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(54) **COMPOSITIONS AND METHODS FOR
PROMOTING BONE DEVELOPMENT**

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ABSTRACT

Compositions and methods useful to promote bone development in a growing animal are disclosed.

COMPOSITIONS AND METHODS FOR PROMOTING BONE DEVELOPMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/891,171, filed on Feb. 22, 2007, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to compositions and methods for promoting bone development in mammals.

BACKGROUND OF THE INVENTION

[0003] Commercially available pet foods, e.g., cat food, include compositions specially formulated to address many different nutritional needs. These include, for example, formulations designed for different breed types, sizes and body conditions. They also include formulations designed to address the nutritional needs of animals in the different stages of their life cycle. Despite the availability of such pet food formulations, however, there is a need to develop formulations and methods to address other aspects of an animal's health.

[0004] Animals are subject to injury, including broken bones and dislocated joints. Animals may also develop degenerative diseases, such as osteoporosis, and osteoarthritis. Accordingly, there is a need for compositions and methods which inhibit such injury and degenerative diseases.

[0005] Bones are metabolically active, undergoing constant resorption and redeposition of calcium. This requires the sequential and coordinated actions of osteoclasts, to remove bone (resorption), and the osteoblasts to replace it (deposition). This is commonly called "bone turnover." In normal bone, following skeletal growth of an animal, the mineral deposition is in equilibrium with mineral resorption; however, in certain conditions, bone resorption exceeds bone deposition, resulting in loss of bone mineral content. High bone turnover with increased bone resorption can compromise bone strength, leading to a thinning of the bone structure. This may result in abnormal bone microarchitecture and reduced bone mineralization. Animals generally lose bone mineral content as they increase in age, resulting in osteopenia, and this loss of bone mineral content is the major cause of osteoporosis, which may cause a greater propensity for fracture. Animals may also be pre-disposed to bone mineral content loss, wherein such bone mineral content loss is associated with various diseases and conditions. Foods and supplements have been developed which retard bone loss, or aid in re-calcification of bone. However, there is a continuing need to develop such compositions, including compositions that promote bone formation in growing animals so as to avoid such conditions when the animal matures.

[0006] It is generally known in the art that bone desorption is accompanied by an increase in bone alkaline phosphatase ("BAP"), as calcium and phosphorous is liberated from bone. Use of various materials may effect the expression of genes involved in bone maintenance or bone formation, including bone morphogenic proteins and matrix metalloproteinases. For example, the use of carnitine for bone formation is

known. However, there needs to be developed other compositions and methods which promote bone formation in animals.

SUMMARY OF THE INVENTION

[0007] In certain aspects, the present invention relates to compositions that are useful to promote bone development in an animal.

[0008] The present invention includes Composition 1.0, a pet food composition useful to promote bone development in an animal comprising:

[0009] about 0.1% to about 0.7% EPA;

[0010] about 50 ppm to about 200 ppm manganese; and

[0011] about 0.5% to about 1.6% methionine.

[0012] The present invention also includes the following compositions:

[0013] 1.1 Composition 1.0 comprising about 0.1% to about 0.7% DHA, e.g., about 0.1% to about 0.5% or 0.6%, e.g., about 0.2%, about 0.3%, or about 0.4%;

[0014] 1.2 Composition 1.0 or 1.1 comprising about 200 to about 1200 IU/kg vitamin E, e.g., about 500 IU/kg to about 1100 IU/kg, about 700, about 800, about 900, or about 1000 IU/kg;

[0015] 1.3 Any of the preceding compositions comprising about 50 to about 500 ppm vitamin C, e.g., about 100 to about 400 ppm Vitamin C, e.g., about 150, about 175, about 200, or about 225 ppm;

[0016] 1.4 Any of the preceding compositions comprising about 100 ppm to about 500 ppm carnitine, e.g., about 200, about 300, or about 400 ppm carnitine;

[0017] 1.5 Any of the preceding compositions comprising about 2.5 g/1000 kcal to about 7 g/1000 kcal lysine;

[0018] 1.6 Any of the preceding compositions comprising about 2400 ppm to about 7500 ppm choline, e.g., about 3000, about 4000, about 4500, about 4600, about 4625, about 4650, about 4700, about 5000, or about 6000 ppm;

[0019] 1.7 Any of the preceding compositions comprising about 0.1% to about 0.6% EPA, e.g., about 0.2%, about 0.3%, about 0.4%, or about 0.5%;

[0020] 1.8 Any of the preceding compositions comprising about 50 ppm to about 150 ppm manganese;

[0021] 1.9 Any of the preceding compositions comprising about 0.8% to about 1.6% methionine, e.g., about 1.3 or about 1.4% methionine.

