Title: TREATMENT OF INFLAMMATORY CONDITIONS WITH \(-3\) POLYUNSATURATED FATTY ACIDS

Abstract: The present invention provides a method for the treatment, control and/or prevention of certain inflammatory conditions selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal, which method comprises administering to said mammal a therapeutically effective amount of at least one \(-3\) polyunsaturated fatty acid.
Treatment of inflammatory conditions with ω-3 polyunsaturated fatty acids

Technical Field

The present invention relates to the treatment, control and/or prevention of certain inflammatory conditions of the respiratory tract and gastrointestinal tract in mammals by the use of polyunsaturated fatty acids in the ω-3 configuration and optionally together with one or more anti-oxidants and optionally one or more compounds which may enhance the immune system.

Background Art

The epithelia which line the gastrointestinal and respiratory systems, of mammals and birds, represent the site of initial contact between many pathogens and the host and there are many such foreign entities which provoke chronic inflammatory reactions in the respiratory and gastrointestinal epithelia of mammals. In humans, for example, cigarette smoking leading to chronic bronchitis, is one well known example with regard to the respiratory tract, as is asthma, a large proportion of which is caused by allergy to various environmental pollutants, while internal parasites, or worms, cause a chronic enteritis or gastro-enteritis. Infections with one or more parasite species are a common problem in people in third world countries, or the lower end of the socio-economic scale in advanced countries, especially in children and specifically, concomitant infections with *Ascaris lumbricoides, Trichuris trichiura* and hookworm cause a debilitating chronic enteritis. Several species of internal parasites provoke a chronic gastro-enteritis in ruminant animals and horses and there is accumulating evidence that strongly suggests that ruminants, in particular, have a genetically determined propensity to mount an exaggerated allergic-type response to worm antigens.

While there are a wide variety of names applied to the different conditions which are engendered by the invasion of allergens and antigens, there are also instances of similar inflammatory conditions, showing closely related or identical pathology, in one or more mammalian species, being known by entirely different names. In the classification of lower respiratory tract diseases of horses various terms are used in the veterinary literature to describe conditions which are clinically similar or even identical. The terms used include chronic obstructive pulmonary disease (COPD), chronic pulmonary disease (CPD), asthma, emphysema, small airway disease (SAD), small airway inflammatory disease (SIAD), inflammatory airway disease (IAD), heaves, chronic emphysema, alveolar emphysema, chronic obstructive lung disease, recurrent airway obstruction, chronic bronchitis, chronic bronchiolitis, hay disease and broken wind, to name some of the more common synonyms.
The term small airway disease (SAD) has been used to describe a range of syndromes including COPD and all other low grade, non-septic inflammatory diseases of the small airways of horses. Other authors have, however, used the terms SAD and COPD interchangeably and it is not known whether COPD and other low grade small airway diseases represent different ends of the same disease spectrum, or diseases of different aetiologies.

COPD is not common in horses in Australia or California, possibly because they spend less time stabled than is the case in other places. However, an inflammatory airway disease which is said to affect between 22% and 50% of young racehorses in training and appears to be as common in Australia as elsewhere is characterised by poor performance, cough and endoscopic findings (nasopharyngeal exudate, pharyngeal lymphoid hyperplasia and tracheal exudate). The aetiology has not been explained.

Despite the lack of any scientific rational for any form of treatment, veterinarians are required to attempt to limit the effects of pulmonary diseases in horses and a review of the approach adopted by Australian veterinary practitioners showed that antibiotics were the most commonly reported drugs in use, with potentiated sulphonamides being the most popular. Mucolytics and bronchodilators were the next most commonly reported treatments, followed by steroidal or non-steroidal anti-inflammatory drugs. A few reported the use of immunostimulants, others vitamin supplementation, acupuncture, homoeopathy or intravenous dimethylsulphoxide.

Allowing for the plethora of possible aetiological agents and the frequent reference to "other agents" in the literature pertaining to the primary and secondary factors involved in the aetiology of pulmonary and some gastrointestinal diseases, together with the variable pathological changes recorded by many authors, elucidation of the underlying causes appears to be unlikely in the short term. Therefore, there is a need to develop an effective method of treatment and/or prophylaxis for the above-mentioned conditions in mammals.

**Disclosure of the Invention**

We have surprisingly found that it is possible to interfere in the process of inflammation in the lower respiratory tract and gastrointestinal tract by use of polyunsaturated fatty acids of the ω-3 configuration.

According to a first aspect of this invention there is provided a method for the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal, which
method comprises administering to said mammal a therapeutically effective amount of at least one \( \omega-3 \) polyunsaturated fatty acid or a physiologically acceptable composition containing a therapeutically effective amount of said \( \omega-3 \) polyunsaturated fatty acid.

