

## Acetyl-L-Carnitine/ $\alpha$ -Lipoic Acid Supplements

### OVERVIEW

**This material was prepared for the National Cancer Institute (NCI) for consideration by the Chemical Selection Working Group (CSWG) by Technical Resources International, Inc. under contract no. N02-07007**

Acetyl-L-carnitine/ $\alpha$ -lipoic acid supplements were identified by the National Cancer Institute (NCI) Division of Cancer Biology (DCB) as a popular combination anti-aging and vitality formula that would be consumed over a period of many years to maximize potential beneficial effects.

In this formulation, acetyl-L-carnitine hydrochloride is thought to increase general metabolic activity and to improve cognitive function.  $\alpha$ -Lipoic acid is added as a potent antioxidant to protect against the elevated levels of free radicals produced from the increase in metabolism. Thus, acetyl carnitine/ $\alpha$ -lipoic acid dietary supplements have a potential market of tens of millions of middle-aged and elderly Americans who desire to improve their general health.

Acetyl-L-carnitine is a mitochondrial metabolite that facilitates the movement of fatty acids into the mitochondria for energy and is also used to generate acetyl coenzyme A.  $\alpha$ -Lipoic acid is a coenzyme involved in mitochondrial ATP production and its reduced form can recycle other antioxidants.

Virtually no information on the potential toxicity of acetyl-L-carnitine/ $\alpha$ -lipoic acid combinations was found in the available literature.  $\alpha$ -Lipoic acid was not mutagenic in the Ames assay.

### INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. Skip Eastin, National Institute of Environmental Health Sciences, National Institutes of Health, provided information on  $\alpha$ -lipoic acid.

### NOMINATION OF ACETYL-L-CARNITINE & ALPHA-LIPOIC ACID TO THE NTP

Based on a review of available relevant literature and the recommendations of the Chemical Selection Working Group (CSWG) held on July 1, 2003, NCI nominates acetyl-L-carnitine,  $\alpha$ -lipoic acid, and their combination used in dietary supplements for testing by the National Toxicology Program (NTP) and forwards the following information:

- The attached Summary of Data for Chemical Selection
- Copies of references cited in the Summary of Data for Chemical Selection
- CSWG recommendations to evaluate the chemicals separately and in combination in toxicity studies using mammals.

### PRIORITY FOR TESTING

The CSWG recommended that testing of these chemicals be carried out with high priority.

### COMMENTS

CSWG members felt that special emphasis should be given to the thyroid as an endpoint.

CSWG members suggested that the Office of Dietary Supplements, National Institutes of Health, be consulted.

Approximately one year following the presentation of acetyl-L-carnitine/ $\alpha$ -lipoic acid at the CSWG meeting on July 1, 2003, a search of PubMed was conducted to identify new published information.

One toxicity study was identified. This study indicated that lipoic acid is 10 times more acutely toxic to cats than in humans, dogs, or rats. The maximum tolerated dose was <30 mg/kg in cats with hepatocellular toxicity reported (Hill *et al.*, 2004).

Although no new studies of acetyl-L-carnitine/ $\alpha$ -lipoic acid combinations were identified in the literature search, several studies describing protective effects for lipoic acid were published in the last year. As examples, these studies include:

- A report that the potency of lipoic acid to protect glutathione S-transferase P1-1 against peroxynitrite-induced damage might be of therapeutic interest (Rezk *et al.*, 2004).
- A report that combined lipoic acid and dimercaptosuccinic acid provided therapeutic benefits to reduce renal damage from lead acetate in male Wistar rats (Sivaprasad *et al.*, 2004).
- A report that  $\alpha$ -lipoic acid treatment partially but significantly reversed diabetes in streptozotocin diabetic rats (Kumar & Prashanth, 2004).
- A report that lipoic acid pretreatment attenuated ferric chloride-induced seizures in male S-D rats (Meyerhoff *et al.*, 2004).
- A report indicating that acetyl-L-carnitine had beneficial effects in animal models of Parkinson's disease (Beal, 2004).

Citations to the above reports are included in the reference list and abstracts of the studies are included in the attached references.

## SUMMARY OF DATA FOR CHEMICAL SELECTION

### CHEMICAL IDENTIFICATION

#### **Acetyl-L-Carnitine Hydrochloride**

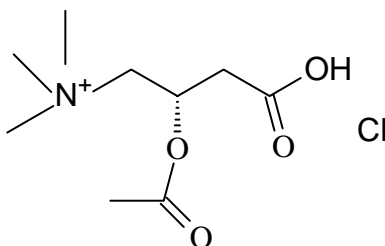
CAS Registry Numbers: 5080-50-2

Chemical Abstracts Service Name: 1-Propanaminium, 2-(acetyloxy)-3-carboxy-*N,N,N*-trimethylchloride, (*R*)- (9CI)

Synonyms and Trade Name: Acetyl-L-carnitine chloride; acetylcarnitine L-form hydrochloride; o-Acetyl-L-carnitine hydrochloride; L-O-Acetylcarnitine chloride; ALC; ALCAR; Branigen; levacecarnine hydrochloride; Nicetile; Normobren; ST-200; Zibren (Budavari, 2001; ChemID, 2003; Sigma-Aldrich, 2003a)

Structural Class: Carnitine derivative

Structure, Molecular Formula, and Molecular Weight:



C<sub>9</sub>H<sub>17</sub>NO<sub>4</sub>•HCl

Mol. wt.: 239.70

### Chemical and Physical Properties:

Description: White crystalline powder (Sigma-Aldrich, 2003b)

Melting Point: 187 °C (Budavari, 2001)

Solubility: Soluble in water and alcohol; insoluble in ether (Budavari, 2001)

Reactivity: Stable (Budavari, 2001)

### **$\alpha$ -Lipoic Acid**

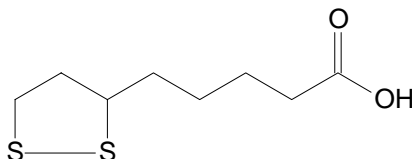
CAS Registry Number: 62-46-4

Chemical Abstracts Service Name: 1,2-Dithiolane-3-pentanoic acid (9CI)

Synonyms and Trade Names: 1,2-Dithiolane-3-valeric acid; acetate-replacing factor; Biletan; 5-(1,2-dithiolan-3-yl)valeric acid; 6,8-dithiooctanoic acid; Heparlipon; lipoic acid; Liposan; Lipothion; protogen A; pyruvate oxidation factor; Thioctacid; thioctic acid; 6,8-thioctic acid; 6-thioctic acid; thioctidase; thiooctanoic acid; Tioctan (Budavari, 2001; ChemFinder, 2003; ChemID, 2003)

Structural Class: Dithiolane carboxylic acid

Structure, Molecular Formula, and Molecular Weight:



$C_8H_{14}O_2S_2$

Mol. wt.: 206.33

Chemical and Physical Properties:

Description: Yellow powder (Sigma-Aldrich, 2003b)

Melting Point: 60-61 °C (Lewis, 2001; Lide, 2003)

Boiling Point: 160-165 °C (Lewis, 2001)

Solubility: Insoluble in water; soluble in fat solvents (Lewis, 2001; Lide, 2003)

Reactivity: Forms a water-soluble sodium salt (Lewis, 2001)

Technical Products and Impurities: Acetyl-L-carnitine hydrochloride (99%) and  $\alpha$ -lipoic acid (98%) are available from Sigma-Aldrich (Sigma-Aldrich, 2003b).