[0022] 1.10 Any of the preceding compositions further comprising:

[0023] 0 to about 90% by weight of carbohydrates;

[0024] about 5% to about 70% by weight of protein;

[0025] about 2% to about 50% by weight of fat;

[0026] about 0.1% to about 20% by weight of total dietary fiber;

[0027] 0 to about 15%, or about 2% to about 8%, by weight of vitamins, minerals, and other nutrients, in varying percentages which support the nutritional needs of the animal.

[0028] 1.11 Composition 1.10 comprising about 5% to about 55%, by weight of carbohydrates;

[0029] 1.12 Composition 1.10 or 1.11 comprising about 20% to about 60%, by weight of protein, e.g., about 30% to about 55%;

[0030] 1.13 Any one of compositions 1.10-1.12 comprising about 5% to about 40%, by weight of fat, e.g., at least about 8% or about 9% to about 40% fat;

[0031] 1.14 Any one of compositions 1.10-1.13 comprising about 1% to about 11%, by weight of total dietary fiber;

[0032] 1.15 Any of the preceding compositions comprising about 1000 to about -4000 ppm taurine;

[0033] 1.16 Any of the preceding compositions comprising about 0.5% to about 6.0% linoleic acid, e.g., about 2.5% to about 5%;

[0034] 1.17 Any of the preceding compositions comprising about 1% to about 3% total n-3 fatty acids, e.g., about 1.3%, about 1.4%, about 1.5%, or about 1.6%;

[0035] 1.18 Any of the preceding compositions comprising about 1% to about 6% total n-6 fatty acids, e.g., 3% to 5%, about 3.5%, or about 4%.

[0036] The compositions of the present invention may be a wet, dry, or semi-dry food.

[0037] The present invention includes Method 2.0, a method to promote bone development and/or joint health in a feline comprising administering to the feline any one of compositions 1.0-1.18.

[0038] The present invention also includes the following methods:

[0039] 2.1 Of method 2.0 wherein the feline is a kitten.

[0040] 2.2 Of method 2.0 or 2.1 wherein the feline is born of a queen fed any one of compositions 1.0-1.18 during pregnancy.

[0041] 2.3 Of method 2.2 wherein the feline is in utero.

[0042] 2.4 Of method 2.2 wherein the queen is fed any one of compositions 1.0-1.18 prior to pregnancy.

[0043] 2.5 Of method 2.2 or 2.4 wherein the queen is fed any one of compositions 1.0-1.18 for a majority of the pregnancy duration.

[0044] 2.6 Of any one of methods 2.2-2.5 wherein the queen is fed compositions consisting essentially of any one of compositions 1.0-1.18 prior to and during pregnancy.

[0045] 2.7 Of any one of the preceding methods wherein the kitten is fed any one of compositions 1.0-1.18 prior to weaning, e.g., while still nursing.

[0046] 2.8 Of any one of the preceding methods wherein the kitten is fed any one of compositions 1.0-1.18 post weaning.

[0047] 2.9 Of method 2.8 wherein the kitten is fed food compositions consisting of any one of compositions 1.0-1.18.

[0048] 2.10 Of any one of the preceding methods wherein an effective amount of the composition is administered to the animal.

[0049] 2.11 Of any one of the preceding methods wherein the composition is administered to the animal for an effective amount of time.

[0050] Other features and advantages of the present invention will be understood by reference to the detailed description of the examples that follow.

[0051] It is also contemplated that, in addition to administering the compositions disclosed herein directly to a growing animal, e.g., to a growing puppy or kitten, the compositions may be administered to the dam of the animal while the animal is still in utero or while the animal is a nursling.