According to a second aspect of this invention there is provided the use of at least one \( \omega-3 \) polyunsaturated fatty acid for the preparation of a physiologically acceptable composition for the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal.

According to a third aspect of this invention there is provided at least one \( \omega-3 \) polyunsaturated fatty acid or a physiologically acceptable composition containing a therapeutically effective amount of said \( \omega-3 \) polyunsaturated fatty acid, when used in the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal.

According to a fourth aspect of this invention there is provided the use of a composition containing at least one \( \omega-3 \) polyunsaturated fatty acid for the preparation of a physiologically acceptable composition for the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal.

The conditions amenable to treatment by the methods of this invention are the profuse inflammatory reactions provoked by a variety of allergens and antigens in the respiratory or gastro-intestinal tracts of mammals.

Without wishing to be bound by theory, but to illustrate the rationale of this invention, chronic inflammation and macrophage activation in humans is blamed for much of the damage to the lungs of smokers, leading to emphysema while in horses such macrophage activation leads to broken wind.

Some animals and humans, react to environmental antigens and allergens with chronic and excessive inflammation of the lining epithelium of the pulmonary airways. The inflammatory response in mammals is governed by intermediates known as prostaglandins and leukotrienes which are elaborated by resident pulmonary mast cells and macrophages. There are two families of these intermediates, one derived from an \( \omega-6 \) fatty acid arachidonic acid ("AA", 20:4 \( \omega-6 \)) and the other from an \( \omega-3 \) fatty acid eicosapentanenoic acid ("EPA", 20:5 \( \omega-3 \)), both of which are C\(_{20}\) acids and the latter
family is up to 100 times less active than is the former, in promoting inflammation. Furthermore, as EPA seems to be the preferred substrate for the enzymes responsible for the transformation of fatty acids to prostaglandins and leukotrienes, then the presence of a sufficient amount of EPA can inhibit the elaboration of the AA derivatives which should have a significant ameliorating effect on allergic inflammatory airway diseases. It is noteworthy that all prostaglandins are C₂₀ compounds and that tuna fish oil contains only about 5% of EPA together with about 25% docosahexaenoic acid ("DHA", 22:6 ω-3), which could not directly be used to produce prostaglandins.

Two of the horses which were treated with tuna fish oil (and which are discussed in Examples 2 and 3) had each been receiving a daily supplement of up to 100 mL of a blend of linoleic (18:2 ω-6) and linolenic (18:3 ω-3) acids prepared for administration to performance horses. Linoleic acid is normally desaturated and elongated to AA thereby “feeding” the aggressively inflammatory prostaglandin 2 series and leukotriene 4 series cascades, while linolenic acid can be similarly transformed to EPA to “feed” the less inflammatory prostaglandin 3 and leukotriene 5 series cascade as well as inhibiting the AA transformations by saturating the enzymes involved. Despite the latter possibilities both horses experienced inflammatory airway disease which was alleviated only by treatment with tuna oil, so it appears that DHA, of itself, or the particular combination with EPA in tuna fish oil, confers some previously unidentified extra activity.

The repeated inhalation of tobacco smoke causes irritation to the epithelium of the pulmonary airways, leading to chronic bronchitis. This inflammation activates the resident pulmonary macrophages so that they release inflammatory intermediates as well as oxidising free radicals leading to tissue damage, activation of fibroblasts, alveolar fibrosis and emphysema. Almost the same process occurs in exercise induced pulmonary haemorrhage (EIPH) in performance horses, where the macrophages are activated by pulmonary haemorrhage and the necessity to remove erythrocytes from the airways. Repeated such haemorrhages lead to alveolar fibrosis and broken wind.

Evidence exists which shows that in ruminants and perhaps other animals and humans, worm antigens provoke an allergic-type inflammatory response in the gastric and/or intestinal epithelium (gastroenteritis), which suggests that treatment with tuna oil will reduce inflammation and limit the deleterious effects of internal parasite infections.

Thus, the conditions amenable to treatment by the methods of this invention, in humans, are those which give rise to chronic inflammatory responses and in particular, asthma, chronic bronchitis and emphysema associated with cigarette smoking as well as internal parasite infection.
Again, without wishing to be bound to theoretical considerations, it is believed that the effect of DHA on the cell membrane of blood corpuscles, arterial walls and blood viscosity could all contribute to a reduction in vascular pressure during racing, thereby alleviating or even eliminating bleeding (EIPH). It is also believed that oil treatment may reduce inflammation of the small airways, thereby reducing macrophage activation and thus, reducing the progress of the disease.

The conditions amenable to treatment by the methods of this invention for horses are some or all of those variously known as chronic obstructive pulmonary disease (COPD), chronic pulmonary disease (CPD), asthma, emphysema, small airway disease (SAD), small airway inflammatory disease (SIAD), inflammatory airway disease (IAD), heaves, chronic emphysema, alveolar emphysema, chronic obstructive lung disease, recurrent airway obstruction, chronic bronchitis, chronic bronchiolitis, hay disease, broken wind and internal parasite infection.

