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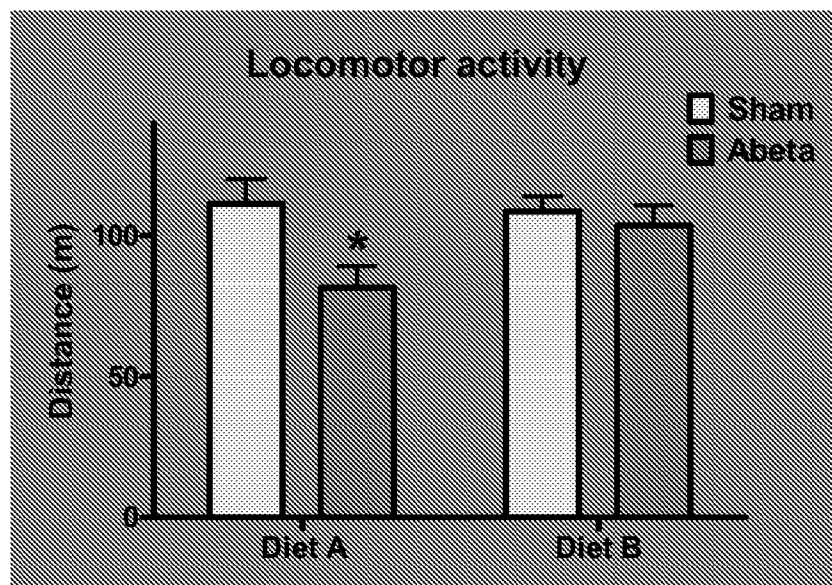


Figure 1

(57) Abstract: The invention provides a method for supporting operational activities in daily living by providing a combination of (a) long-chain polyunsaturated fatty acids, particularly DHA and/or EPA, and (b) nucleosides or nucleotides, particularly uridine or its equivalent. The operational activities comprise independent housekeeping, transportation, shopping or personal hygiene activities, independent walking, bathing, grooming, dressing, use of communication equipment, use of household appliances, cleaning dishes, preparation of meal or drink or writing.

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SUPPORTING ACTIVITIES OF DAILY LIVING

FIELD OF THE INVENTION

5 The invention relates to preparations, which comprise long chain polyunsaturated fatty acids and/or nucleotides or their equivalents, and which support the activities of daily living.

BACKGROUND OF THE INVENTION

10 Neuropathies or neurological problems may find their cause in aging, in prevalent pathologies in the brain, like those associated with the formation of plaques or neurofibrillary tangles in the brain. In many occasions neuropathies or neurological problems lead to a loss of independency and a need to provide extra care or a need to move the person to a nursing home or the like, in order to ensure a sustainable life of these persons.

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WO02088159 describes the neuroprotective effect of a lipoic acid derivative of uridine. WO2006/031683 relates to methods of improving cognitive and neurological functions and increasing synthesis and release of neurotransmitters and membrane synthesis by neural cells and brain cells, comprising administering a composition comprising a uridine. WO2007/004685 describes a composition containing DHA and arachidonic acid that has an activity of ameliorating reduced higher brain functions resulting from organic brain lesions. WO2007004689 discloses a composition having an activity of ameliorating the reduced amount of diurnal activity and/or depressive symptoms, comprising arachidonic acid and/or a compound having arachidonic acid as a constituent fatty acid. US2007/0004670 describes methods of improving memory, learning, cognition, synaptic transmission and synthesis and release of neurotransmitters and increasing brain phospholipid levels in a subject.

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SUMMARY OF THE INVENTION

30 The present inventors found that the administration of the present composition improves activities wherein the (i) operational activities and the executive brain functions play an important role (i.e. the instrumental and/or basic daily activities). Such activities include many activities that take place throughout the day, particularly housekeeping, personal hygiene practices and meal preparation. This finding particularly enables persons that are suffering from difficulty in performing such activities (e.g. humans suffering from Alzheimer's disease, dementia and/or elderly) to prolong an independent way of living.

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The improvement in ability to perform the instrumental and/or basic activities of daily living is often considered more important than improving memory and/or cognitive function.

- 5 This finding is particularly unexpected as the coordination of these complex daily life activities is coordinated by different parts of the brain, i.e. the operational parts of the activities are (mainly) coordinated by the motor cortex, the executive (e.g. planning) parts of the daily activities are (mainly) coordinated by the prefrontal cortex, while memory functions are (mainly) coordinated by the hippocampus and temporal cortex.
- 10 Experimental results showed that administration of the present composition to subjects suffering from impaired brain functions (particularly Alzheimer's disease) restored the activities, to near normal levels. Hence, the present inventors found that the present composition has an important stimulatory effect on the instrumental and/or basic daily activities, particularly in humans suffering from Alzheimer's disease. The present
- 15 composition supports and enable those complex activities where initiation, planning and effective operation performance play a role.

