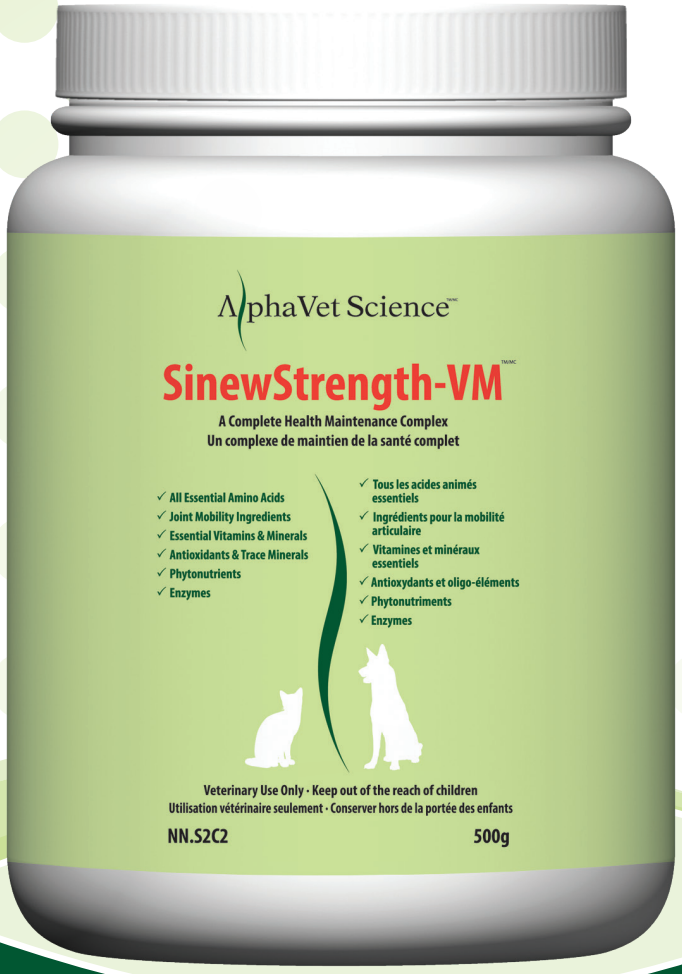
AlphaVet Science™/MC



Just Natural Science™

La science au naturel, simplement™/MC

FUN AMUSEMENT

AlphaVet Science™

SinewStrength-VM™

A Complete Health Recovery Complex **NN.B4T1**

- ✓ **All essential amino acids**
- ✓ **Joint mobility ingredients**
- ✓ **Essential vitamins and minerals**
- ✓ **Antioxidants and trace minerals**
- ✓ **Phytonutrients**
- ✓ **Enzymes**

SinewStrength-VM™ combines a broad spectrum of micro- and macronutrients to maintain musculoskeletal health and functional ability every day by maintaining the structural integrity of joints and connective tissue, along with epithelial tissue, muscle tissue, and nervous tissue.

INDICATIONS • To maintain and rejuvenate vitality

INGREDIENTS ACTIONS
- Alterative
- Digestant
- Nutritive
- Restorative
- Tonic
- Vulnerary

PACKAGING 100 g, 250 g, and 500 g

ADMINISTRATION Oral

DOSAGE

1 - 10 lbs	0.5-4.5 Kg	1.25g	¼ Scoop
11 - 20 lbs	5-9.1 Kg	2.5g	½ Scoop
21 - 50 lbs	9.5-22.7 Kg	5g	1 Scoop
51 - 75 lbs	23.1-34 Kg	6.25g	1¼ Scoop
76-100 lbs	34.5-45.4 Kg	7.5g	1½ Scoop
> 100 lbs	45.4	10 Kg	2g Scoop

STORAGE Do not refrigerate.
Store protected from light and moisture.
Keep out of the reach of children.