The prevalence of EIPH and broken wind in racehorses increases with age and appears to be associated with the development of progressive alveolar fibrosis. The severity of EIPH varies widely from life threatening, large volume haemorrhage into the lung to minute haemorrhages which are clinically silent and almost impossible to detect with an endoscope. Pulmonary haemorrhage follows the rupture of small pulmonary blood vessels engendered by the very high vascular pressure during racing. Repeated small volume haemorrhages may produce cumulative damage which is as serious as that caused by larger single events. The presence of blood causes a modest but long-standing inflammatory reaction in the alveoli and small bronchi. While half of the erythrocytes are removed in the first three days after a haemorrhage, some persist for 21 days or even longer. Erythrophagocytic activity commences at about three days, reaches a maximum at about 10 days, but large numbers of macrophages are still present at three weeks and some may still be present three months later. The chronic stimulation of macrophages causes the release of intermediates which stimulate fibroblasts leading to alveolar fibrosis, angiogenesis, reduced oxygen uptake and reduced performance. The pulmonary inflammation is both a result of pulmonary haemorrhage and a predisposing factor for further and perhaps more severe episodes of EIPH. Pulmonary inflammation not related to haemorrhage also predisposes the lung to EIPH and may be responsible for the first episode.

Commonly, the class of horse to which the method of this invention is applicable is a high performance horse used in the racing industry but may be found useful in events and endurance horses, show horses, hacks or ponies.
In the case of ruminants and other animals and again, without being bound by theoretical considerations, it is believed that parasitism increases the amino acid demand of gastro-intestinal tissue. There appears to be a direct competition between the immune system and the inflamed gastro-intestinal epithelium on the one hand and other body tissues, on the other, for amino-acids. Peripheral tissue (muscle, bone, etc) are consequently denied the nutrients required for optimal growth and production. Parasitic enteritis is, thus, often described as a “protein losing enteropathy”.

The ω-3 polyunsaturated fatty acid may be administered by itself or in the form of a pharmaceutical composition for human or veterinary use, a feed or other suitable form. The ω-3 polyunsaturated fatty acid may also be administered in the form of an oil or crude extract.

The above fatty acid or composition containing said fatty acid may be administered together with an anti-oxidant and/or together with a compound which may enhance the immune system.

The ω-3 polyunsaturated fatty acid may be a C18 to C22 ω-3 polyunsaturated fatty acid.

The ω-3 polyunsaturated fatty acid such as DHA or EPA may be administered alone or in combination with other ω-3 polyunsaturated fatty acids such as an ω-linolenic acid or stearidonic acid (18:4 ω-3), or may be blended with an ω-6 polyunsaturated fatty acid such as a γ-linoleic acid (18:3 ω-6).

If given as a single fatty acid, DHA is the most preferred ω-3 polyunsaturated fatty acid. If given as a mixture, the most preferred option is a mixture of DHA and EPA acids in varying proportions from about 6:1 to about 1:6.

The ω-3 polyunsaturated fatty acid may be isolated from, or present in an extract derived from certain fish such as tuna, salmon, trout, cod, flounder, menhaden, sardine, mackerel, herring, halibut or other fish. Cod liver oil which is derived from cod is an example of an extract containing ω-3 polyunsaturated fatty acids. The ω-3 polyunsaturated fatty acid may also be isolated from, or present in an extract derived from plants or plant derived material, or present in an extract derived from plants or plant derived material, either marine or land based. Examples of plants or plant derived material or extracts derived from plants or plant derived material, include algae (including spirulina), beans (such as soya beans), soya bean oil, bean sprouts, chia, flaxseeds (linseeds), flax, flaxseed (or linseed) oil, spirulina, mustard seeds, butternuts, macadamia nuts, oat germ, oat germ oil, hickory nuts, pumpkin seeds, whole grains (such as brown rice), kukui, tofu, walnuts,
walnut oil, pecan nuts, pecan nut oil, borage, borage oil, rapeseed, rapeseed oil, olives, olive oil, pinto beans, broccoli, canola, canola oil, wheatgerm wheatgerm oil and green leafy vegetables. The ω-3 polyunsaturated fatty acid may also be isolated from some bacteria. Further, the ω-3 polyunsaturated fatty acid may be prepared by use of genetic engineering methods applied to the above organisms, for example, to produce transgenic oil seeds; or may be prepared by laboratory synthesis.

When given as an extract, typical oils would be tuna oil, salmon oil, menhaden fish oil, sardine oil, mackerel oil, or herring oil; linseed oil or blends of such oils; or oils made from aquaculture or mariculture. Preferably, the ω-3 polyunsaturated fatty acid may be recovered from tuna fish.