$\alpha$ -Lipoic acid is a racemic mixture of  $R^+$  ( $d$ -form) and  $S^-$  ( $l$ -form) enantiomers. The  $R$ -isomer [CAS No. 1200-22-2] is the natural co-factor of pyruvate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase in mitochondria (Hermann *et al.*, 1996). The  $R$ -form of  $\alpha$ -lipoic acid can be purified from the  $S$ -form but deteriorates rapidly at room temperature (Juvenon, Inc., 2003a).

Another racemic mixture,  $dl$ - $\alpha$ -lipoic acid [CAS No. 1077-28-7] is also available from Sigma-Aldrich at 99% purity (Sigma-Aldrich, 2003b).

## EXPOSURE INFORMATION

### Production and Producers:

*Manufacturing Process:* Acetyl-L-carnitine hydrochloride is prepared by acetylation of L-carnitine (Dubroeuq *et al.*, 2003).

$\alpha$ -Lipoic acid can be prepared by reacting 6,8-dichlorooctanoic acid with sodium disulfide. Industrial production of  $\alpha$ -lipoic acid involves the conversion of monomethyl or monoethyl adipate into the corresponding acid chloride by reaction with thionyl chloride. This mixture is treated with ethylene and anhydrous aluminum chloride yielding an intermediate compound that after reduction is treated with sodium disulfide. This process produces a dithionooctyl ester that gives  $\alpha$ -lipoic acid after hydrolysis (Csomós & Leuschner, 2003).

*Producers and Importers:* Chemical Sources International (2003) lists the following US suppliers: 6 for acetyl-L-carnitine hydrochloride, 9 for  $\alpha$ -lipoic acid, 5 for  $\alpha$ -lipoic acid (as thioctic acid), and 11 for *dl*- $\alpha$ -lipoic acid.

Acetyl-L-carnitine hydrochloride is manufactured and/or distributed by Aceto Corp.; Barrington Chemical Corp.; Compound Solutions, Inc.; Fabrichem, Inc.; Marcor Development Corp.; Robima Corp.; Sigma-Tau Health Science Inc.; Tanabe U.S.A., Inc.; and Westco Fine Ingredients, Inc. (Chemical Week Associates 2003; Tilton, 2002).

$\alpha$ -Lipoic acid is manufactured and/or distributed by AIDP, Inc.; Allchem Industries; American Ingredients, Inc.; American International Chemical Inc.; Arzneimittelwerk Dresden; Ashland Distribution Company; Barrington Chemical Corp.; Belmont Chemicals Inc.; Biosynergy Nutraceuticals; Charles Bowman & Co.; Buckton Scott USA, Inc.; CPB International, Inc.; Creative Compounds, LLC; DNP International CO., Inc.; Eastwest United Group Inc.; Eby Sales International, Inc.; European Manufacturers Assoc. Inc.; FCC Products Inc.; Fabrichem, Inc.; Flavine International Inc.; Helm New York, Inc.; Henkel Corp.; Labochim - Laboratorio Chimico Internazionale SpA; Marcor Development Corp.;

Maypro Industries, Inc.; MDS Chemical Co.; MW International; Pharmline, Inc.; Pharmore Ingredients; WM.E. Phillips Co.; RIA International LLC; Rochem International, Inc.; Paul Schueller International Inc.; Seltzer Chemicals, Inc.; E.M. Sergeant Pulp & Chemical Co.; Shanghai Desano Industrial Co., Ltd.; Spectrum Chemical Mfg. Corp.; Stryka Botantics Co., Inc.; Traco Labs, Inc./Degussa BioActives; Universal Preserv-A-Chem, Inc.; and Westco Fine Ingredients, Inc. (Chemical Week Associates, 2003; Tilton, 2002).

*dl*- $\alpha$ -Lipoic acid is manufactured and/or distributed by Acros Organics USA; Aceto Corp.; AIDP Inc.; Degussa Corporation; F.T.L. International, Inc.; Marcor Development Corp.; Santec Chemicals Corp.; and Schweizerhall, Inc. (Carroll, 2002; Hunter, 2002; Tilton, 2002).

*Production/Import/Export Level:* Acetyl-L-carnitine hydrochloride and  $\alpha$ -lipoic acid are not listed in the EPA Toxic Substances Control Act (TSCA) Inventory (ChemID, 2003).

In the 36-month period from March 2000 to March 2003, the Port Import/Export Reporting Service (PIERS) database reported  $\alpha$ -lipoic acid imports with a cargo weight of 376,903 pounds. The exporting countries were China and South Korea (Dialog Information Service, 2003).

Use Pattern: Juvenon, Inc., founded by Dr. Bruce Ames, is the primary developer of dietary supplements based on a combination of acetyl-L-carnitine and  $\alpha$ -lipoic acid. Juvenon markets this dietary supplement, Juvenon Energy Formula™ as an anti-aging product to increase natural energy and reduce toxic oxidants and cellular damage. Thus, the market segment for Juvenon Energy Formula™ is comprised of individuals over 50 years of age (Juvenon, Inc., 2003a,b).

Other dietary supplement suppliers produce acetyl-L-carnitine/  $\alpha$ -lipoic acid formulations that include additional ingredients, such as coenzyme Q10, vitamin C, vitamin E, creatine,



or Ginkgo Biloba extract. Supplemental acetyl-L-carnitine is advertised on the Internet as a substance that can enhance cognition, improve memory, and provide more energy by increasing metabolic activity (Biosynergy, 2003; Center of Hope, 2003; iHerb.com, 2003).

Juvenon, Inc., has posted information on the company website relating to research it is conducting on acetyl-L-carnitine/ $\alpha$ -lipoic acid supplements in humans, and has posted information on its website. In a single-center, randomized, double-blind, placebo-controlled study lasting 17 weeks, Juvenon Energy Formula™ (acetyl-L-carnitine/ $\alpha$ -lipoic acid) given to 18 healthy men, age 60-71, produced positive effects for 8 of 9 measures of exercise-induced oxidative stress in the majority of subjects. Based on scores from the Psychological General Well Being Index, the majority of subjects had higher scores assessing perceptions related to mood and general health (Juvenon, Inc., 2003c).