SinewStrength-VM™ FORMULA

1 teaspoon (5 mL) contains:

VITAMINS

beta-Carotene		600 mcg (1000 IU)
Vitamin B1	(Thiamine hydrochloride)	2 mg
Vitamin B2	(Riboflavin)	2 mg
Vitamin B3	(Niacinamide)	20 mg
Vitamin B5	(D-Pantothenic acid)	5 mg
Vitamin B6	(Pyridoxine hydrochloride)	2 mg
Vitamin B7	(Biotin)	200 mcg
Vitamin B9	(L-Methylfolate)	300 mcg
Vitamin B12	(Cyanocobalamin)	100 mcg
Vitamin C	(L-Ascorbic acid)	100 mg
Vitamin D3	(Cholecalciferol)	12.5 mcg (500 IU)
Vitamin E	(d-alpha Tocopheryl acetate)	16.8 mg AT (25 IU)
Vitamin K2	(Menaquinones)	10 mcg
Choline	(Choline bitartrate)	10 mg
Inositol	(Myo-inositol)	10 mg
Rutin		10 mg

MINERALS*		
Boron	(Sodium borate)	250 mcg
Calcium	(Calcium citrate)	50 mg
Chromium	(Chromium polynicotinate)	100 mcg
Copper	(Cupric gluconate)	1000 mcg
Magnesium	(Magnesium citrate)	50 mg
Manganese	(Manganese sulfate)	2 mg
Molybdenum	(Sodium molybdate)	100 mcg
Selenium	(L-Selenomethionine)	10 mcg
Silicon	(Sodium metasilicate)	1 mg
Zinc	(Zinc citrate)	1 mg
PHYTONUTRIENTS		
Boswellia serrata	(Frankincence Resin)	25 mg
Chlorella vulgaris	(Chlorella Broken Cell)	100 mg
Curcuma longa	(Turmeric Rhizome)	15 mg
Harpagophytum procumbens	(Devil's claw Root)	20 mg
Moringa oleifera	(Drumstick Tree Leaf & Seed)	200 mg
ACCESSORY NUTRIENTS		
D-Chondroitin sulphate		500 mg
D-Glucosamine sulphate		1000 mg
Hyaluronic acid		75 mg
Hydrolyzed collagen		1000 mg
Methylsulphonylmethane (MSM)		400 mg
AMINO ACIDS		
L-Arginine		20 mg
L-Carnitine		50 mg
L-Glutamine		50 mg
L-Histidine		20 mg
L-IsoLeucine		20 mg
L-Leucine		20 mg
L-Lysine		20 mg
L-Methionine		20 mg
L-Phenylalanine		20 mg
L-Taurine		20 mg
L-Threonine		20 mg
L-Tryptophan		20 mg
L-Valine		20 mg
ENZYMES**		
alpha-Amylase		15 mg (330 FCC DU)
Cellulase		10 mg (35 FCC CU)
Lipase		35 mg (42 FCC LU)
Protease		40 mg (720 FCC HUT)

*MINERALS | Elemental Quantities

**Enzymatic Units

FCC (Food Chemicals Codex)
FCC CU (Cellulase Units)
FCC DU (alpha-Amylase Dextrinizing Units)
FCC HUT (Hemoglobin Unit on a Tyrosine Basis)
FCC LU (Lipase Units)

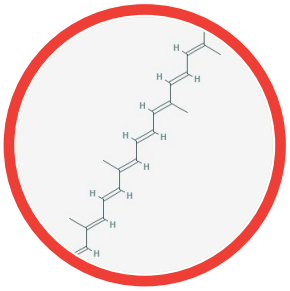
NON-MEDICINAL INGREDIENTS

Apple Fibre, Citrus bioflavonoids, Spirulina

SinewStrength-VM™ is manufactured under strict GMP standards and contains no dairy, yeast, corn, wheat or gluten. Does not contain animal by-products.