At least one anti-oxidant with or without added metal inactivators acting in synergy with each other may be administered together with the ω-3 polyunsaturated fatty acids alone or with other fatty acid blends. Suitable anti-oxidants are synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propylgallate (PG), tert-butylhydroquinone (TBHQ), ethoxyquin, vitamin C in the acid form or as vitamin C salts alone or blended with others, or natural antioxidants such as vitamin E as part of tocopherols, tocotrienols, co-enzyme Q10, phytochemicals extracted from botanicals such as rosemary extract containing phenolic dilarpene, carotenoids, flavonoids and green tea catechins alone or blended with others, antioxidant enzymes like glucose oxidase and antioxidants created by the maillard reaction alone or blended with others. Suitable metal inactivators are for example citric acid, ethylenediamine tetraacetic acid (EDTA), phosphoric acid, and ascorbic acid. The most preferred anti-oxidants are vitamins C and E alone or in blends.

The compositions of this invention may also contain as deemed to be appropriate by a person of skill in this field, such additives as lubricants, binders, colourants etc, all of which are well known to those in the veterinary pharmaceutical and feed disciplines. Also, emulsifiers, surfactants, flavourants, natural gums and mucilages, would also be considered for inclusion in such formulations and would also be well appreciated by a person of skill in this field. Suitable carriers, diluents and excipients used in the compositions of this invention are natural oils, saturated or unsaturated, derived from fish or plant material, wheat flower, corn flour, mill run, pollard and linseed meal.

In addition, when given as a feed, it is preferable to have present sealants, such as any edible vegetable oil, for example, palm oil. There must always be a vehicle which either absorbs the active or bulks it out (a dry diluent) and typical vehicles are grains
and/or their offals, oil seeds or meals derived from them, flour, rice flour, corn flour etc. Additives other than the actives may be sealants, pelletisers, (or bonding agents which help maintain the physical integrity of pellets) and antioxidants. For example, in the formulations below wheat is both vehicle and pelletiser, palm oil a very common sealant, which also helps to reduce dust during manufacture and vitamins C and E the antioxidants.

**Treatment regimes for humans and other mammals**

**Humans**

Humans may be treated with a composition or medicated product in accordance with this invention, with dose rates of tuna fish oil varying from about 5 to 40 mL/day for adults (with an average bodyweight of 70kg) and from about 2 to 30 mL/day for children with an average bodyweight of 35 kg. The dose rate for adults would provide about 1.25 to 10 mL of DHA daily (0.018 to 0.143 mL/kg) and 0.25 to 2 mL of EPA (0.0036 to 0.0286 mL/kg), while that for children would provide from 0.5 to 7.5 mL of DHA daily (0.01 to 0.21 mL/kg) and from 0.1 to 1.5 mL of EPA daily (0.0036 to 0.0286 mL/kg). More typically the dose for an adult human should be about 10 to 25 mL of oil daily and that for children from about 5 to 15 mL daily. The adult dose would provide from 2.5 to 6.25 mL of DHA daily (0.036 to 0.09 mL/kg) and from 0.5 to 1.25 mL of EPA daily (0.007 to 0.018 mL/kg). The child dose would provide from about 1.25 to 3.75 mL of DHA daily (0.017 to 0.107 mL/kg) and from about 0.25 to 0.75 mL of EPA daily (0.007 to 0.21 mL/kg).

If administered as a fatty acid rather than tuna oil, suitable doses for DHA and EPA are: DHA is from about 0.25mL/day to about 15mL/day, preferably about 1mL/day to about 10mL/day, and more preferably about 5mL/day to about 8mL/day; and EPA is from about 0.1mL/day to about 5mL/day, preferably from about 0.5mL/day to about 4mL/day, and more preferably from about 1mL/day to about 3mL/day for adults; and DHA is from about 0.25mL/day to about 7.5mL/day, preferably about 0.5mL/day to about 7mL/day, and more preferably about 1mL/day to about 5mL/day; and EPA is from about 0.1mL/day to about 5mL/day, preferably from about 0.5mL/day to about 4mL/day, and more preferably from about 1mL/day to about 3mL/day for children.

Treatment should be taken orally, twice daily and the actual dose can be adjusted to suit the severity of the condition.
Treatment should be continued for at least six weeks but longer periods may be necessary or intermittent periods of treatment may be appropriate, depending on the severity of the condition.

The compositions of this invention may be presented as a liquid, emulsion, paste, tablet or pellets or granules to be sprinkled on food.

