on choline synthesis, etc., may be appropriate in this section of the report.]

Millington et al. (1978) of M.I.T. reported that Deaner inhibited choline transport through the blood-brain barrier in rats. [This was reference was mentioned in the human metabolism section of the 1997 ILS report.]

DMAE, a choline oxidase inhibitor, reduced synthesis of betaine from choline and reduced betaine accumulation in the renal medulla of rats (Moeckel and Lien, 1997). Lohr and Acara (1990) also showed that DMAE inhibited betaine synthesis in the rat kidney.

Pedata et al. (1977) reported that Deaner did not affect acetylcholine brain concentrations in rats, cause behavioral changes, or antagonize the effect of HC-3 on striatal acetylcholine. HC-3 is hemicholinium 3 [2,2'-(1,1'-biphenyl)-4,4'-diylbis(2-hydroxy-4,4-dimethylmorpholinium) dibromide (9CI); CAS RN 312-45-8], a quaternary ammonium compound.

Phosphatidyldimethanolamine in fish oils enhanced the antioxidative properties of tocopherol isomers (vitamin E is alpha-tocopherol) during autoxidation of the fish oil at 30 °C in the dark, possibly by promoting regeneration of tocopherol isomers from the tocopheryl radicals (Segawa et al., 1995) [Japanese].

DMAE bitartrate protected rats and mice from the hepatotoxic effects of paracetamol (acetaminophen). Mixed function oxidases that metabolize paracetamol were inhibited, and elimination of free paracetamol and its glucuronide was enhanced (Siegers and Younes, 1979) [German].

Meclofenoxate at 100 mg/kg for 10 days "alleviated learning and memory disability" of 3-month-old rats with fetal alcohol syndrome. Usefulness for prophylaxis was suggested (Vaglenova and Vasselikov, 2001).

Reproductive and Developmental Toxicity (10)

The 1997 ILS report cited only one study (Katyal and Lombardi, 1978).

Recent Publications

Fisher et al. (2001, 2002) reported that the DMAE-induced perturbations of choline uptake and metabolism caused neural tube defects and craniofacial hypoplasia in nerulating mouse embryos *in vitro*. The embryos were exposed to 250- to 750-micromolar concentrations of DMAE.

IUCLID (1997) described an inhalation study in pregnant rats by Union Carbide in 1986 (not in TSCATS). No concentration-related abnormalities or consistent embryonic or fetal toxicity were reported.

Leung et al. (1996) [not entered into TOXLINE until November 1997] of Union Carbide published the details of an inhalation study mentioned in IUCLID (1997). Inhaled DMAE induced developmental toxicity in pregnant Fischer 344 rats, which were exposed to 10 to 100 ppm DMAE on gestation days 6 to 15. DMAE induced maternal toxicity at concentrations above 10 ppm. Skeletal deformities and lethality were observed in the offspring. However, a lack of a consistent pattern was noted. The study may have been performed at Research Triangle Institute. Tyl et al. (1987) published an abstract with a similar title in *The Toxicologist*.

Older Publications Not in 1997 Report

Benesova et al. (1980 abstr.) and Peterka et al. (1980) reported that meclofenoxate was cardiotoxic to chicken embryos.

Gramette et al. (1986) dosed pregnant rats with DMAE from day 12 of gestation and then dosed the neonates through the 10^{th} day of postnatal life. DMAE diminished behavioral decrements induced by postnatal hypoxia. Side effects of DMAE were not mentioned in the abstract.

Neumann (1985) [German] found that treating pregnant Wistar rats with meclofenoxate reduced teratogenicity, significantly increased the weight of the fetuses, and increased fertility in subsequent generations.

Neumann and Seyfarth (1982) [German] 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 days 11 to 14 post coitum (during embryogenesis). The increase in embryo weights did not continue into postnatal life.

Zahniser et al. (1978) fed pregnant rats a choline-deficient diet supplemented with 1% DMAE for 15 days pre-delivery until 15 days after birth. Most pups died within 36 hours of birth. [This

is apparently the same study as described by Katyal and Lombardi, 1978, which was cited in the 1997 ILS report. Those authors are co-authors of this paper.] Choline and acetylcholine concentrations were increased in the brains of the pups, phosphatidylcholine was decreased, and phosphatidyl-DMAE was present.

Carcinogenicity (07a)

No additional publications were found.

Co-Carcinogenesis (07b)

LM fibroblasts (LM primary tumor cells) grown in serum-free medium incorporated DMAE into membrane phospholipids. 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). See also Kier and Schroeder (1982). See other studies of effects of choline analogs in altering phospholipid composition in LM cell fibroblasts in anticarcinogenesis (Group 07c) and SAR (Group 25).