Juvenon, Inc. is presently conducting a clinical trial to evaluate the effect of Juvenon Energy Formula™ on cardiovascular patients. The goal is to measure effects on endothelial function and blood pressure in 40 elderly subjects (55-95 years of age) (Juvenon, Inc., 2003d).

Acetyl-L-carnitine hydrochloride has demonstrated some efficacy as a neuroprotective agent and its administration may be indicated for use in strokes, Alzheimer's disease, Down's syndrome, and managing some neuropathies (Hendler & Rorvik, 2001; Salvioli & Neri, 1994). Other human conditions reported to benefit from acetyl-L-carnitine administration are geriatric depression, cerebellar ataxia, type 2 diabetes, and HIV (Zdanowicz, 2001).

Acetyl-L-carnitine alone is also marketed as an anti-aging dietary supplement (Life Extension Magazine, 2000). It is thought that acetyl-L-carnitine may improve mental impairments in aging humans and animals through mechanisms that increase energy metabolism in the brain and enhance brain cholinergic activity through acetylcholine release

(Bossoni & Carpi, 1986; Imperato *et al.*, 1989; Toth *et al.*, 1993). Animal studies suggest that supplemental acetyl-L-carnitine may enhance cognitive functioning by elevating nerve growth factor (NGF) levels in the brain, stabilizing cell membranes and improving synaptic morphology, and decreasing the accumulation of potentially toxic fatty acids (Zdanowicz, 2001).

$\alpha$ -Lipoic acid dietary supplements are also sold as antioxidants and free radical quenchers. Supplemental  $\alpha$ -lipoic acid is currently used in Germany to treat peripheral nerve degeneration resulting from diabetes. It has also been used as a therapeutic agent for hepatic coma, chronic hepatitis, cirrhosis of the liver, and has been partially successful in treating glaucoma and Amanita mushroom poisoning (Biosynergy, 2003; Conemaugh Health System, 2001a; Csomós & Leuschner, 2003; Herbal Advisor, 2003; Nichols, 1977).

The beneficial effects of  $\alpha$ -lipoic acid have been attributed to its anti-oxidant activity.  $\alpha$ -Lipoic acid can scavenge hydroxyl radicals, hypochlorous acid, and singlet oxygen, but not hydrogen peroxide or peroxy and superoxide radicals (Nichols, 1977; Scott *et al.*, 1994).

The National Center for Complementary and Alternative Medicine (NCCAM) is conducting two clinical trials involving  $\alpha$ -lipoic acid. A Phase II clinical trial to determine immunomodulatory and antiviral effects of  $\alpha$ -lipoic acid in HIV-infected persons unresponsive to highly active antiretroviral treatment is recruiting 42 patients and anticipates a 2003 completion date. A Phase I/Phase II project to assess three natural anti-oxidant regimens, including  $\alpha$ -lipoic acid/essential fatty acids, for their ability to suppress autoimmune encephalomyelitis in multiple sclerosis patients was not yet open for patient recruitment as of the last record review date (ClinicalTrials.gov, 2003).

As of March 2003, the number of patents on file with the US Patent and Trademark Office for acetyl-L-carnitine and  $\alpha$ -lipoic acid were 140 and 1,059, respectively (US Patent and Trademark Office, 2003).

Human Exposure:

*Consumer Exposure:* One source of human exposure to acetyl-L-carnitine and  $\alpha$ -lipoic acid occurs from their ingestion in dietary supplements. These dietary supplements appeal to older persons as substances that rejuvenate the body by increasing available energy and mental acuity, although students and athletes are a secondary target market (Conemaugh Health System, 2001a,b).

The natural dietary source of acetyl-L-carnitine is red meat while  $\alpha$ -lipoic acid is present in meats and vegetables such as spinach (Juvenon, Inc., 2003a).

There are no standard doses for acetyl-L-carnitine and  $\alpha$ -lipoic acid supplements. The highest doses recommended for acetyl-L-carnitine (no salt specified) and for  $\alpha$ -lipoic acid are 1,500 and 600 mg/day, respectively (Biosynergy, 2003; Conemaugh Health System, 2001a; Juvenon, Inc., 2003a).

Other supplements have lower quantities of these compounds, 20-30 mg of acetyl-L-carnitine (no salt specified) and 20-50 mg of  $\alpha$ -lipoic acid, but additional antioxidants may be present in these formulations (Biosynergy, 2003; Center of Hope, 2003; iHerb.com, 2003).

An oral dose of 800 mg per day of  $\alpha$ -lipoic acid was reported to be beneficial in treating patients with diabetic neuropathies (Conemaugh Health System, 2001a).

*Occupational Exposure:* The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981-1983, estimated that 429 workers, including 141 females, in 138 facilities representing 2 industries were potentially exposed to  $\alpha$ -lipoic acid in the workplace (RTECS, 1996). The NOES database does not contain information on the frequency, level, or duration of

exposure to workers of any chemical listed therein, and it does not reflect recent increased usage of  $\alpha$ -lipoic acid as a dietary supplement and therapeutic agent.

Environmental Occurrence: As described in the section on metabolism, acetyl-L-carnitine and  $\alpha$ -lipoic acid are produced in vertebrates naturally. In addition,  $\alpha$ -lipoic acid has been described as a growth factor for certain protozoa and bacteria (Csomós & Leuschner, 2003). No information on any other environmental occurrence of acetyl-L-carnitine or  $\alpha$ -lipoic acid was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by NIOSH or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of acetyl-L-carnitine hydrochloride or  $\alpha$ -lipoic acid. Furthermore, these compounds were not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). The DSHEA requires no proof of safety for dietary supplements on the market prior to October 15, 1994. Labeling requirements for dietary supplements allow warnings and dosage recommendation as well as substantiated “structure or function” claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement “This product is not intended to diagnose, treat, cure, or prevent any disease” (FDA, 1995).

## TOXICOLOGY INFORMATION

Human Data: No epidemiological studies or case reports investigating exposure to acetyl-L-carnitine and/or  $\alpha$ -lipoic acid and cancer risk in humans were identified in the available literature.

Juvenon, Inc. performed a study in humans given Juvenon Energy Formula™ (500 mg of acetyl-L-carnitine and 200 mg of  $\alpha$ -lipoic acid) twice a day. No toxic endpoints were reported or investigated in this study. Another clinical trial with Juvenon Energy Formula™ to assess potential benefits on endothelial function is underway (Juvenon, Inc., 2003c,d).

Mild adverse reactions, including gastrointestinal effects, have been reported after acetyl-L-carnitine administration. However, acetyl-L-carnitine may interfere with thyroid metabolism. In individuals with seizure disorders, an increase in seizure frequency and severity has also been reported (De Grandis *et al.*, 1995; Hendler & Rorvik, 2001; Juvenon, Inc., 2003a; Zdanowicz, 2001).