Horses

Horses may be treated with a composition or feed in accordance with this invention, with dose rates of tuna fish oil varying from about 5 to about 150 mL/day for adults (with an average bodyweight of about 450 kg) and from about 2 to about 80 mL/day for foals or growing horses (with an average bodyweight of about 250 kg). The dose for adult horses would supply from about 1.25 to 37.5 mL or docosahexaenoic acid (DHA) daily (0.003 to 0.08 mL/kg) and from about 0.25 to 7.5 mL of eicosapentaenoic acid (EPA) daily (0.006 to 0.02 mL/kg). The dose for foals and growing horses would supply from about 0.05 to 20 mL of DHA daily (0.002 to 0.08 mL/kg) and 0.1 to 4 mL of EPA daily (0.0004 to 0.016 mL/kg). Typically, however, the dose range is from about 20 to about 80 mL of tuna fish oil for mature horses and from about 5 to 40 mL/day for foals and growing horses. The dose for adult horses would provide from about 5 to 20 mL of DHA daily (0.01 to 0.04 mL/kg) and from about 1 to 4 mL of EPA (0.002 to 0.009 mL/kg). The dose for foals and growing horses would provide from about 1.25 to 10 mL of DHA daily (0.005 to 0.04 mL/kg and from about 0.25 to 2.0 mL of EPA (0.001 to 0.008 mL/kg).

If administered as a fatty acid rather than tuna oil, suitable doses for DHA and EPA are: DHA is from about 1 mL/day to about 40 mL/day, preferably about 5 mL/day to about 30 mL/day, and more preferably about 10 mL/day to about 25 mL/day; and EPA is from about 0.25 mL/day to about 10 mL/day, preferably from about 0.5 mL/day to about 7.5 mL/day, and more preferably from about 1 mL/day to about 5 mL/day for adults; and DHA is from about 0.5 mL/day to about 20 mL/day, preferably about 1 mL/day to about 15 mL/day, and more preferably about 5 mL/day to about 10 mL/day; and EPA is from about 0.1 mL/day to about 4 mL/day, preferably from about 0.5 mL/day to about 3 mL/day, and more preferably from about 1 mL/day to about 2 mL/day for foals or growing horses.

Treatment should be administered twice daily, in equal amounts, and the actual dose can be adjusted to suit the severity of the condition.

Treatment should be continued for at least six weeks but longer periods may be necessary, depending on the severity of the condition.
The compositions of this invention may be presented as a liquid, emulsion, paste, tablet, pellets or granules to be used as top dressing or additive to the horse’s ration.

The compositions of this invention should be administered orally.

Sheep

Treatment with a composition, or feed, in accordance with this invention should deliver oil at from 5 to 30 mL/day for adult or well grown sheep (of 40kg average bodyweight) and at from 0.25 to 10 mL for lambs or growing sheep (of 20 kg average bodyweight). The dose for adult sheep would provide about 1.25 to 3.75 mL of DHA daily (0.03 to 0.09 mL/kg) and about 0.25 to 0.75 mL of EPA daily (0.006 to 0.02 mL/kg). The dose for lambs or growing sheep would provide about 0.06 to 2.5 mL of DHA daily (0.003 to 0.125 mL/kg) and about 0.0125 to 0.5 mL of EPA daily (0.0006 to 0.025 mL/kg).

The more typical daily dose for adult and grown sheep should deliver about 8 to 20 mL of oil daily thereby providing 2 to 5 mL of DHA daily (0.05 to 0.125 mL/kg) and 0.4 to 1 mL of EPA daily (0.01 to 0.025 mL/kg).

The more typical dose for lambs and growing sheep would deliver about 1 to 7.5 mL of oil daily thereby providing about 0.25 to 1.9 mL of DHA (0.0125 to 0.095 mL/kg) and about 0.05 to 0.375 mL of EPA daily (0.0025 to 0.019 mL/kg).

If administered as a fatty acid rather than tuna oil, suitable doses for DHA and EPA are: DHA is from about 1mL/day to about 7.5mL/day, preferably about 1.5mL/day to about 5mL/day, and more preferably about 25mL/day to about 3mL/day; and EPA is from about 0.1mL/day to about 1.5mL/day, preferably from about 0.5mL/day to about 1.2mL/day, and more preferably from about 0.7mL/day to about 1mL/day for adults; and DHA is from about 0.5mL/day to about 2.5mL/day, preferably about 0.75mL/day to about 2mL/day, and more preferably about 1mL/day to about 1.5mL/day; and EPA is from about 0.1mL/day to about 1mL/day, preferably from about 0.2mL/day to about 0.8mL/day, and more preferably from about 0.5mL/day to about 0.75mL/day for lambs or growing sheep.

Cattle

Treatment with a composition, or feed, in accordance with this invention should deliver oil from about 5 to 130 mL/day for adult or well grown cattle (of 400kg average bodyweight) and from about 2 to 50 mL for calves or growing cattle (of 200 kg average...
bodyweight). The dose for adult cattle would provide about 1.25 to 32.5 mL of DHA daily (0.003 to 0.08 mL/kg) and about 0.25 to 6.5 mL of EPA daily (0.0006 to 0.016 mL/kg). The dose for calves or growing cattle would provide about 0.5 to 12.5 mL of DHA daily (0.0025 to 0.0625 mL/kg) and 0.1 to 2.5 mL of EPA daily (0.0005 to 0.0125 mL/kg).