- In a further aspect, the present inventors found, in addition to the above, that the present composition for supporting the daily activities advantageously comprises folic acid,
- 20 vitamin B12 and/or vitamin B6, preferably in relatively high dosages. It was found that these vitamins can be advantageously included in the present invention. The administration of the B vitamins was found to decrease locomotor activity during the resting period, hence ensuring a good rest during the night. Hence, the present composition, when including B-vitamins advantageously supports the present daily
- 25 activities, while providing a good resting period.

- The present finding enables a solution for an important problem for humans suffering from Alzheimer's, dementia and/or aging (i.e. the elderly). Many subjects fear the time that they become dependent on the help and support from others when desiring to
- 30 perform daily activities. Hence, for these subjects it is particularly desirable to extend the period of independence. The present inventors solved this problem by providing a (nutritional) composition that is easy to ingest, and enables a prolonged capacity to perform the relatively complex activities of daily living.

- 35 In particular, the present invention relates to improvements in independent performance of activities wherein the operational aspect has a dominant role. The present invention

particularly relates to improvements in independent performance of the following activities: coordination of movements, particularly when eating or drinking; grasping goods; putting objects on a desired location/position; making rapid movements; walking; maintaining balance in body position; doing the laundry; doing the dishes.

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In a further aspect the present invention relates to improvements in independent performance of activities wherein the operational aspect has a main role, in addition to other higher brain functions. The present invention particularly relates to improvements in independent performance of the following activities: using communication
10 equipment, especially telephone; using household appliances, especially television; personal hygiene practices, particularly cutting nails, doing hair properly or apply shaving practices; dressing, preparing a meal, shopping, travelling.

It was found that particularly the administration of a preparation that comprises DHA
15 and uridine results in the desired improvements. It is considered particularly advantageous to co-administer with the DHA and/or uridine at least one of vitamin B6, vitamin B12 and/or folic acid. Inclusion of these vitamins improves the effects of the administration of DHA and/or nucleotide. Further improvements can be achieved by co-administration of phospholipids. Without wishing to be bound by theory, the present
20 inventors believe that the phospholipids enable effective membrane function, further improving effectiveness of the present composition in it's support for daily living activities.

At the same time, the present product preferably is formulated so that it has a relatively
25 low impact on appetite and consumption patterns of other food, and is easy to consume. It preferably does not comprise herb extracts, which may be varying in quality, and under normal circumstances are difficult to include in stable sterilized liquid products and may comprise components which have a badly defined biological action.

30 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention provides the use of a composition comprising (a) DHA and/or EPA, and (b) uridine or its equivalent, in the manufacture of a composition for supporting activities in daily living. Alternatively the present invention provides a
35 method for supporting activities in daily living, said method comprising administering

to a patient (particularly a patient suffering from Alzheimer's disease) a composition comprising (a) DHA and/or EPA, and (b) uridine or its equivalent.

In a further aspect the present invention provides a liquid composition comprising per 100 ml, 0.2–2 gram uridine; 0.5–5 g DHA; 0.5 – 10 g protein; 2– 20 g carbohydrates; 0.5–15 microgram vitamin B12; 50–1000 microgram folic acid and 0.1 – 10 mg vitamin B6, wherein the composition has a viscosity of 1 – 40 mPas measured at a shear rate of 100 per sec at 20 °C; an osmolality of 300 to 800 mOsm/kg and a caloric density between 0.2 and 3 kcal/ml.

LC-PUFA

The present invention comprises the use of long chain polyunsaturated fatty acids (LCP), preferably at least one LCP selected from docosahexaenoic acid (22:6 ω -3; DHA), docosapentaenoic acid (22:5 ω -3; DPA) and eicosapentaenoic acid (20:5 ω -3; EPA). Preferably the present composition contains at least DHA, preferably DHA and EPA. More preferably the composition contains DHA and at least one precursor of DHA selected from EPA and DPA, more preferably the present composition comprises DHA, DPA and EPA. The inventors recognized that only part of the DHA incorporated in the brain is from orally ingested DHA. An important part of the DHA incorporated in the brain is derived from conversion of DPA to DHA in the brain. In a further aspect the present composition preferably contains a significant amount of EPA. EPA is converted to DPA (ω -3), increasing subsequent conversion of DPA (ω -3) to DHA in the brain. Hence, the present composition preferably also contains a significant amount of EPA, so to further stimulate in-vivo DHA formation.

The LCP is preferably provided as triglycerides, diglycerides, monoglycerides, free fatty acids or their salts or esters, phospholipids, lysophospholipids, glycerol ethers, lipoproteins, ceramides, glycolipids or combinations thereof. Preferably, the present composition comprises at least DHA in triglyceride form.