In studies where acetyl-L-carnitine was given to Alzheimer's disease patients at doses of 1.5-3.0 g/day for two to six months, no serious side effects were observed. In a clinical trial where 1,097 patients received 1,000 mg/day of acetyl-L-carnitine hydrochloride intramuscularly (i.m.) route for 10 days followed by 2,000 mg orally for 20 days, six patients withdrew from the study due to gastrointestinal side effects (Zdanowicz, 2001).

Oral  $\alpha$ -lipoic acid has been well tolerated in doses up to 600 mg/day. Adverse side effects reported were allergic skin conditions, possible hypoglycemia in diabetic patients, and thiamine deficiency at high doses (Juvenon, Inc., 2003a; Nichols, 1997).

The National Center for Complementary and Alternative Medicine (NCCAM) is conducting a Phase 2 clinical trial to investigate the immunomodulatory and antiretroviral effects of

dietary  $\alpha$ -lipoic acid in HIV-infected patients. NCCAM is also sponsoring studies of anti-oxidant therapies including a combination of  $\alpha$ -lipoic acid and essential fatty acids in animal models of multiple sclerosis (MS). Clinical trials on successful therapies will be conducted in MS patients (ClinicalTrials.gov, 2003a,b).

Animal Data: No 2-year carcinogenicity studies of acetyl-L-carnitine hydrochloride and/or  $\alpha$ -lipoic acid compounds in animals were identified in the available literature.

*Acute Toxicity:*

The LD<sub>50</sub> values for  $\alpha$ -lipoic acid are listed in Table 1.

**Table 1. Acute Toxicity Values for  $\alpha$ -lipoic acid**

Species	Route of administration	LD <sub>50</sub> (mg/kg)
mouse	oral	502
rat	oral	1,130
dog	oral	400-500

Source: Nichols, 1997; RTECS, 1996

$\alpha$ -Lipoic acid, administered intraperitoneally (i.p.) to rats at 0.5-1.5 mmol/kg, inhibited glycine conjugation of injected benzoic acid and depleted hepatic acetyl coenzyme A (CoA), L-carnitine, and glutathione, but not ATP, while increasing hepatic levels of glycine. It also reduced urine formation in a dose-dependent manner causing acute renal failure at the highest dose (Gregus *et al.*, 1996).

$\alpha$ -Lipoic acid administered intravenously (i.v.) at 60 or 100 mg/kg inhibited gluconeogenesis, causing a rapid reduction of blood glucose in both diabetic and control rats. This effect was secondary to  $\alpha$ -lipoic acid interference in fatty acid oxidation in the liver (Khamaisi *et al.*, 1999).

*Subchronic Toxicity:* No information on the subchronic toxicity of acetyl-L-carnitine,  $\alpha$ -lipoic acid, or combinations was found in the available literature.

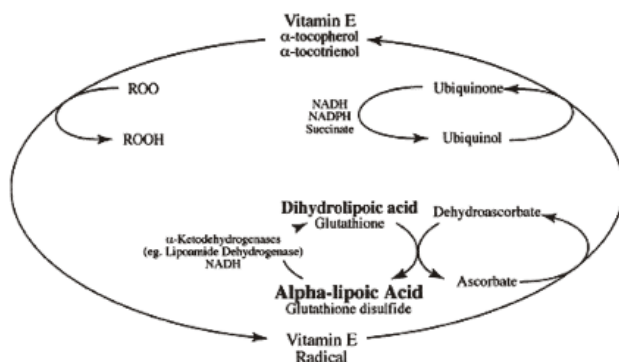
Short-Term Tests: In a study completed in 1998,  $\alpha$ -lipoic acid was negative in *Salmonella typhimurium* TA97, TA98, TA100, and TA1535 with and without rat and hamster liver S-9 (NTP, 2004).

Metabolism:

*Acetyl-L-Carnitine:* Acetyl-L-carnitine is formed in the mitochondria by carnitine acetyltransferase, which combines L-carnitine with an acetyl group from CoA. Acetyl-L-carnitine is then transported across the inner mitochondrial membrane by carnitine acetyltranslocase, where it diffuses out of the mitochondria into the cytoplasm and serves as a source of acetyl groups for cytosolic proteins. The acetyl group also provides for the generation of acetylcholine (Hendler & Rorvik, 2001; Zdanowicz, 2001).

Acetyl-L-carnitine does not significantly bind to albumin or other serum proteins. It readily crosses the blood-brain barrier and its elimination occurs via the kidneys (Zdanowicz, 2001).

*$\alpha$ -Lipoic Acid:* In the mitochondria,  $\alpha$ -lipoic acid is covalently linked to a lysyl residue as a lipoamide in proteins. At the expense of NADPH,  $\alpha$ -lipoic acid is reduced to dihydrolipoic acid (DHLA) which reacts with oxidants such as superoxide and hydroxy radicals. It also reduces oxidized vitamin C and glutathione, which in turn recycle ascorbic acid and vitamin E (Figure 1).  $\alpha$ -Lipoic acid also acts as a coenzyme in mitochondrial multienzyme complexes in the oxidative decarboxylation of  $\alpha$ -keto acids such as pyruvate and  $\alpha$ -ketoglutarate (Breithaupt-Grögler *et al.*, 1999; Csomós & Leuschner, 2003; Liu *et al.*, 2002a).



**Figure 1.  $\alpha$ -Lipoic acid: Antioxidant Regeneration**

Food-derived  $\alpha$ -lipoic acid originates from multienzyme complexes. Due to the lack of effective proteolytic enzymes,  $\alpha$ -lipoic acid from the diet is absorbed as a lypoyllysine. In addition,  $\alpha$ -lipoic acid can be produced by *de novo* biosynthesis, where cysteine appears to be the source of sulfur and octanoate serves as the intermediate precursor for the 8-carbon fatty acid. Only minor amounts of  $\alpha$ -lipoic acid will enter the circulation from food or biosynthesis. The concentration of  $\alpha$ -lipoic acid has been found to be highest in the liver (Biewenga *et al.*, 1997; Csomós & Leuschner, 2003; Nichols, 1997).

In humans,  $\alpha$ -lipoic acid is excreted mainly in the urine within 24 hr of a single oral or parenteral dose. The main plasma and urine metabolite of  $\alpha$ -lipoic acid is 4,6-bismethylmercapto-hexanoic acid following oral administration, indicating that  $\alpha$ -lipoic acid undergoes predominantly  $\beta$ -oxidation and methylation at the sulfur atoms. In addition, methyl sulfoxide metabolites are also formed (Hermann *et al.*, 1996; Nichols, 1997; Schupke *et al.*, 2001; Teichert *et al.*, 1998).

In humans administered a single oral dose of  $\alpha$ -lipoic acid, maximum plasma concentrations of both enantiomers were attained rapidly ( $\leq 1$  hr) and were 40-50 percent higher for the *R*-form. The plasma half-lives were short ( $< 1$  hr) for both enantiomers, however the *S*-form has a higher total plasma clearance, suggesting stereoselective



differences during drug absorption, transport, and hepatic extraction (Breithaupt-Grögler *et al.*, 1999; Hermann *et al.*, 1996).