[0052] Other features and advantages of the present invention will be understood by reference to the detailed description of the examples that follow.

DETAILED DESCRIPTION OF THE INVENTION

[0053] It is contemplated that the invention described herein is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention in any way.

[0054] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. In addition, all references cited herein are hereby incorporated by reference in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0055] As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

[0056] The present invention relates to any animal, preferably a mammal, more preferably a companion animal. The term "companion animal" refers to any animal that lives in close association with humans and includes, but is not limited to, canines and felines of any breed. It is contemplated herein, however, that any animal whose diet may be controlled by humans may benefit from feeding the formulations disclosed herein. These animals may include, for example, domesticated farm animals (e.g., cattle, horses, swine, etc.) as well as undomesticated animals held in captivity, e.g., in zoological parks and the like. Preferably, the animal is a feline, either a kitten, or adult cat.

[0057] As used herein, "an amount effective to" or "an effective amount" to achieve a particular result, and like terms, refer to that amount of a compound, material or composition as described herein that may be effective to achieve a particularly desired biological result. As contemplated herein, such results include, for example, enhancement of neurologic development, bone and joint health, immune function and/or promotion of a healthy body composition of an animal, either while developing in utero and/or during its growth stage after birth, e.g., up to 6 months, 9 months, 12 months, or 15 months after birth. Such effective activity may be achieved, for example, by administration of compositions of the present invention to the dam of said animal while the animal is in utero or nursing, as well as by direct administration to the animal during its growth stage.

[0058] As used herein, the "enhancement" of a particular biological process or body condition in a growing animal such as described herein refers to an improvement in the biological process or body condition of a growing animal compared to a control animal. Improvement in such a process or condition may be determined by one of skill in the art.

[0059] As used herein, "enhancement of the development of a growing animal," "enhanced growth," or "promoting growth" and like terms refer to an overall improvement in one or more biological processes and/or the body condition of a growing animal, including but not limited to, biological processes central to the growth and development of an organism, including, but not limited to, the biological processes described herein, e.g., bone and joint health, neurologic and immune system development and body weight gain (e.g., increase in lean muscle mass instead of adipose tissue).

[0060] The “growth” life stage of an animal refers to the period from birth or weaning (approximately 8 weeks of age) to about 1 year of age.

[0061] As used herein, the term “kitten” refers to an immature feline, typically between the ages of birth and 12 months.

[0062] “Essential amino acids” as used herein refers to those amino acids that cannot be synthesized *de novo* by an organism and thus must be supplied in the diet. It is understood by one of skill in the art that the essential amino acids varies from species to species, depending upon the organism’s metabolism. For example, it is generally understood that the essential amino acids for dogs and cats (and humans), are phenylalanine, leucine, methionine, lysine, isoleucine, valine, threonine, tryptophan, histidine and arginine. In addition, taurine, while technically not an amino acid but a derivative of cysteine, is considered an essential for cats. A balanced diet can provide all the essential amino acids, however, there are certain essential amino acids that are more critical, as a diet deficient in one of them will limit the usefulness of the others, even if the other essential amino acids are present in sufficient quantities.

[0063] As understood by one of skill in the art, a “limiting amino acid” refers to an amino acid which if present in insufficient quantities in a diet, results in the limitation in usefulness of other essential amino acids, even if the other essential amino acids are present in otherwise large enough quantities. Lysine is the limiting essential amino acid in the compositions disclosed herein. Thus, the remaining essential amino acids are quantitatively formulated or “balanced” in relationship to the amount of lysine determined critical to affect the desired biological result. As used herein, “balanced amino acids” refers to the relationship of the essential amino acid lysine to energy to assure optimal animal growth and development.

[0064] “Essential nutrients” as used herein refers to nutrients required for normal body functioning that cannot be synthesized by the body. Categories of essential nutrient include vitamins, dietary minerals, essential fatty acids, and essential amino acids. It is understood by one of skill in the art that the nutrients deemed essential varies from species to species, depending upon the organism’s metabolism. For example, essential nutrients for dogs and cats include Vitamins A, D, E, K, B1, B6, B12, riboflavin, niacin, pantothenic acid, folic acid, calcium, phosphorous, magnesium, sodium, potassium, chlorine, iron, copper, zinc, manganese, selenium and iodine. Choline, generally regarded as a B complex vitamin, may be included among the semi-essential nutrients.