The present method preferably comprises the administration of 400–5000 mg (DHA+EPA) per day, more preferably 500–3000 mg per day. The proportion of (DHA+EPA) of the total fatty acids is preferably 5–50 wt.%, more preferably 10–45 wt.%, most preferably 15–40 wt.%. The present method preferably comprises the administration of DHA, preferably in an amount of 300–4000 mg per day, more

preferably 500-2500 mg per day. The present method preferably comprises the administration of DHA, preferably a composition comprising 300-4000 mg DHA per 100 ml day, more preferably 500-2500 mg DHA per 100 ml. The present composition preferably comprises 1-40 wt.% DHA based on total fatty acids, preferably 3-36 wt.%
5 DHA based on total fatty acids, more preferably 10-30 wt.% DHA based on total fatty acids. The present composition preferably comprises 0.5-20 wt.% EPA based on total fatty acids, preferably 2-10 wt.% EPA based on total fatty acids, more preferably 5-10 wt.% EPA based on total fatty acids. The ratio of the weights of DHA to the sum of EPA and DPA (ω -3) is preferably larger than 1.0, more preferably 1.2-10, more
10 preferably 2-8. The above-mentioned ratios and amounts take into account and optimise several aspects, including taste (too high LCP levels reduce taste, resulting in a reduced compliance), balance between DHA and precursors thereof to ensure optimal effectiveness in relation to maximum dosage and possibility of product formulations such as liquid form, bar or capsule.

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As the present composition preferably contains a very low amount of arachidonic acid (AA; 22:4 ω -6). The arachidonic acid is believed to counteract the effects of the present composition. The present subject normally ingest sufficient (precursors of) AA, and an excess daily dosage may stimulate inflammatory responses, inhibiting daily activities.
20 Preferably the weight ratio DHA/AA in the present composition is at least 5, preferably at least 10, more preferably at least 15. The present method preferably comprises the administration of a composition comprising less than 5 wt.% arachidonic acid based on total fatty acids, more preferably below 2,5 wt.%. The ratio omega-6/omega-3 fatty acids in the present product is preferably below 0.5, more preferably below 0.2.

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The present composition preferably contains at least one oil selected from fish oil, algal oil and eggs lipids. Preferably the present composition contains fish oil comprising DHA, EPA and preferably DPA.

30 Folic acid, vitamin B12 and/or vitamin B6

The present composition preferably contain folic acid, vitamin B12 and/or vitamin B6, particularly in (relatively) high dosages. Inclusion of these vitamins advantageously provides the combination of support and enablement of daily activities, while providing a reduced locomotor activity during the resting period. Further advantage of co-
35 administration of folic acid, vitamin B12 and/or vitamin B6 is that is relief's patients of deficiencies in these vitamins. Preferably the present composition comprises at least two

selected from the group consisting of folic acid, vitamin B12 and/or vitamin B6. More preferably the present composition comprises folic acid, vitamin B12 and vitamin B6.

The present composition preferably comprises 50-1000 microgram folic acid per 100 g liquid product, more preferably 150-750 microgram folic acid per 100 g liquid product, more preferably 200 – 500 microgram folic acid per 100 g liquid product. The present method preferably comprises the administration 50-1000 microgram folic acid per day, more preferably 150-750 microgram folic acid per day, more preferably 200 – 500 microgram folic acid per day. The present composition preferably comprises 0.5-15 microgram vitamin B12 per 100 g liquid product, more preferably 1-10 microgram vitamin B12 per 100 g liquid product, more preferably 1.5 – 5 microgram vitamin B12 per 100 g liquid product. The present method preferably comprises the administration 0.5-15 microgram vitamin B12 per day, more preferably 1-10 microgram vitamin B12 per day, more preferably 1.5-5 microgram vitamin B12 per day. The present composition preferably comprises 0.1 - 10 mg vitamin B6 per 100 g liquid product, more preferably 0.4-5 mg vitamin B6 per 100 g liquid product, more preferably 0.6 – 5 mg vitamin B6 per 100 g liquid product. The present method preferably comprises the administration 0.1-10 microgram vitamin B6 per day, more preferably 0.5-5 mg vitamin B6 per day, more preferably 0.75 - 5 mg vitamin B6 per day.

20 Saturated and monounsaturated fatty acids

The present composition preferably comprises saturated and/or mono-unsaturated fatty acids. The amount of saturated fatty acids is preferably 6-60 wt.% based on total fatty acids, preferably 12-40 wt.%, more preferably 20-40 wt.% based on total fatty acids. In particular the amount of C14:0 (myristic acid) + C16:0 (palmitic acid) is preferably 5-50 wt.%, preferably 8-36, more preferably 15-30 wt.% based on total fatty acids. The total amount of monounsaturated fatty acids, such as oleic acid and palmitoleic acid, is preferably between 5 and 40 wt.%, more preferably between 15 and 30 wt.%. Including of the saturated and/or monounsaturated fatty acids provides an energy source, improving the present activities of daily living.