The more typical dose for adult cattle should deliver oil from about 15 to 60 mL/day, which would provide from 3.75 to 15 mL of DHA daily (0.0094 to 0.0375 mL/kg) and 0.75 to 3 mL of EPA daily (0.0019 to 0.0075 mL/kg). The more typical dose range for calves and growing cattle would be from about 5 to 40 mL of oil daily and this would provide about 1.25 to 10 mL of DHA daily (0.0063 to 0.05 mL/kg) and about 0.25 to 2 mL of EPA daily (0.00025 to 0.01 mL/kg).

If administered as a fatty acid rather than tuna oil, suitable doses for DHA and EPA are: DHA is from about 0.5mL/day to about 35mL/day, preferably about 5mL/day to about 25mL/day, and more preferably about 10mL/day to about 20mL/day; and EPA is from about 0.1mL/day to about 1mL/day, preferably from about 0.2mL/day to about 0.8mL/day, and more preferably from about 0.3mL/day to about 0.5mL/day for adults; and DHA is from about 0.5mL/day to about 12.5mL/day, preferably about 1mL/day to about 10mL/day, and more preferably about 5mL/day to about 7.5mL/day; and EPA is from about 0.1mL/day to about 0.25mL/day, preferably from about 0.1mL/day to about 0.2mL/day, and more preferably from about 0.15mL/day to about 0.2mL/day for calves or growing cattle.

In general, the compositions of this invention may be presented as a liquid, emulsion, paste, granules, pellets or free flowing powder for humans or as a liquid, emulsion or paste for direct oral administration through an appropriate paste syringe or drench gun or as a granulated, pelleted or free flowing coarse powder formulation to be used as a top dressing or additive to the animal’s ration.

When supplied as a top dressing or additive for horse rations, a suitable combination for use as pellets or granules would comprise a mixture for example, as follows:
<table>
<thead>
<tr>
<th>Material</th>
<th>Content % by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Hipro soya” or equivalent meal from oilseeds</td>
<td>5 - 25</td>
</tr>
<tr>
<td>Brewers Yeast</td>
<td>0.1 – 2.5</td>
</tr>
<tr>
<td>Wheat</td>
<td>30 – 75</td>
</tr>
<tr>
<td>Sealant (palm oil)</td>
<td>0.1 – 0.5</td>
</tr>
<tr>
<td>Tuna oil</td>
<td>20 – 33</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>0.1 – 0.5</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>0.25 – 2.5</td>
</tr>
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</table>

With the content of tuna oil varying from 20% to 30% the amount per kg of solid feed will vary from 200 to 300 mL and where the desired dose of oil is 20 mL twice daily, then the amount of solid feed provided will vary from 66 to 100 grams per feed and that these amounts will deliver about 16.5 to about 25 mL of DHA and about 3.3 to about 5 mL of EPA. The solid feed can be fed alone or as an additive or “top dressing” to the normal ration supplied to a horse.

The method of delivery to ruminants preferably uses slow release technology as presently employed for the continuous controlled release of anthelmintics for the control of internal parasites in sheep and cattle, using a winged capsule deposited in the rumen. This capsule contains a matrix in which the anthelmintic is suspended and which is slowly eroded by ruminal liquor at the open end of the capsule, thereby releasing the anthelmintic. The rate of release can be controlled by the diameter of the aperture at the open end of the capsule. Thus, it would be preferable to administer the fatty acids in the form of calcium salts, as such salts of DHA and EPA, being insoluble, would pass out of the rumen untouched, but would be attacked in the acid conditions of the abomasum (true glandular stomach) to release free fatty acids, in the same manner as that employed to make the fatty acids of tallow, rumen inert. Calcium salts of DHA and EPA are suitably included in the rumen capsule.

Worm control in sheep employs the same anthelmintics as those used in horses and the problem of parasite resistance with reduced efficacy of treatment has arisen. As a result of continuous infection with internal parasites, ruminants suffer reduced appetite and the chronic verminous gastro-enteritis which robs them of protein (and thus essential amino acids) required to ensure growth and production of meat, milk and fibre. It can, thus, be anticipated that, like the horse, ruminants will show a positive response to treatment with the DHA and EPA.
Best Mode and Other Modes for Carrying out the Invention

The present invention will now be described with reference to the following examples which should not be construed as limiting on the scope thereof.

Example 1
Use in humans

A person (of about 65 years of age) who had been an asthmatic since childhood was confined to bed for a long period by another unrelated condition, during which time the asthma made breathing difficult and seriously affected sleep. This person took 20 mL of tuna oil, twice daily, the same dose as that administered to the horse in Example 2. Some quite noticeable improvement occurred after three days and continued to further improve so long as treatment continued.

