

## ANTIOXIDANT COMPOSITIONS AND METHODS FOR AMELIORATING INFLAMMATORY SYMPTOMS OF RESPIRATORY DISEASE

### TECHNICAL FIELD

This invention concerns novel dietary and therapeutic antioxidant compositions containing as an active agent the amino acid methionine (also known as "Met"), and/or one or more related compounds including certain metabolic precursor compounds. The invention also concerns novel methods employing the compositions for ameliorating or alleviating inflammatory symptoms of respiratory disease in a subject.

### BACKGROUND OF THE INVENTION

A variety of efforts have been made over many years to elucidate the mechanisms and origins of the various forms of environmental risk factors thought to contribute to inflammatory symptoms of respiratory disease, especially in the case of smoke and toxic materials that are inhaled, e.g. air-borne asbestos particles.

Many substances that are risk factors have been identified in smoke. The urine of smokers has been shown to contain substances that are mutagenic for replicating bacteria.

Tobacco smoke contains other materials that may contribute to symptoms of respiratory disease. For example, in the blood nicotine has been shown to attract immunocytes (white cells) known as neutrophils; these can contribute to respiratory cell damage. Symptoms of respiratory disease include chronic coughing, increased cough frequency, impaired lung function and capacity, abnormal mucous production, and the like. For a review of life-style risk factors and of protective factors in the diet, see the article by Bruce N. Ames entitled "Dietary Carcinogens and Anticarcinogens", *Science*, 221: 1256-1263, 1983, incorporated herewith by reference.

Methionine has been shown to be a target for the products of stimulated polymorphonuclear neutrophils (PMNs) (Tsan and Chen, *J. Clin. Invest.*, 65:1041-1050, 1980). The granular fraction of PMNs oxidizes methionine to its sulfoxide in the presence of peroxide. Peroxide does not oxidize methionine to its sulfoxide at normal physiological concentrations.

Some of the differences measured in the relative effectiveness of methionine compounds and other chemicals, especially antioxidants, can be attributed to the control mechanisms that operate in animals and man to regulate the amounts of these substances wherein giving more of a substance does not significantly increase blood and tissue levels of that substance. Stegink, *J. Nutrition*, 116: 1185-1192, 1986, showed that 0.5 gm of methionine elevated total blood methionine 2-fold for 2 hours with 1-methionine but 3-fold for 4 hours with d-methionine.

Elevated methionine levels can affect concentration of other metabolites. Increasing dietary methionine 3-fold above normal values in rats causes a decrease in serine and betaine in the liver (Finkelstein and Martin, *J. Biol. Chem.* 261: 1582-1587, 1986).

Regarding human nutrition, 1-methionine is an essential amino acid (*The Merck Index*, IX, 5840, 1976), whereas d-methionine is not essential. Stegink, *supra*, shows that adult humans do not utilize d-methionine efficiently as a methionine source. For purposes of metabolism, 1-methionine via S-adenosylmethionine has an important methylating function. In this function it

loses a methyl group from its sulfur atom to become homocysteine. Homocysteine, as is known, when in excess can lead to homocysteinuria and may be disease associated.

Cuperus, *Arthritis and Rheumatism*, 28: 1228-1233, 1985, describes a feature of inflamed synovial fluid, such as that occurring in arthritis patients, as the accumulation of polymorphonuclear (PMN) leukocytes. The function of the leukocytes as has been alluded to, is the destruction of invading elements such as micro-organisms. For this destruction, the leukocyte releases hydrogen peroxide and enzymes, e.g., myeloperoxidase, into the extracellular fluid. In the presence of hydrogen peroxide and chloride ion, myeloperoxidase catalyzes the formation of reactive hypochlorous acid (HOCl) which can oxidize tissue components and plasma protease inhibitors. Oxidation and subsequent inactivation of these protease inhibitors in vivo may lead to unrestrained proteolysis, resulting in severe tissue damage.

dl-Methionine is available as a one-a-day food supplement in 500-mg. oral tablet form. The normal serum level of methionine in man is 15 ppm.

U.S. Pat. No. 3,952,115 describes foodstuffs containing N-acyl 1-methionine esters and N-acyl l-cysteine esters.

In view of the widespread incidence of inflammatory symptoms of respiratory disease, a need exists for means of preventing or ameliorating the symptoms and serious consequences of the disease.

It is therefore an object of the present invention to provide compositions for the alleviation and treatment of inflammatory respiratory disease conditions of man and animals.

It is also an object of the invention to provide means for the prevention, inhibition and treatment of disease conditions of the kind described.

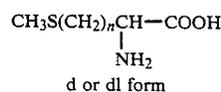
It is a further object of the invention to provide means for preventing or alleviating symptoms of homocysteinuria that may result from excess methionine intake.

These and other objects, features and advantages will be seen from the following detailed description of the invention.

### SUMMARY AND DETAILED DESCRIPTION OF THE INVENTION

Our invention is based on the discovery that certain methionine or methionine-type compounds in the dl-form or d-form at relatively high, well-tolerated doses are utilized well and due to the presence of the d-form, are potent antioxidant and antiinflammatory agents in man and animals. The invention includes means for inhibiting or treating conditions presented as an inflammatory response of respiratory disease.

For purposes of the invention, one uses in the dl-or d-form at least one methionine-type compound selected from the methionine hydroxy analog, the S-methyl methionine analog, and methionine compounds having the structural formula I:



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