$\alpha$ -Lipoic acid enantiomers were absorbed more slowly from solid oral formulations than from oral solutions. Food intake also significantly reduced the bioavailability of  $\alpha$ -lipoic acid in healthy volunteers (Hermann *et al.*, 1996; Teichert *et al.*, 1998).

In animal studies, 93 percent of a dose of radioactive-labeled  $\alpha$ -lipoic acid was absorbed at all parts of the gastrointestinal tract. Another report found that 25 percent of the administered dose of radiolabeled  $\alpha$ -lipoic acid was exhaled as CO<sub>2</sub> within two hours, reaching 30 percent within 24 hours of administration (Harrison & McCormick, 1974; Peter & Borbe, 1995).

Uptake of exogenously administered  $\alpha$ -lipoic acid occurs in all areas of the central nervous system and peripheral nerves (Packer *et al.*, 1997).

#### Other Biological Effects:

*Tumor Inhibition Studies:*  $\alpha$ -Lipoic acid, given in drinking water at 45 and 180 mg/kg/day to male Sprague-Dawley rats administered 10 mg/kg of *N*-nitroso-diethylamine orally twice weekly for life, did not significantly change tumor frequencies, induction times, or histology of liver and esophageal tumors (Habs *et al.*, 1980).

Intravenous (i.v.), subcutaneous (s.c.), or intraperitoneal (i.p.) administration of  $\alpha$ -lipoic acid at a daily dose of 100 mg/kg for five days to NMRI mice implanted with Ehrlich ascites carcinoma had no effects on tumor growth. A decrease in survival time was thought to be due to the high dose of  $\alpha$ -lipoic acid administered (Kunstler, 1980).

*Reproductive or Developmental Effects Studies:*  $\alpha$ -Lipoic acid administered i.p. to pregnant diabetic rats reduced the number of malformations and fetal loss when compared to the

offspring of untreated diabetic rats.  $\alpha$ -Lipoic acid also protected against growth reduction of diabetic embryos (Wiznitzer *et al.*, 1996).

$\alpha$ -Lipoic acid induced malformations of body segments and appendages in developing horseshoe crabs (Itow, 1980).

*Studies Designed to Investigate Beneficial Effects of Acetyl-L-Carnitine or  $\alpha$ -Lipoic Acid*

- *Effects on Mitochondrial Metabolic Activity:*

Carnitine acetyltransferase (CAT) regenerates CoA in the mitochondria allowing  $\beta$ -oxidation to proceed. A decrease in CAT activity in brain and muscles has been shown to be age-related. The combination of acetyl-L-carnitine hydrochloride and *R*- $\alpha$ -lipoic acid given orally to old rats significantly restored CAT activity and CAT's binding affinity for the substrates acetyl-L-carnitine and CoA to the levels observed in young rats (Liu *et al.*, 2002b).

Oral administration of acetyl-L-carnitine hydrochloride to rats reversed the age-associated decrease in cytochrome *c* oxidase and phosphate carrier activity in heart mitochondria (Hagen *et al.*, 2002a).

- *Pro- and Anti-oxidant Properties:*

Acetyl-L-carnitine hydrochloride and *R*- $\alpha$ -lipoic acid dietary administration increased hepatocellular ascorbate in old rats to levels comparable to those found in young untreated rats (Hagen *et al.*, 2002b).

Malondialdehyde (MDA) levels in brain and hepatocytes are significantly higher in old rats when compared to young rats. Dietary administration of acetyl-L-carnitine hydrochloride/*R*- $\alpha$ -lipoic acid combinations or *R*- $\alpha$ -lipoic acid alone lowered the brain MDA concentrations in old rats. Oral doses of acetyl-L-carnitine hydrochloride and  $\alpha$ -lipoic acid also decreased hepatic MDA levels in old rats (Hagen *et al.*, 2002b; Liu *et al.*, 2002b).

Oral doses of acetyl-L-carnitine increased the rate of oxidant production in the liver of old rats when compared to cells from control old animals. This regimen did not raise the oxidative stress in cardiac cells of old rats (Hagen *et al.*, 2002a).

$\alpha$ -Lipoic acid increased *in vivo* and *in vitro* intracellular glutathione concentrations (Busse *et al.*, 1992; Packer, 1998).

Preincubation of non-diabetic and diabetic human erythrocytes with oxidized  $\alpha$ -lipoic acid increased nitrite-mediated formation of methemoglobin but significantly reduced the 4-aminophenol-mediated formation of methemoglobin in diabetic and non-diabetic cells (Coleman & Walker, 2000).

- *Effects on Neuronal Function:*

Dietary administration of acetyl-L-carnitine hydrochloride and/or *R*- $\alpha$ -lipoic acid improved age-related mitochondrial structural decay in hippocampal neurons in old rats (Liu *et al.*, 2002a).

Acetyl-L-carnitine accelerated the maturation of cerebellar neurons *in vitro*, activated nerve growth factor receptors, and prevented the loss of substance P in the peripheral nerves in diabetic animals (De Grandis *et al.*, 1995).

Old rats given oral  $\alpha$ -lipoic acid showed delayed hearing loss while rats treated with acetyl-L-carnitine hydrochloride experienced hearing improvement (Seidman *et al.*, 2000).

- *Regulation of Programmed Cell Death:*

Acetyl-L-carnitine administration to HIV-1-infected subjects decreased the levels of apoptotic CD4 T-cells (Di Marzio *et al.*, 1999).

*In vitro* Fas-mediated apoptosis of human acute leukemic Jurkat T-cells was significantly potentiated by  $\alpha$ -lipoic acid through an increase in caspase 3 activity (Sen *et al.*, 1999).

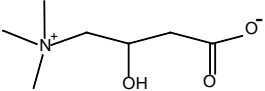
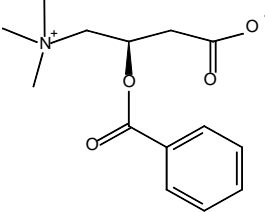
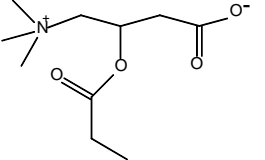
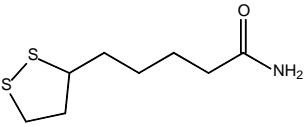
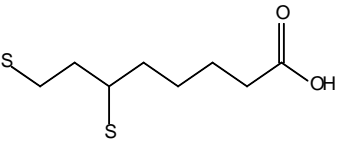
- *Effects on Gene Expression:*

$\alpha$ -Lipoic acid inhibited the activation of the NF- $\kappa$ B transcription factor induced by tumor necrosis factor- $\alpha$  in Jurkat T cells (Packer, 1998).