[0065] Carnitine, also known as L-carnitine, (levocarnitine) is a quaternary ammonium compound synthesized from the amino acids lysine and methionine and is responsible for the transport of fatty acids from the cytosol into the mitochondria.

[0066] Without being limited to any theories or particular modes of action, the present invention is based on the surprising discovery that the addition of certain ingredients to pet food compositions and administration of these compositions to animals can enhance the bone development/health and/or joint health of a growing animal. Data indicates that animals fed the compositions of the present invention (or those whose dams were fed the compositions during gestation and prior to weaning but continued throughout growth of their litters), demonstrate reduced levels of BAP and deoxypyridinoline. Thus, in one aspect, the invention relates to a method to promote the development of bone in an animal comprising

administering to said animal a composition of the present invention. Increased bone development may be indicated by reduced levels of BAP or deoxypyridinoline. Thus, in another aspect, the invention relates to a method to reduce the BAP and/or deoxypyridinoline levels in an animal comprising administering to the animal a composition of the present invention.

[0067] Type I collagen tissue is one of the most abundant collagen type in an animal, and is the only collagen type found in mineralized bone, where it accounts for more than 90% of the organic matrix. In addition, type I collagen is found in connective tissues, such as joints, together with other collagen types. Carboxyterminal cross-linked telopeptide of type I collagen (“ICTP”) is the carboxyterminal telopeptide region of type I collagen. The peptide is derived from bone resorption and degradation of connective tissues. It is believed that increased serum concentrations of ICTP is indicative of loss of bone or joint materials. Thus, in one aspect, the invention relates to a method to promote the healthy bones and joints in an animal comprising administering to said animal a composition of the present invention. In another aspect, the invention relates to a method to reduce the ICTP, e.g., serum levels, in an animal comprising administering to the animal a composition of the present invention.

[0068] As contemplated herein, the compositions of the present invention comprise nutritionally complete and balanced animal feed compositions. Such compositions include, among other nutrients and ingredients, recommended healthful amounts of protein, carbohydrate and fat. “Nutritionally complete and balanced animal feed compositions”, as well as nutrients and ingredients suitable for animal feed compositions, and recommended amounts thereof, are familiar to one of skill in the art (see, for example, National Research Council, 2006 Nutritional Requirements for Dogs and Cats, National Academy Press, Washington D.C. or the Official Publication of the Association of American Feed Control Officials, Inc. Nutrient Requirements for Dogs and Cats 2006).

[0069] It is contemplated herein that the compositions disclosed herein may also comprise antioxidants, additives, stabilizers, thickeners, flavorants, palatability enhancers and colorants in amounts and combinations familiar to one of skill in the art. “Antioxidants” refers to a substance that is capable of reacting with or decreasing the production of free radicals and neutralizing them. Examples include, but are not limited to, beta-carotene, selenium, coenzyme Q10 (ubiquinone), lutein, tocotrienols, soy isoflavones, S-adenosylmethionine, glutathione, taurine, N-acetylcysteine, vitamin E, vitamin D, vitamin C, flavonoids, anthocyanidins, and lipoic acid.

[0070] While foods of any consistency or moisture content are contemplated, preferably the compositions of the present invention may be, for example, a wet, semi-dry or dry animal food composition. “Wet” food refers to food which is sold in cans or foil bags and has a moisture content of about 70% to about 90%. “Dry” food refers to compositions with about 5% to about 15% moisture content and is often manufactured in the form of small bits or kibbles. Semi-dry compositions refer to compositions having about 15% to about 70% moisture. Also contemplated herein are compositions of intermediate moisture consistency and those that may comprise components of various consistency as well as components that may include more than one consistency, for example, soft, chewy meat-like particles as well as kibble having an outer cereal component and an inner cream component. Also contem-

plated herein are compositions of intermediate moisture consistency and those that may comprise components of various consistency as well as components that may include more than one consistency, for example, soft, chewy meat-like particles as well as kibble having an outer cereal component and an inner cream component as described in, e.g., U.S. Pat. No. 6,517,877.