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Phospholipids

Preferably, the present composition preferably comprises phospholipids, preferably 0.1-50 wt.% phospholipids based on total weight of lipids, more preferably 0.5-20 wt.%, more preferably between 1 and 5 wt.% based on total weight of lipids. The total amount of lipids is preferably between 10 and 30 wt.% on dry matter, and/or between 2 and 6 g lipid per 100 ml for a liquid composition. Inclusion of phospholipids beneficially

improves membrane function, thereby enabling an improved functioning of the different parts of the brain that play a (main) role in daily activities. Furthermore, the phospholipids improve stability of the present product.

5 Nucleotides

The present composition preferably comprises uridine and/or an equivalent thereof, preferably at least one uridine or an equivalent thereof selected from the group consisting of uridine (i.e. ribosyl uracil), deoxyuridine (deoxyribosyl uracil), uridine phosphates (UMP, dUMP, UDP, UTP), nucleobase uracil and acylated uridine derivatives. Preferably the present composition comprises an uridine phosphate selected from the group consisting of uridine monophosphate (UMP), uridine diphosphate (UDP and uridine triphosphate (UTP). Most preferably the present composition comprises UMP, as UMP is most efficiently being taken up by the body. Preferably at least 50 wt.% of the uridine in the present composition is provided by UMP, more preferably at least 75 wt.%, most preferably at least 95 wt.%. The present method preferably comprises the administration of uridine (the cumulative amount of uridine, deoxyuridine, uridine phosphates, nucleobase uracil and acylated uridine derivatives) in an amount of 0.08-3 g per day, preferably 0.1-2 g per day, more preferably 0.2-1 g per day.

20 Preferably the present composition comprises uridine phosphate, preferably uridine monophosphate (UMP). The UMP very efficiently taken up by the body. Hence, inclusion of UMP in the present product enables a high effectiveness at the lowest dosage and/or the administration of a low volume to the subject. Preferably the weight ratio of uridine to cytidine is larger than 1.0, more preferably 2.0, most preferably more than 5.0. The term uridine as used herein relates to uridine and/or equivalents thereof. The term cytidine as used herein relates to cytidine and/or equivalent thereof. Although cytidine is a precursor of uridine, which passes the blood brain barrier, it is more efficient and effective to include uridine in the present composition.

30 The present method preferably comprises the administration of uridine monophosphate (UMP) in an amount of 0.08-3 g per day, preferably 0.1-2 g per day, more preferably 0.2-1 g per day. The present method preferably comprises the administration of a composition comprising uridine in an amount of 0.08-3 g UMP per 100 ml liquid product, preferably 0.1-2 g UMP per 100 ml liquid product, more preferably 0.2-1 g per 100 ml liquid product. Preferably 1-37.5 mg UMP per kilogram body weight is

administered per day. The required dosages of the equivalents on a weight base can be calculated from the dose for UMP by taking equimolar amounts using the molecular weight of the equivalent and of UMP, the latter being 324 Dalton. The amount of nucleotides or nucleosides and derivatives is preferably 3-115 μmol , preferably 5-35 μmol per kg body weight per day, or 0.25 to 9 mmol, preferably 0.3-6, most preferably 0.45-2.8 mmol per day.

Uridine derivatives like UDP, which is readily formed from dietetic UMP, appear to be important for transport of glycoproteins and glycolipids within the cell and availability thereof in the cytosol and plasma membrane.

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In a further preferred embodiment the present composition preferably does not contain high amounts of other nucleotides. Hence, preferably the weight ratio uridine/ adenosine in the present composition is below 0.1, more preferably below 0.01, most preferably 0. Preferably the weight ratio uridine/guanosine in the present composition is below 0.1, more preferably below 0.01, most preferably 0. Preferably the weight ratio uridine/inosine in the present composition is below 0.1, more preferably below 0.01, most preferably 0.

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Combination of uridine and LCP

It was found by the inventors that the nucleotide equivalents as defined, and in particular the uridine sources as defined are important to support and/or enhance the effect of the lipid fractions as defined above on daily activities. The present combination, particularly of (i) uridine and (ii) DHA and/or EPA is surprisingly effective. On a biochemical level this may be observed by an improvement of ceramide metabolism in membranes and in particular an increase in glycolipids at the expense of the presence of simple ceramides.

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Methyl donors

Preferably the present composition contains methyl donors. Methyl donors are those food grade compounds which are capable of providing a methyl, methylene or formyl group when administered to a human individual in vivo. The methyl donor included in the present composition is preferably selected from the group consisting of serine, methionine, choline, betaine, dimethylglycine and sarcosine and derivatives thereof. Preferably the present composition contains choline and/or phosphatidylcholine. The present method preferably comprises the administration of more than 50 mg choline per day, preferably 80-2000 mg choline per day, more preferably 120-1000 mg choline per

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day, most preferably 150-600 mg choline per day. The present composition preferably comprises 50 mg to 3 gram choline per 100 ml of the present liquid formula, preferably 200mg – 1000 mg choline/100ml. The methyl donor (particularly choline) is an important precursor of the brain membrane and thereby enables a improved functioning of the brain area involved in supporting daily activities. In a particularly preferred embodiment the present composition comprises phospholipids and choline. It was found that the administration of phospholipids with choline results in maintenance of high choline level. As choline is an important precursor of muscle neurotransmitters, high choline levels (as a result of administration of phospholipids) support of daily living activities.