Structure-Activity Relationships: Three compounds structurally-related to acetyl-L-carnitine and two compounds structurally-related to  $\alpha$ -lipoic acid have been selected for review. These chemicals were L-carnitine, benzoylcarnitine, propionylcarnitine, lipoamide, and dihydrolipoic acid. No information on the carcinogenicity of any of these chemicals was identified in the available literature.

A brief review of the pharmacological and toxicological data on the five chemicals is presented in Table 2.

**Table 2. Pharmacological and Toxicological Information  
on Chemicals Structurally-Related to Acetyl-L-Carnitine and  $\alpha$ -Lipoic Acid**

Chemical/CAS No.	Structure	Pharmacological/Toxicological Effects
<b>L-Carnitine</b> 541-15-1		Not mutagenic in standard assays (Hendler & Rorvik, 2001)
<b>Benzoylcarnitine</b> 105450-08-6		Urinary metabolite of sodium benzoate and L-carnitine therapy to treat hyperammonemia (Sakuma <i>et al.</i> , 1989)
<b>Propionylcarnitine</b> 17298-37-2		Anti-oxidant activity (Hendler and Rorvik, 2001; Vanella <i>et al.</i> , 2000)
<b>Lipoamide</b> 940-69-2		Anti-oxidant activity (Bustamante <i>et al.</i> , 1995; Goloshchapov & Agranovskii, 1976)
<b>Dihydrolipoic acid</b> 462-20-4		Anti-oxidant activity (Biewenga <i>et al.</i> , 1997; Bustamante <i>et al.</i> , 1995)

## References

- Beal, M.F. (2003) Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann. Neurol.*, **53** (Suppl 3), 39-48 [abstract]
- Biewenga, G.P., Haenen, G.R.M.M. & Bast, A. (1997) The pharmacology of the antioxidant lipoic acid. *Gen. Pharmac.*, **29**(3), 315-331
- Biosynergy (2003) Bioendurance™. *Biosynergy Health Alternatives*. [<http://www.biosynergy.com/endur.htm>] Searched March 4, 2003
- Bossoni, G. & Carpi, C. (1986) Effect of Acetyl-L-carnitine on conditioned reflex learning rate and retention in laboratory animals. *Drugs Exptl. Clin. Res.*, **12**(11), 911-916
- Breithaupt-Grögler, K.B., Niebch, G., Schneider, E., Erb, K., Hermann, R., Blume, H.H., Schug, B.S. & Belz, G.G. (1999) Dose-proportionality of oral thioctic acid – coincidence of assessments via pooled plasma and individual data. *European Journal of Pharmaceutical Sciences*, **8**, 57-65
- Budavari, S., ed. (2001) *The Merck Index*, 13<sup>th</sup> ed., Whitehouse Station, NJ, Merck & Co., Inc., p 16, 1663
- Busse, E., Zimmer, G., Schopohl, B. & Kornhuber, B. (1992) Influence of  $\alpha$ -lipoic acid on intracellular glutathione *in vitro* and *in vivo*. *Arzneim.-Forsch./Drug Res.*, **42**(6), 829-831
- Bustamante, J., Slater, A.F.G. & Orrenius, S. (1995) Antioxidant inhibition of thymocyte apoptosis by dihydrolipoic acid. *Free Radical Biol. Med.*, **19**(3), 339-347
- Carroll, K.M. (2002) Lipoic acid, Thioctic acid. *Chemyclopedia 2003*, Wayne, PA, American Chemical Society, p 153, 215
- Center of Hope (2003) Mitochondrial Resuscitate™. "Making Ripples." [<http://www.makeripples.com/Shop/ProductPage.asp?StockNum=MT001>] Searched March 7, 2003
- ChemFinder (2003) Acetylcarnitine, Acetyl-L-carnitine, Lipoic Acid. *ChemFinder.Com Search Result Page*. [<http://chemfinder.cambridgesoft.com/result.asp>] Searched February 28, 2003
- ChemID (2003) Acetylcarnitine, Acetyl-L-carnitine, Acetylcarnitine L-form hydrochloride, Thioctic acid, Thioctic acid d-form, Thioctic acid dl-form, Thioctic acid l-form. *ChemIDplus*. National Library of Medicine, Bethesda, MD. [Record Nos.005080502 and 000062464]. [<http://chem.sis.nlm.nih.gov/chemidplus/>] Searched February 27 and March 6, 2003

Chemical Sources International (2003) *All Chemical Suppliers for: Acetyl-L-carnitine hydrochloride, Acetyl-L-carnitine,  $\alpha$ -Lipoic acid, DL- $\alpha$ -Lipoic acid, Thioctic acid.* [<http://www.chemsources.com>] Searched March 3, 2003 and April 18, 2003

Chemical Week Associates (2003) Search Results for “Acetyl-L-carnitine HCL”, “Alpha lipoic acid”, “R(+)-Thioctic acid” in products. *Chemical Week Buyers' Guide.* [<http://redirect.chemweek.com/cw/buyersguide>] Searched April 18, 2003

ClinicalTrials.gov (2003a) *Immune restoration by lipoic acid in AIDS.* [<http://clinicaltrials.gov/ct/show/NCT00033176?order=1>] Searched August 20, 2003

ClinicalTrials.gov (2003b) *Natural anti-oxidants in the treatment of multiple sclerosis.* (<http://clinicaltrials.gov/ct/show/NCT00010842?order=2>) Searched August 20, 2003

Coleman, M.D. & Walker, C.L. (2000) Effects of oxidized alpha-lipoic acid and alpha-tocopherol on xenobiotic-mediated methaemoglobin formation in diabetic and non-diabetic human erythrocytes in-vitro. *Environ. Toxicol. Pharmacol.*, **8**(2), 127-132 [abstract]

Conemaugh Health System (2001a) Alpha lipoic acid. *Health Library.* [<http://www.conemaugh.org/Library/HealthGuide/CAM/topic.asp?hwid=hn-2799001>] Searched March 7, 2003

Conemaugh Health System (2001b) Acetyl-L-carnitine. *Health Library.* [<http://www.conemaugh.org/Library/HealthGuide/CAM/topic.asp?hwid=hn-2795007>] Searched March 7, 2003

Csomós, G. & Leuschner, U. (2003) Gallbladder and liver therapy. In: *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. 15, Wiley-VCH Publishers, p 215-230

De Grandis, D., Santoro, L. & Di Benedetto, P. (1995) L-Acetylcarnitine in the treatment of patients with peripheral neuropathies. A short term, double-blind clinical study of 426 patients. *Clin. Drug Invest.*, **10**(6), 317-322