Example 2
Use in horses – amelioration of small airway allergic inflammatory disease and exercise induced pulmonary haemorrhage

A performance horse (a pacer) was put into training to prepare it for professional harness racing. The schooling and conditioning period was quite prolonged, so that several months elapsed before the horse was required to perform at or near its maximum capability. When so required however, the horse, a gelding had trouble maintaining the speed required for successful competition. At the request of the owner the horse was subjected to a series of tests at an equine performance laboratory and found to be exercise intolerant and evaluation of the broncho-alveolar lavage (BAL) revealed that it was suffering from an allergic inflammatory condition and was also a bleeder, that is, it was subject to exercise induced pulmonary haemorrhage (EIPH). The final evaluation from the laboratory advised that all thoughts of a racing career for the horse should be abandoned.

Within a week the horse began treatment with 25mL of refined tuna fish oil containing 25% docosahexaenoic acid and 5-7% eicosapentaenoic acid, (together with small amounts of other \(\omega-3\) fatty acids) administered twice daily. After a few days copious exudate was produced from the nose, the horse’s health and demeanour began to improve and continued to do so. A second evaluation of the BAL, collected after some 30 days of treatment, was pronounced normal with no indication of inflammation or EIPH.
The horse was returned to training and subsequently has been placed in 2 of its 6 starts, in
times that bode well for its future as a pacer.

Example 3

Use in horses – amelioration of cough and exercise intolerance associated
with small airway allergic inflammatory disease

A thoroughbred filly had been prepared for racing on two occasions but the frequent
coughing fits and lack of stamina caused her to be turned out to spell for prolonged
periods. She was withdrawn to a resting establishment and even though no endoscopic
examination with evaluation of the BAL had been undertaken, treatment with 20mL/day
of the same oil as was applied to the pacer in Example 1, was instituted. Within 7 to 10
days most of the coughing ceased and the horse was soon back in full work preparatory to
racing. The filly still coughed occasionally after strenuous work so the dose of oil was
increased to 20mL/twice daily, which stopped all coughing. The filly, at the time of this
application has now raced three times during the space of one month and when inspected
about three weeks after the last race was in excellent condition. There have been no
episodes of violent coughing after racing as happened in the past.

It should be noted that, in the above examples, the response to continued treatment
was rapid and sustained, which suggests that it was specific with regard to an important
factor or, factors, in the disease process, the manifestations of which were quite different.

Example 4

Use in horses – amelioration of the effects of worm infections

All performance horses are regularly treated with anthelmintics to reduce the
burdens of intestinal worms because of the adverse effects such infections engender. The
drugs administered come from two chemical classes, the benzimidazole carbamates, first
introduced in the early 1970s and the macrocyclic lactones first introduced in the 1980s.
Following continued and widespread use of, initially, very effective drugs, strains of
worms with reduced susceptibility to those drugs appeared, built up and began to reduce
the efficiency of treatment. As a result some animals had a reduced appetite and the
chronic verminous enteritis caused the continuous loss of protein which reduced
bodyweight gains.

In two training establishments some horses subject to the usual routine worming
regimen were also receiving treatment with tuna fish oil. These horses showed an
increased appetite, they also gained in bodyweight soon after the first treatment with oil
and one such was weighed on three occasions in order to discover how quickly the weight gain followed the first treatment with tuna oil. The bodyweight prior to treatment was 508 kg, seven days later 513 kg and 4 days later still, 517 kg and the gain continued for another three weeks. This horse had a history as a slow, finicky eater but this was quickly reversed and he ingested his ration quite quickly, though no extra was supplied. In the first 11 days of oil treatment this horse gained nearly 1.8% of its bodyweight and this change was evident to the practiced eyes of the trainer, as was the subsequent, unmeasured gain. It was also a very rapid response to the oil treatment which was the only deviation from the normal training and feeding regimen. The response may indicate a diminution in the loss of essential protein from the inflamed intestinal mucosa. Additionally, a trainer who pays particular attention to the effects of anthelmintic administration recorded that the number of worms passed, at the first worming after the commencement of treatment with tuna oil, was the heaviest he has seen in years.

**Industrial Applicability**

It is envisaged that this invention will find wide applicability in the fields of medicine and veterinary science, specifically in the treatment of inflammation of the respiratory tract and gastrointestinal tract in mammals.

The foregoing describes only some embodiments of the present invention and modifications thereto by one skilled in the art can be made without departing from the scope of the invention.
CLAIMS

1. A method for the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal, which method comprises administering to said mammal a therapeutically effective amount of at least one ω-3 polyunsaturated fatty acid or a physiologically acceptable composition containing a therapeutically effective amount of said ω-3 polyunsaturated fatty acid.