Minerals & Trace elements

The present composition can be further improved by including one or more minerals. Preferably the present composition comprises at least one mineral selected from zinc, magnesium, copper, manganese and molybdenum. Preferably the present composition comprises manganese and molybdenum.

Manganese

Inclusion of manganese in a diet is important for improving membrane function of cells, in particular the membrane function of nerve cells. Especially those persons that are malnourished or have an inherited or metabolic disorder involving impaired metabolic capacity for producing sphingomyelin and/or related compounds like sulfatides and glycosylated ceramides, benefit from inclusion of the mineral fraction.

The amount of manganese administered per day is preferably more than 0.1 mg, more preferably 0.1-1 mg. Preferably the present method comprises the administration of a (liquid) composition comprising 0.05 to 2 mg manganese per 100 ml, preferably 0.1-1 mg manganese per 100 ml.

Molybdenum

Additional molybdenum is strongly preferred to allow proper functioning of the cofactors, which appears important for creating a proper composition of the membranes, e.g. their sulfatide content, and in particular ensures a proper functioning of nerve cells. Further, inclusion of a proper amount of molybdenum delays brain shrinkage in part of the elderly during aging. The present method preferably comprises the administration of a composition comprising 0.1 – 100 microgram molybdenum per 100 ml, preferably 1-50 µg molybdenum per 100 ml.

Zinc

It is also preferred to include additional zinc into the product which comprises the lipids or nucleotide fraction as described above, in order to stabilize proteins in the brain and prevent agglomeration thereof, which could impart daily life activities. The present method preferably comprises the administration of a composition comprising 0.05 mg – 25 mg zinc per 100 ml, preferably 0.1-10 mg zinc per 100 ml.

Selenium

The present composition preferably contain selenium. The antioxidant activity of selenium advantageously prevents and/or inhibits damaged to the brain areas which enable daily activities. A low selenium levels increases the risk for hospitalisation, particularly in elderly and patients suffering from Alzheimer's disease.

Preferably the present method provides the administration of a composition comprising 0.01 and 5 mg selenium per 100 ml liquid product, preferably 0.02 and 0.1 mg selenium per 100 ml liquid product. The amount of selenium administered per day is preferably more than 0.01 mg, more preferably 0.01-0.5 mg.

Product

The present composition is preferably a ready-to-use liquid, solid, or semi-liquid product. It can also be in a concentrated form suitable for dissolving or dilution or suitable for the purpose of fortifying a second product. The preparation can be a drink, an emulsion, a dispersion, a pill or capsule, a bar, a powder, granulated or not, a pudding, a sauce, a gel, an ice cream, a soup, a cookie, a lollipop, sweetie, or other form known in the art. The present composition is preferably enterally administered, more preferably orally. Most preferably the present composition is administered through a straw.

The subjects that can benefit from the method and composition of the invention (particularly patients suffering from Alzheimer's, dementia and/or elderly) often experience problems with eating. Their sensoric capabilities and/or control of muscles has become impaired, as well as in some instances their ambition to apply proper eating habits. Swallowing and/or mastication are often problematic. The present invention therefore preferably has a low viscosity, preferably a viscosity between 1 and 2000 mPa.s measured at a shear rate of 100 sec⁻¹ at 20 °C. More preferably, the present composition is preferably provided in the form of a drink capable of being ingested

through a straw which makes the product even easier to ingest and improves compliance. In a preferred embodiment the present composition has a viscosity of 1– 80 mPas at a shear rate of 100 per sec at 20 °C, more preferably of 1-40 mPas at a shear rate of 100 per sec at 20 °C. To be optimally accepted by the patient, the present composition preferably has an osmolality of 300 to 800 mOsm/kg.

Additionally many of the subjects (e.g. suffering from Alzheimer's, dementia and/or elderly) experience a general loss in appetite and/or become malnourished. Hence it is advantageous to include within the present composition other nutrients. However, the energy density of the product is preferably not so high that it interferes with normal eating habits. When in liquid form, the present product preferably contains between 0.2 and 3 kcal/ml, more preferably between 0.5 and 2, between 0.7 and 1.5 kcal/ml.

Advantageously the present composition contains digestible carbohydrates. The digestible carbohydrates positively influence the operational skills of the subject, and have an advantageous effect over and above the effects for the present composition containing LCP and/or uridine. The present composition preferably contains between 1 and 50 gram digestible carbohydrates per 100 ml of a liquid product, more preferably between 5 and 30 grams per 100 ml, more preferably 10-30 grams carbohydrates/100 ml. The total amount of digestible carbohydrates is preferably between 25 and 80 wt.% on dry matter, preferably 40 – 80 wt.% based on dry matter.