Dialog Information Services (2003) Search for alpha lipoic acid and thioctic acid. *PIERS (Files Imports [US Ports] (File 573)*, Palo Alto, CA, [Record nos. 0032025690, 0032013283, 0031993953, 0031980539, 0031969448, 0031943089, 0031942724, 0031940137, 0031919470, 0031916287, 0031911679, 0031882061, 0031863532, 0031860271, 0031594580, 0031538429, 0031443613, 0031120639, 0030911413, 0030679644, 0030670199, 0030524188, 0030445559, 0030286613, 0030286391, 0028850648, 0026758786, 0025899832, 0025738713, 0025631821, 0025506055, 0025404809, 0024878061, 0024387276, 0024133209, 0023981255, 0023832370, 0023482609, 0022985411, 0020002090] Searched May 8, 2003

Di Marzio, L., Moretti, S., D'Alo, S., Zazzeroni, F., Marcellini, S., Smacchia, C., Alesse, E., Cifone, M.G. & De Simone, C. (1999) Acetyl-L-carnitine administration increases insulin-like growth factor 1 levels in asymptomatic HIV-1-infected subjects: Correlation with its suppressive effect on lymphocyte apoptosis and ceramide generation. *Clin. Immuno.*, **92**(1), 103-110

Dubroeuq, M.-C., Stutzmann, J.-M., Manfre, F., Capet, M. & Bohme, G.A. (2003) Psychopharmacological agents. In: *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. 30, Wiley-VCH Publishers, p 397-442

FDA (1995) Dietary Supplement Health and Education Act of 1994. *US Food and Drug Administration*. [<http://vm.cfsan.fda.gov/~dms/dietsupp.html>] Searched April 23, 2003

Goloshchapov, O.D. & Agranovskii, M.Z. (1976) Lipoamide as a component of a prophylactic diet in exposure to formaldehyde. *Gig. Sanit.*, **3**, 25-28 [abstract]

Gregus, Z., Fekete, T., Halaszi, E. & Klaassen, C.D. (1996) Lipoic acid impairs glycine conjugation of benzoic acid and renal excretion of benzoglycine. *Drug Metab. Dispos.*, **24**(6), 682-8 [abstract]

Habs, M., Habs, H. & Schmahl, D. (1980) Influence of thioctic acid (alpha-lipoic acid) on N-nitroso-diethylamine-induced carcinogenesis in male Sprague-Dawley rats. *Arzneimittelforschung*, **30**(10), 1715-1717

Hagen, T.M., Moreau, R., Suh, J.H. & Visioli, F. (2002a) Mitochondrial decay in the aging rat heart. Evidence for improvement by dietary supplementation with acetyl-L-carnitine and/or lipoic acid. *Ann. N.Y. Acad. Sci.*, **959**, 491-507

Hagen, T.M., Liu, J., Lykkesfeldt, J., Wehr, C.M., Ingersoll, R.T., Vinarsky, V., Bartholomew, J.C. & Ames, B.N. (2002b) Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *PNAS*, **99**(4), 1870-1875

Harrison, E.H. & McCormick, D.B. (1974) The metabolism of dl-[1,6-<sup>14</sup>C]lipoic acid in the rat. *Arch. Biochem. Biophys.*, **160**, 514-522 [cited in Hermann *et al.*, 1996]

Hendler, S.S. & Rorvik, D., eds. (2001) Acetyl-L-carnitine, L-carnitine. *PDR for Nutritional Supplements*. Montvale, Medical Economics Company, Inc., p 9-11, 255-259

Hermann, R., Niebch, G., Borbe, H.O., Fieger-Buschges, H., Ruus, P., Nowak, H., Riethmuller-Winzen, H., Peukert, M. & Blume, H. (1996) Enantioselective pharmacokinetics and bioavailability of different racemic  $\alpha$ -lipoic acid formulations in healthy volunteers. *European Journal of Pharmaceutical Sciences*, **4**, 167-174

Hill, A.S., Werner, J.A., Rogers, Q.R., O'Neill, S.L. & Christopher, M.M. (2004) Lipoic acid is 10 times more toxic in cats than reported in humans, dogs or rats. *J. Anim. Physiol. Anim. Nutr. (Berl.)*, **88**(3-4), 150-156 [abstract]

Hunter, D., ed. (2002) Acetyl-L-carnitine, Lipoic acid reagent, D,L-Thioctic acid. *Chemical Week 2003 Buyers' Guide & Industry Almanac*, New York, BPA International, p 116, 301, 443

iHerb.com (2003) Advanced Ginkgo Smart, Irwin Naturals, 90 Liquid Gel Caps. *iHerb.com*. [<http://www.iherb.com/advancedginkgo.html>] Searched March 7, 2003

Imperato, A., Ramacci, M.T. & Angelucci, L. (1989) Acetyl-L-carnitine enhances acetylcholine release in the striatum and hippocampus of awake freely moving rats. *Neurosci. Lett.*, **107**(1-3), 251-255 [abstract]

Itow, T. (1980) Teratogenesis of the horseshoe crab by alpha-lipoic amide (6,8-thioctic amide) in marketed vitamin tablets. *J. Nutr. Sci. Vitaminol. (Tokyo)*, **26**(3), 237-45 [abstract]

Juvenon, Inc. (2003a) Questions & Answers. *Juvenon*<sup>TM</sup>. [<http://www.juvenon.com/qa.html>] Searched April 21, 2003

Juvenon, Inc. (2003b) *Juvenon Energy Formula*<sup>TM</sup>. [[http://www.juvenon.com/Product Brochure.pdf](http://www.juvenon.com/Product%20Brochure.pdf)] Searched April 21, 2003

Juvenon, Inc. (2003c) Energy Study. *Juvenon*<sup>TM</sup>. [<http://www.juvenon.com/energy.html>] Searched April 21, 2003

Juvenon, Inc. (2003d) Current Research. *Juvenon*<sup>TM</sup>. [<http://www.juvenon.com/research.html>] Searched April 22, 2003

Khamaisi, M., Rudich, A., Potashnik, R., Tritschler, H.J., Gutman, A. & Bashan, N. (1999) Lipoic acid acutely induces hypoglycemia in fasting nondiabetic and diabetic rats. *Metabolism*, **48**(4), 504-510 [abstract]

Kumar, M.S. & Prashanth, K.V. (2004) alpha-Lipoic acid ameliorates altered colonic contractility and intestinal transit in STZ-diabetic rats. *Indian J. Exp. Biol.*, **42**(3), 279-282 [abstract]

Kunstler, K. (1980) The influence of thioctic acid on the growth of Ehrlich ascites carcinoma. *Arzneim. Forschung*, **30**(10), 1717-1718 [abstract]

Lewis, R.J. Sr. (2001) *dl*- $\alpha$ -Lipoic acid. *Hawley's Condensed Chemical Dictionary*, 14<sup>th</sup> ed., John Wiley & Sons, Inc., New York, p 671



Lide, D.R., ed. (2003) Thiocctic acid. *CRC Handbook of Chemistry and Physics*, Version 2003 on CD-ROM, Boca Raton, CRC Press