[0071] The following examples further illustrate the present invention and are not intended to limit the invention. As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. It is understood that when formulations are described, they may be described in terms of their ingredients, as is common in the art, notwithstanding that these ingredients may react with one another in the actual formulation as it is made, stored and used, and such products are intended to be covered by the formulations described.

[0072] The following examples further describe and demonstrate illustrative embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations are possible without departing from the spirit and scope thereof. Various modifications of the invention in addition to those shown and described herein should be apparent to those skilled in the art and are intended to fall within the appended claims.

Example 1

[0073] Formulations to enhance the development of growing animals are disclosed here-in-below. These compositions are developed taking into account the “ideal protein concept” (Baker and Czarnecki-Maulden, 1991 *Annu. Rev. Nutr.* 11:239-63).

[0074] Foods are developed for the “growth” life stage. These foods include formulations for canine growth and feline growth. The minimum nutrient recommendations for these foods, as well as the targeted values for a prototype food, are listed below in Table 1.

TABLE 1

Key Nutrients for Kitten Formula			
Nutrient	Target	Minimum	Maximum
Protein, %	45.5	30	55
Methionine, %	1.4	0.8	1.5
Manganese, ppm	90	50	200
DHA, %	0.21	0.1	0.5
EPA, %	0.31	0.1	0.7
Choline, ppm	4880	2500	7500
Taurine, ppm	2380	1000	4000
Linoleic acid, %	3.8	2.5	6
Total n-3 fatty acids, %	1.35	1	3
Vitamin E, IU/kg	900	200	1200
Vitamin C, ppm	90	50	500
Lysine, g/1000 kcal	4	2.5	7

Example 2

[0075] Four foods are used for the study, experimental Formulation X, Commercial A, Commercial A1, and Commercial B. The composition of the foods is presented in Table 2. Commercial A, A1, and B foods are available from commercial sources. Commercial A and A1 are the same brand of food, but produced in different lots.

TABLE 2

Nutrient	Analyzed nutrients of foods fed to queens and kittens			
	Formula X	Commercial A	Commercial A1	Commercial B
Crude Protein, %	41.63	41.2	36.09	35.47
Fat, %	23.15	14.47	12.43	22.94
Ca, %	1.23	1.12	1.50	1.06
P, %	1.11	1.11	1.19	0.96
DHA, %	0.22	0.06	0.04	<0.01
EPA, %	0.32	0.06	0.04	<0.01
Linoleic Acid, %	3.79	1.59	1.96	1.37
Total n-3 fatty acids, %	1.47	0.34	0.25	0.53
Total n-6 fatty acids, %	3.86	1.88	1.91	1.44
Taurine, %	0.24	0.17	0.23	0.20
Methionine, %	1.3	0.76	0.62	0.99
Cystine, %	0.49	0.51	0.44	0.35
Manganese, ppm	78	63	77	56
Vitamin E, IU/kg	914	35	76	138
Vitamin C, ppm	183	—	—	—
Choline, ppm	4624	3010	2807	3331

[0076] 19 queens are fed Formulation X or Commercial A for at least 2 weeks prior to conception. Queens are maintained in group lodging until they are confirmed pregnant via palpation, and are then moved to maternity lodging. 48 kittens are produced from queens fed Commercial A, and 16 kittens are produced from queens fed Formulation X. Following birth of kittens, the kittens from queens are kept on same foods until the kittens are weaned.

[0077] Following weaning, the 48 kittens produced from queens fed Commercial A were

[0078] divided as follows: 16 kittens are fed Commercial A1; 16 kittens are fed Commercial B; and 16 kittens are fed Formulation X. Following weaning, the 16 kittens produced from the queens fed Formulation X are maintained on Formulation X.

[0079] Serum samples are taken from kittens prior to weaning, at 3, 6 and 9 months of age, and are kept frozen until use. Samples are then thawed and subjected to assay as previously described in Yamka, et al., *INTERN J APPL RES VET MED*, Vol 4, No. 3, 2006, and commercial assays as presented in Table 12.