The product is mainly administered to frail elderly, wherein muscle strength is preferably improved. The present composition preferably contains protein to improve muscle strength. The improved muscle strength provides an important stimulus for support of daily activities, and advantageously contributes to the present method. The present composition preferably contains 0.5 – 15 gram protein per 100 ml of the liquid product, preferably 1-10 grams per 100 ml of the liquid product, more preferably 1-5 grams per 100 ml of the liquid product. Preferably the present composition contains at least 80 wt.% milk derived protein (e.g. whey and/or casein) based on total protein.

The present method preferably comprises the administration of a composition of 50 to 250 ml, preferably 75 to 150 ml.

Subjects

The present composition is preferably administered to a human, more preferably to (i) an elderly human and/or a human suffering from Alzheimer's disease, (senile)

dementia, Parkinson's Disease, Multiple Sclerosis, aphasia, apraxia, ataxia, dystonia or dyskinesia. Although there is no sharp delimitation of 'elderly' or 'aged', an age of 65 can be considered herein as an average lower limit for elderly human.

5 The present method is particularly suitable for patients suffering from Alzheimer's disease and/or MCI. Preferably the present composition is administered to a subject suffering from Alzheimer's, more preferably subject suffering from early or mild Alzheimer's, preferably a to subject suffering from Alzheimer's disease, wherein said subject with a mini mental state examination (MMSE) score of 16 to 27, preferably 20
10 to 26. It was found that in this subgroup of Alzheimer patients the present composition was particularly effective. This patient group is often on the edge of losing independence on the activities of daily living. Hence, restoring and improving the present skills of this group of patients have a particularly high benefit.

15 Uses

The present method particularly aims to (i) support and/or enhance the activities of daily living and/or prolong independent living.

The term "activities of daily living" as used in the present invention relates to instrumental and/or basic activities of daily living. In particular the present invention
20 provides a method for supporting and/or enhancing the instrumental and/or basic activities of daily living. Preferably at least one of the following instrumental activities of daily living is supported and/or enhanced: performing light and/or heavy housework, preparing meals and/or drinks, shopping for groceries, using household appliances (particularly the telephone) and taking medication. Preferably at least one of the
25 following basic activities of daily living is supported or enhanced: personal hygiene activities (particularly washing and/or bathing), dressing, walking and/or using the toilet.

"Prolonging independent living" as used in the present invention can be easily determined by tests which determine the effect of a therapy on the time before the
30 patient is moving to an institution. The present invention also relates to a method for increasing the time to nursing home admission, comprising administering the present composition. A further benefit of the present invention is a reduced caregiver burden.

In one aspect the present invention provides for a method (or use) of the present
35 composition for improving the ability to/for: (i) independent housekeeping, transport, shopping or personal hygiene activities; and/or (ii) stimulating independent walking,

bathing, grooming, dressing, use of communication equipment (particularly telephone), use of household appliances (particularly television), cleaning dishes, preparation of meal or drink or writing. Typically, the method of the invention aims at supporting or improving the capability of performing practical operations which more rely on motor capacities than on cognitive capacities. The method of the invention thus serves at improving quality of life.

The activities of daily living also include the power or capability to make rapid or secure movements, or to walk safely or without feelings of fear of falling on the ground or to maintain equilibrium of the body under those conditions that for young healthy persons give no problem. The support of these activities in persons in need of such support result in a maintenance, a restoration or a decrease in the decline of the capabilities to go out walking safely, to go shopping, walk timely to the bathroom or climb the stairs.

Other daily activities include sensory-motor skills, whose adequate presence becomes evident in the capability to coordinate movements of muscles or limbs, in particular during eating or drinking, while wanting to grasp goods, or while aiming to put things on an exact location or in a particular position. Support of these activities in persons in need of such support, is meant to be the maintenance, restoration or a decrease in the rate of decline of the capabilities to prepare or consume a meal, a drink.

The activities of daily life also include the capability to feel, notify, touch or clean all areas of the body. Support of these activities in persons in need of such support is meant to be a restoration, maintenance or decrease of the decline of feeling or full sensation of all parts of the body, of cleaning practices and of the application of hygienic practices of the person's own body and the person's environment.

Such support of the activities as occur in normal daily life, to a level which keeps the persons in a state of independency and/or self maintenance in the society, can be achieved by administration of an effective amount of the present composition.

In one embodiment the present invention provides the present composition together with instructions for (preferably oral) administration of the composition and indication that said product can be used for one or more of (i) supporting the activities of daily living and/or prolong independent living; or (ii) stimulating independent housekeeping, transportation, shopping or personal hygiene activities; or (iii) stimulating independent

walking, bathing, grooming, dressing, use of communication equipment (particularly telephone), use of household appliances (particularly television), cleaning dishes, preparation of meal or drink or writing.