Liu, J., Head, E., Gharib, A.M., Yuan, W., Ingersoll, R.T., Hagen, T.M., Cotman, C.W. & Ames, B.N. (2002a) Memory loss in old rats is associated with brain mitochondrial decay and RNA/DNA oxidation: Partial reversal by feeding acetyl-L-carnitine and/or R- $\alpha$ -lipoic acid. *PNAS*, **99**(4), 2356-2361

Liu, J., Killilea, D.W. & Ames, B.N. (2002b) Age-associated mitochondrial oxidative decay: Improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L-carnitine and/or R- $\alpha$ -lipoic acid. *PNAS*, **99**(4), 1876-1881

Meyerhoff, J.L., Lee, J.K., Rittase, B.W., Tsang, A.Y. & Yourick, D.L. (2004) Lipoic acid pretreatment attenuates ferric chloride-induced seizures in the rat. *Brain Res.*, **1016**(2), 139-144 [abstract]

Nichols, T.W., Jr. (1997)  $\alpha$ -Lipoic acid: Biological effects and clinical implications. *Alternative Med. Rev.*, **2**(3), 177-183

NTP (2004) NTP studies on alpha-lipoic acid. *National Toxicology Program Database Search*. [[http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?)] Searched August 20, 2004

Packer, L., Tritschler, H.J. & Wessel, K. (1997) Neuroprotection by the metabolic antioxidant  $\alpha$ -lipoic acid. *Free Radical Biology & Medicine*, **22**(1-2), 359-378

Packer, L. (1998)  $\alpha$ -Lipoic acid: a metabolic antioxidant which regulates NF- $\kappa$ B signal transduction and protects against oxidative injury. *Drug Metabolism Reviews*, **30**(2), 245-275

Peter, G. & Borbe, H.O. (1995) Absorption of [7,8-<sup>14</sup>C]rac- $\alpha$ -lipoic acid from in situ ligated segments of the gastrointestinal tract of the rat. *Arzneim. Forsch./Drug Res.*, **45**, 293-299 [cited in Hermann *et al.*, 1996]

Rezk, B.M., Haenen, G.R., van der Vijgh, W.J. & Bast, A. (2004) Lipoic acid protects efficiently only against a specific form of peroxynitrite-induced damage. *J. Biol. Chem.*, **279**(11), 9693-9697 [abstract]

RTECS (1996) 1,2-Dithiolane-3-valeric acid. National Institute for Occupational Safety and Health. [<http://www.cdc.gov/niosh/rtecs/jp122870.html>] Searched April 17, 2003 [RTECS No. JP1190000]

Sakuma, T., Asai, K., Ichiki, T., Sugiyama, N., Kidouchi, K. & Wada, Y. (1989) Identification of benzoylcarnitine in the urine of a patient of hyperammonemia. *Tohoku J. Exp. Med.*, **159**(2), 147-51 [abstract]

Salvioli, G. & Neri, M. (1994) L-acetylcarnitine treatment of mental decline in the elderly. *Drugs Exptl. Clin. Res.*, **20**(4), 169-176

Schupke, H., Hempel, R., Peter, G., Hermann, R., Wessel, K., Engel, J. & Kronbach, T. (2001) New metabolic pathways of  $\alpha$ -lipoic acid. *Drug Metab. Dispos.*, **29**(6), 855-862

Scott, B.C., Aruoma, O.I., Evans, P.J., O'Neill, C., Van der Vliet, A., Cross, C.E., Tritschler, H. & Halliwell, B. (1994) Lipoic and dihydrolipoic acids as antioxidants. A critical evaluation. *Free Radical Res.*, **20**(2), 119-133

Seidman, M.D., Khan, M.J., Bai, U., Shirwany, N. & Quirk, W.S. (2000) Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. *Am. J. Otol.*, **21**, 161-167

Sen, C.K., Roy, S. & Packer, L. (1999) Fas mediated apoptosis of human Jurkat T-cells: intracellular events and potentiation by redox-active  $\alpha$ -lipoic acid. *Cell Death Differ.*, **6**, 481-491

Sigma-Aldrich (2003a) Acetyl-L-carnitine, Thioctic acid, and DL-6,8-Thioctic acid. *Search Results*. [<http://www.sigma-aldrich.com>] Searched March 3-7, 2003

Sigma-Aldrich (2003b) *Acetyl-L-carnitine, Thioctic acid, DL-6,8-Thioctic acid Material Safety Data Sheets*. [<http://www.sigma-aldrich.com>] Searched March 3-6, 2003

Sivaprasad, T.R., Malarkodi, S.P. & Varalakshmi, P. (2004) Therapeutic efficacy of lipoic acid in combination with dimercaptosuccinic acid against lead-induced renal tubular defects and on isolated brush-border enzyme activities. *Chem.-Bio. Interact.*, **147**(3), 259-271 [abstract]

Teichert, J., Kern, J., Tritschler, H.-J., Ulrich, H. & Preib, R. (1998) Investigations on the pharmacokinetics of  $\alpha$ -lipoic acid in healthy volunteers. *Intl. J. Clin. Pharmacol. Ther.*, **36**(12), 625-628

Tilton, H., ed. (2003) Acetyl-L-carnitine hydrochloride, Lipoic acid, DL- $\alpha$ -Lipoic acid. *OPD 2003 Chemical Buyers Directory*, New York, Schnell Publishing Co., p 65, 340

Toth, E., Harsing, L.G. Jr., Serchen, H., Ramacci, M.T. & Lajtha, A. (1993) Effect of acetyl-L-carnitine on extracellular amino acid levels *in vivo* in rat brain regions. *Neurochem. Res.*, **18**(5), 573-578 [abstract]

U.S Patent and Trademark Office (2003) Results of search (all years) of database for "acetyl carnitine": 63 patents, "acetyl-L-carnitine": 77 patents, "lipoic acid": 745 patents, "thioctic acid": 314 patents, *USPTO Patent Full-Text and Image Database*. [<http://patft.uspto.gov/netahtml/search-bool.html>] Searched March 3, 2003

Vanella, A., Russo, A., Acquaviva, R., Campisi, A., Di Giacomo, C., Sorrenti, V. & Barcellona, M.L. (2000) L-propionyl-carnitine as superoxide scavenger, antioxidant, and DNA cleavage protector. *Cell. Biol. Toxicol.*, **16**(2), 99-104 [abstract]

Wiznitzer, A., Hershkovitz, R., Mimon, E., Mazor, M., Leiberman, J.R., Bashan, N. & Reece, E.A. (1996) The antioxidant lipoic acid - prevents malformations in offspring of diabetic rats. *Am. J. Obstet. Gynecol.*, **174**(1 Pt 2), 310 [abstract]

Zdanowicz, M.M. (2001) Acetyl-L-carnitine's healing potential. *Natural Healing Track*. [[http://www.nhir.com/tests/oct\\_2001.pdf](http://www.nhir.com/tests/oct_2001.pdf)] Searched April 21, 2003