TABLE 12

Commercial Assays		
Kit	Vendor	Catalog Number
Metra BAP EIA	Quidel (San Diego, CA)	8012
Metra Total Dpd EIA	Quidel (San Diego, CA)	8032

TABLE 12-continued

Commercial Assays		
Kit	Vendor	Catalog Number
UniQ ICTP EIA	Immunodiagnostic Systems, Inc. (Fountain Hills, AZ)	OD-06099

[0080] For pre-weaned kittens, data is analyzed by a 2 tailed t-test which reveals a significantly lower concentration of C terminal crosslinked telopeptide (P=0.014) and a lower (P=0.051) concentration of BAP in the kittens originating from queens fed Formula X food, wherein the kittens were also fed Formula X.

[0081] Bone Alkaline Phosphatase—Global ANOVA reveals significant differences at 3 months of age but not 6 or 9 months of age time points. Further analysis of the data by a t-test comparison between the Commercial A-Commercial A1 kitten and Formula X-Formula X kitten groups reveals a significantly lower activity of BAP in the Formula X-Formula X group at all time points.

[0082] Carboxy-terminal c-telopeptide of type I cartilage (ICTP)-Global ANOVA analysis reveals a significant difference between group means at all time points except at 9 months of age. An analysis of the three kitten groups from Formulation A fed dams reveals significant differences between means only at 3 months of age. Comparison of the Formula X-Formula X fed group to the Commercial A-Commercial A1 fed group by t-test reveals significantly lower values for the Formula X-Formula X group at all time points measured except at 6 months (P=0.054 at 6 months).

[0083] Deoxy-pyridinoline (DPD)-Global ANOVA analysis reveals significant differences between means at 3, 6 and 9 months of age. Analysis of the three kitten groups from dams only fed Formulation A yields the same result. Individual t-test comparison between the Formula X-Formula X kittens and the Commercial A-Commercial A1 kittens reveals significant differences at 3 and 6 months of age with the Formula X-Formula X group having a lower value at those two points.

1. A pet food composition comprising: about 0.1% to about 0.7% EPA; about 50 ppm to about 200 ppm manganese; and about 0.5% to about 1.6% methionine.

2. The composition of claim 1 comprising about 0.1% to about 0.7% DHA.

3. The composition of claim 1 comprising about 200 to about 1200 IU/kg vitamin E.

4. The composition of claim 1 comprising about 50 to about 500 ppm vitamin C.

5. The composition of claim 1 comprising about 100 ppm to about 500 ppm carnitine.

6. The composition of claim 1 comprising about 2.5 g/1000 kcal to about 7 g/1000 kcal lysine.

7. The composition of claim 1 comprising about 2400 ppm to about 7500 ppm choline.

8. The composition of claim 1 comprising about 0.1% to about 0.6% EPA.

9. The composition of claim 1 comprising about 50 ppm to about 150 ppm manganese.

10. The composition of claim 1 comprising about 0.8% to about 1.6% methionine.

11. A method to promote bone formation in a feline comprising administering to the feline or to the mother of the feline while the feline is in utero the pet food composition of claim 1.

12. The method of claim 11 wherein the feline is a kitten.

13. The method of claim 11 wherein the feline is born to a queen fed the pet food composition.

14. The method of claim 13 wherein the feline is in utero.

15. The method of claim 13 wherein the queen is fed the pet food composition prior to pregnancy.

16. The method of claim 13 wherein the queen is fed the pet food composition for a majority of the pregnancy duration.

17. The method of claim 13 wherein the queen is fed the pet food compositions prior to and during pregnancy.

18. The method of claim 12 wherein the kitten is fed the pet food composition prior to weaning.

19. The method of claim 12 wherein the kitten is fed the pet food composition according to post weaning.

20. A method of promoting bone formation by inhibiting bone alkaline phosphatase comprising administering to a mammal the composition of claim 1.

21. A method to promote joint health in a feline comprising feeding the feline a pet food composition according to claim 1.

22. A method to promote joint health in a kitten comprising feeding the mother of the kitten a pet food composition according to claim 1 during her pregnancy with the kitten.

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