- 5 In a further embodiment present invention provides the present composition together with instructions for (preferably oral) administration of the composition and indication that administration of the present composition provides the health benefit as described in a published scientific paper, said scientific paper describing a positive outcome for one or more of (i) supporting of the activities of daily living and/or prolong independent
- 10 living; or (ii) stimulating independent housekeeping, transportation, shopping or personal hygiene activities; or (iii) stimulating independent walking, bathing, grooming, dressing, use of communication equipment (particularly telephone), use of household appliances (particularly television), cleaning dishes, preparation of meal or drink or writing.

EXAMPLES

Example 1: In-vivo study

- 5 Rats can be modelled for the capacity to deal with difficulties in instrumental and/or basic activities of daily living by infusing the rats with beta-amyloid, a protein causing toxicity in the brain leading to neuropathies, into the lateral ventricle of the brain. Rats infused this way show impairment in spontaneous activity in a new environment, which is an important part of activities of daily living, and indicative for the instrumental and/or basic activities of daily living in humans, particularly humans suffering from Alzheimer's disease. The infused rats do not explore the new environment as extensively as control rats do, which is reflected in reduced exploration time and a decrease in walking distance. This study uses a dietary composition (diet B) to overcome the difficulties in daily life activities.

15

Experimental design

- Four groups of rats received either an infusion into the lateral ventricle with beta-amyloid (Abeta) or a saline solution (Sham). Five weeks prior to the infusions the rats were fed one of two diets, A or B. The four groups are summarized in table 1. Table 2 lists the dietary composition of the two diets. Diet A serves as a control diet. Diet B is enriched in e.g. DHA, uridine and choline. The rats are placed in a new environment (circular arena, 120 cm in diameter) for 15 minutes and their walking pattern is analyzed.

- 25 Table 1: Groups of rats differing in infusion solutions and diet.

Group	Infusion	Diet
1	Sham	A
2	Abeta	A
3	Sham	B
4	Abeta	B

Results

On the control diet (A) rats infused with abeta show decreased walking distance in the new environment. When fed the experimental diet (B) to abeta infused rats restored exploration of the new environment to levels of control rats (Sham operated rats, no abeta infusion). Figure 1 shows that Abeta infused rats displayed ~25% reduced locomotor activity in the Open Field on diet A diet, but not in animals on diet B.

Lateral ventricle infusions of abeta induce a reduction in activity. These effects were completely diminished by feeding the present treatment diet. The beneficial effects are indicative for the advantageous use of the present composition in the present method, particularly for improving instrumental and/or basic activities of daily living.

Example 2: Compositions with package

Packaged composition comprising per 125 ml:

- Energy 125 kcal; Protein 3.75 g; Carbohydrate 16.75 g; Fat 4.81 g.
Fat includes 300 mg EPA, 1200 mg DHA and 160 mg phospholipids (soy lecithin); Choline 400 mg; UMP (uridine monophosphate) 625 mg; Vitamin E 40 mg α -TE (400% RDA); Vitamin C 80 mg (133% RDA); Selenium 60 μ g; Vitamin B12 3 μ g (300% RDA); Vitamin B6 1 mg (50 % RDA); Folic acid 400 μ g (200% DA);
Minerals: Magnesium 29 mg; Zinc 1.5 mg; Manganese 0.41 mg; Molybdenum 12.5 μ g
The package indicates that the composition improves the activities of daily living, particularly stimulating independent walking, bathing, grooming, dressing, use of communication equipment (particularly telephone), use of household appliances (particularly television), cleaning dishes, preparation of meal or drink and/or writing.
The composition is suitable for administration to patients suffering from dementia or Alzheimer's disease.

Example 3: In vivo study

- Rats were fed diets specific in B-vitamins (vitamin B₆, vitamin B₁₂, and folic acid) content during four weeks. One group was fed a diet deficient of B-vitamins and the other group was fed a B-vitamin enriched diet. The rats were housed in groups of four and locomotor activity was assessed in the home cages. The average percentage of the change in activity between the four week intervention period and a control period was calculated.

During the sleep (inactive) period, the average change in activity was decreased in rats fed the B-vitamin enriched diet as compared to the B-vitamin deficient diet ($p=0.046$). In fact, the locomotor activity increased in the rats fed the B-vitamin deficient diet, while it decreased in the rats fed the B-vitamin enriched diet as compared to the control period. Locomotor activity was increased during the sleep period of the rat by feeding a B-vitamin deficient diet. In contrast, activity during the sleep period was decreased by feeding B-vitamin enriched diet. This indicates that rats show a disturbed sleeping pattern when a B-vitamin deficiency is induced. Hence, wellbeing is affected by the B-vitamin deficient diet, as a disturbed sleeping pattern most likely decreases wellbeing. In contrast, wellbeing was improved in rats fed the B-vitamin enriched diet: locomotor activity was decreased and therefore time spent at rest increased.