2. The method according to claim 1, wherein the ω-3 polyunsaturated fatty acid is a C18 to C22 fatty acid.

3. The method according to claim 2 wherein the fatty acid is DHA, EPA or another ω-3 polyunsaturated fatty acid.

4. The method according to claim 3 wherein the other ω-3 polyunsaturated fatty acid is α-linolenic acid or stearidonic acid.

5. The method according to claim 4 further comprising a γ-linoleic acid.

6. The method according to claim 1 wherein the fatty acid is a mixture of DHA and EPA.

7. The method according to claim 6 wherein the proportion of DHA:EPA is from about 6:about 1 to about 1:about 6.

8. The method according to claim 1 or claim 2 wherein the at least one fatty acid is present in the form of tuna oil.

9. The method according to claim 1 or claim 2 wherein the daily dose for humans is selected from the group consisting of:

   (a) when tuna oil is used is from about 5mL/day to about 40mL/day for adults; and about 2mL/day to about 30mL/day for children; and (b) when DHA and/or EPA are used: DHA is from about 0.25mL/day to about 15mL/day; and EPA is from about 0.1mL/day to about 5mL/day for adults; and DHA is from about 0.25mL/day to about 7.5mL/day; and EPA is from about 0.1mL/day to about 5mL/day for children.

10. The method according to claim 1 wherein the inflammation is selected from the group consisting of asthma, chronic bronchitis, emphysema associated with cigarette smoking, and internal parasite infection.

11. The method according to claim 1 or claim 2 wherein the daily dose for horses is selected from the group consisting of:

   (a) when tuna oil is used is from about 5mL/day to about 150mL/day for adults; and about 2mL/day to about 80mL/day for foals or growing horses; and (b) when DHA and
/or EPA are used: DHA is from about 1mL/day to about 40mL/day; and EPA is from about 0.25mL/day to about 10mL/day for adults; DHA is from about 0.05mL/day to about 20mL/day; and EPA is from about 0.1mL/day to about 4mL/day for foals or growing horses.

12. The method according to claim 11 wherein the inflammation is selected from the group consisting of chronic obstructive pulmonary disease (COPD), chronic pulmonary disease (CPD), asthma, emphysema, small airway disease, heaves, chronic emphysema, alveolar emphysema, chronic obstructive lung disease, recurrent airway obstruction, chronic bronchitis, chronic bronchiolitis, hay disease, broken wind and internal parasite infection.

13. The method according to claim 1 or claim 2 wherein the daily dose for sheep is selected from the group consisting of:

(a) when tuna oil is used is from about 5mL/day to about 30mL/day for adults; and about 0.25mL/day to about 10mL/day for lambs or growing sheep; and (b) when DHA and /or EPA are used: DHA is from about 1mL/day to about 7.5mL/day; and EPA is from about 0.1mL/day to about 1.5mL/day for adults; and DHA is from about 0.05mL/day to about 2.5mL/day; and EPA is from about 0.01mL/day to about 1mL/day for lambs or growing sheep.

14. The method according to claim 1 or claim 2 wherein the daily dose for cattle is selected from the group consisting of:

(a) when tuna oil is used is from about 5mL/day to about 130mL/day for adults; and about 2mL/day to about 50mL/day for calves or growing cattle; and (b) when DHA and /or EPA are used: DHA is from about 0.5mL/day to about 35mL/day; and EPA is from about 0.1mL/day to about 1mL/day for adults; and DHA is from about 0.5mL/day to about 12.5mL/day; and EPA is from about 0.1mL/day to about 0.25mL/day for calves or growing cattle.

15. Use of at least one ω-3 polyunsaturated fatty acid for the preparation of a physiologically acceptable composition for the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal.

16. At least one ω-3 polyunsaturated fatty acid or a physiologically acceptable composition containing a therapeutically effective amount of said ω-3 polyunsaturated fatty acid, when used in the treatment, control and/or prevention of certain inflammatory
conditions selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal.

17. Use of a composition containing at least one ω-3 polyunsaturated fatty acid for the preparation of a physiologically acceptable composition for the treatment, control and/or prevention of an inflammatory condition in a mammal, said condition selected from the group consisting of inflammation of the respiratory tract of said mammal and inflammation of the gastrointestinal tract of said mammal.
# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/AU03/01318

## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.?:  A61K 031/20; 031/201; 031/202; A61P 1/00; 11/00; 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, Medline: keywords: inflammation, asthma, bronchitis, emphysema, heaves, bronchiolitis, DHA, EPA, linoleic acid, stearidonic acid, omega fatty acid, tuna oil, eicosapentaenoic acid, docosapentaenoic acid

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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**T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the International search: 25 November 2003

Date of mailing of the International search report: 2 - DEC 2003

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