Anticarcinogenicity (07c)

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 another database record on antineoplastic effects, but it was not 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.

Genotoxicity (09)

Holmen et al. (1988) reported no elevation in micronuclei, sister chromatid exchange, or chromosomal aberrations in the peripheral blood lymphocytes of 22 workers at a flexible polyurethane foam factory, where they had been exposed to tolylene diisocyanate (TDI) and amines such as DMAE, triethylenediamine, and *N*-methylmorpholine.

IUCLID (1997) reviewed three Salmonella studies and a mammalian sister chromatid exchange assay. All results were negative (references 45-48).

Leung and Ballantyne (1997) of Union Carbide reported that DMAE was negative in Salmonella, Chinese hamster ovary (CHO) cells (the CHO/HGPRT forward gene mutation assay and a SCE assay), and a micronucleus assay in peripheral blood lymphocytes of mice.

Immunotoxicity (08)

Several reviews include DMAE in discussions of compounds that induce occupational immunologic lung disease: HSE (1997) [mentioned in the authoritative reviews group]; Grammer (1997); Karol et al. (1996, 2001) [focus is on SAR and the molecular basis of chemical allergenicity]; Newcombe and Terry (1992); and Salvaggio (1992).

IUCLID (1997) described a murine LLNA (local lymph node assay) experiment to determine dermal sensitization potential, citing an unpublished ICI report.

Leung and Blaszcak (1998) reported that DMAE did not clearly show dermal sensitization in the guinea pig maximization test.

Other Biological Activities (14)

DMAE concentrations higher than 0.0001 M 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.

DMAE increased biliary phospholipid secretion in bile-duct cannulated male rats and increased canicular membrane fluidity (Yasumiba et al., 2001).

In aging rats, brain concentrations of malondialdehyde and lipofuscin increase as do the activities of certain endopeptidases. Cleregil and meclofenoxate reduced the activities of these enzymes, which are associated with memory and learning disturbances (Zolotov et al., 1991) [Russian].

Structure-Activity Relationships (25)

Several studies investigating related compounds for different biological activities are included in this group. Of these, three publications were published in 1997 and one was published in 2002.

Aside from the articles on *N*-methyldiethanolamine [L168; $CH_3N(CH_2CH_2OH)_2$] and *N*-methylmonoethanolamine [L173; $CH_3NHCH_2CH_2OH$] that ILS collected almost three years ago, no attempt was made to collect information on other ethanolamines.

Akesson (1977) reported that DMAE and diethylaminoethanolamine were the strongest inhibitors of choline incorporation into phospholipids in rat hepatocytes among analogs of ethanolamine and choline.

Ancelin et al. (1998) and Calas et al. (1997) studied DMAE as one of about 80 potential inhibitors of the growth of the malaria mosquito *Plasmodium falciparum*.

Bhattacharyya et al. (1990) studied DMAE analogs that protected mice from the lethal effects of paraoxon, the oxygen analog of methyl parathion.

Do Amaral et al. (1997) studied the physical-chemical properties associated with the lethal toxicity of DMAE 4-substituted benzoate hydrochlorides related to procaine. DMAE hydrochloride was indexed in the CA record. This was a QSAR study; the animal species was/were not mentioned.

Graham et al. (1997) studied chemicals that cause human respiratory sensitization and identified structural alerts.

Kodithala et al. (2002) predicted skin irritation potential "using membrane-interaction QSAR analysis."

Newton et al. (1985) reported that feeding *N*-amino-DMAE to rats on a low-choline and low-methionine synthetic diet for 33 days led to the production of the false transmitter *O*-acetyl-*N*-amino-DMAE but no obvious toxicity.

Nikolova-Karakashian et al. (1997) studied sphingomyelin metabolism in livers of rats fed *N*-amino-DMAE on a low-choline, low-methionine diet for 18 months.

Nouwen et al. (1997) included DMAE among the environmentally occurring chemicals that they classified into four groups "using structural fragments and PLS discriminant analysis." (This publication was entered into TOXLINE in November 1997).

Ono et al. (1995) reported on the antiamnestic and antihypoxic effect of cognitive-enhancing agents, including DMAE and carboxamide and ether derivatives, in mice.

Schroeder and co-workers studied the physiological effects of altering plasma membrane phospholipid polar head group composition by choline analogs, including DMAE (Feller et al., 1983; Kier et al., 1986; Schroeder, 1981; Schroeder and Doi, 1978). See also Fontaine et al. (1987) in Group 07c and in Group 07b, see Kier and Schroeder (1982) and Kier et al. (1988). All studies used LM fibroblasts.

Zs-Nagy (1994) published a 13-page review on the pharmacology of BCE-001, an analog of meclofenoxate.