CLAIMS

1. Use of a composition comprising (a) DHA and/or EPA, and (b) uridine or its equivalent, in the manufacture of a composition for supporting activities in daily living.
2. Use according to claim 1, wherein the composition is administered to a subject having difficulty with performing the daily activities.
3. Use according to any one of the preceding claims wherein the composition further comprises folic acid, vitamin B12 and/or vitamin B6.
4. Use according to any one of the preceding claims, wherein the activities comprise the ability for:
 - (i) independent housekeeping, transportation, shopping or personal hygiene activities; or
 - (ii) bathing, grooming, dressing, use of communication equipment, use of household appliances, cleaning dishes, preparation of meal or drink or writing.
5. Use according to claim 1 or 2 wherein the subject is a human suffering from Alzheimer and having a mini mental state examination (MMSE) score between 16 and 27.
6. Use according to any one of the preceding claims, wherein the composition contains 0.1 – 2 g uridine, calculated as uridine monophosphate, per daily dosage unit.
7. Use according to any one of the preceding claims, wherein the composition contains 300 – 3600 mg DHA per daily dosage unit.
8. Use according to any one of the preceding claims, wherein the weight ratio between DHA and arachidonic acid is at least 2.0.

9. Use according to any one of the preceding claims, wherein the composition is a liquid with a viscosity of 1 – 40 mPa.s measured at a shear rate of 100 per sec at 20 °C.
10. Use according to any one of the preceding claims, wherein the composition further contains 80 – 2000 mg choline per daily dosage unit.
11. Use of a composition comprising (a) DHA and/or EPA, and (b) uridine or its equivalent for prolonging independent living.
12. A liquid composition comprising per 100 ml, 0.2–2 gram uridine; 0.5-5 g DHA; 0.5 – 10 g protein; 2- 20 g carbohydrates; 0.5-15 microgram vitamin B12; 50-1000 microgram folic acid and 0.1 - 10 mg vitamin B6, wherein the composition has a viscosity of 1 – 40 mPas measured at a shear rate of 100 per sec at 20 °C; an osmolality of 300 to 800 mOsm/kg and a caloric density between 0.2 and 3 kcal/ml.

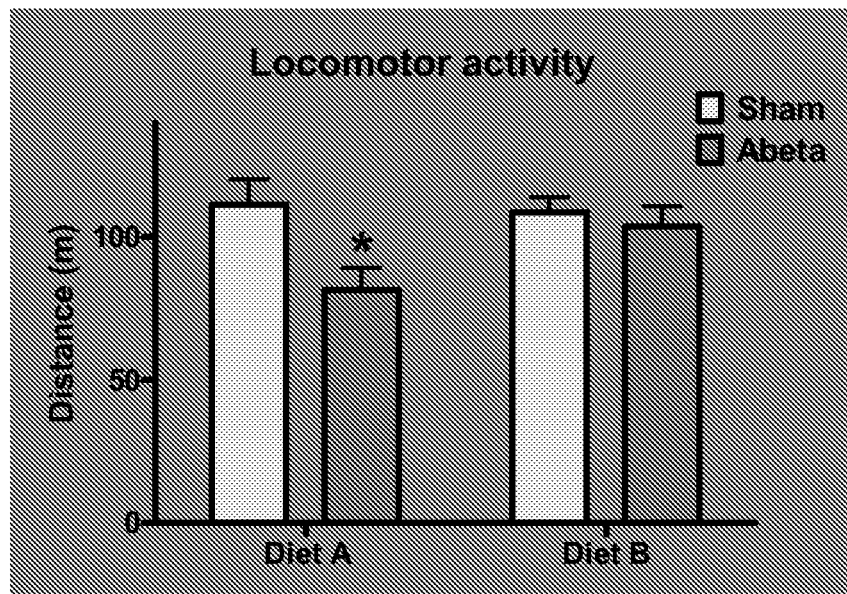


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2007/050307

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/20 A23L1/29 A23L1/30 A23L1/304 A23L1/305
A61K31/14 A61K31/202 A61K31/7072 A61P25/28 A61P43/00

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)

A61K A23L

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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/127620 A (MASSACHUSETTS INST TECHNOLOGY [US]; WURTMAN RICHARD J [US]; RICHARDSON) 30 November 2006 (2006-11-30) claims 13-15,17-20; examples 1-11	1-11
X	WURTMAN ET AL: "Synaptic proteins and phospholipids are increased in gerbil brain by administering uridine plus docosahexaenoic acid orally" BRAIN RESEARCH, ELSEVIER, AMSTERDAM, NL, vol. 1088, no. 1, 9 May 2006 (2006-05-09), pages 83-92, XP005446770 ISSN: 0006-8993 abstract ----- -/--	1,2,4,5, 11

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

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

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

22 February 2008

Date of mailing of the international search report

03/03/2008

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INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2007/050307

G(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2007/008586 A (MARTEK BIOSCIENCES CORP [US]; ELLIS LORIE A [US]) 18 January 2007 (2007-01-18) abstract; claims 1-17	1-12
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL2007/050307

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2007/050307

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