VITAMINS

beta-Carotene (Pro-vitamin A) [$C_{40}H_{56}$]



- In nature, all of the vitamin A ingested by animals originates from carotenoids synthesized by plants. Cats and ferrets inefficiently utilize β-carotene as a precursor of vitamin A (NRC, 2006). Cats provide a potential model for the study of the role of β-carotene as an antioxidant and as an immune modulator independent of its pro-vitamin A activity (Schweigert et al., 2002). Five primary functions of vitamin A have been identified including vision, growth, cellular differentiation, morphogenesis, and immune function (NRC, 2006).
- Vitamin A is required for bone remodeling (Nieves, 2005).
- β-Carotene reduces the risk of osteoarthritis progression (McAlindon et al., 1996).
- Acts as a lipid radical scavenger and as a singlet oxygen quencher (Grune et al., 2010).
- Signs of deficiency include anorexia, weight loss, ataxia, xerophthalmia, conjunctivitis, corneal opacity and ulceration, retinal degeneration, skin lesions, metaplasia of the bronchiolar epithelium, pneumonitis, and increased susceptibility to infections (NRC, 2006).

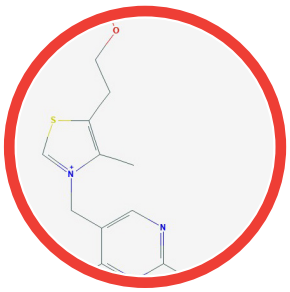
TOXICOLOGY

Toxicity for beta-carotene has not been documented in dogs and cats when administered orally in therapeutic doses.

In humans, excess vitamin A may be detrimental to bone health with intakes of higher than 1500 µg of retinol equivalent (RE) [5000 IU] related to 2-fold increased risk of hip fracture. There is no evidence of any association between β-carotene intake and osteoporosis or related fracture (Nieves, 2005).

DRUG INTERACTIONS

β-carotene preparations can make simvastatin and niacin less effective; Cholestyramine, a medication used to lower cholesterol, can lower levels of dietary beta-carotene in the blood by 30 to 40%; Orlistat, a weight loss medication, can reduce the absorption of β-carotene by as much as 30%; and mineral oil (used to treat constipation) may lower blood levels of beta-carotene (Penn State Hershey Medical Center, 2020).



Thiamin Hydrochloride (Vitamin B1) [$C12H_{18}C_{l2}N_4OS$]

- The active form of thiamine, thiamine diphosphate (synonym: thiamin pyrophosphate), plays an important role as a cofactor in carbohydrate metabolism, in the production of nucleotides and of nicotinamide adenine dinucleotide (NADH), and for nervous system function (Kritikos, et al., 2017).
- Influences collagen synthesis (Alvarez & Gilbreath, 1982).
- Enhances chondroprotective effects of glucosamine hydrochloride and chondroitin sulfate (Kobayashi et al., 2005).
- Thiamine deficiency occurs in cats and dogs fed primarily diets of overcooked meats or fish containing thiaminase (raw fish), canned diets that have sustained extensive processing, or in those with prolonged anorexia (Brody, 1998; Ettinger & Feldman, 2000). Cats have a higher requirement than dogs for thiamine (Ettinger & Feldman, 2000).
- Thiamine is not synthesized in the tissues of cats and dogs and cats are more susceptible to thiamine deficiency than dogs. Neurological abnormalities include central nervous system depression, sensory ataxia, paraparesis, torticollis, circling, tonic-clonic convulsions, profound muscular weakness, and recumbence (NRC, 2006). Cats can initially develop the central vestibular disease, head tremor, mydriasis, and cervical ventroflexion, which may progress to opisthotonos, coma, and death (Ettinger & Feldman, 2000).
- In senior animals, thiamine deficiency can become a problem due to reduced appetite and difficulty in eating (Dai & Koh, 2015)

TOXICOLOGY

Toxicity for thiamine has not been documented in dogs and cats when administered orally in therapeutic doses.

However, intravenous injection of 5 to 50 mg/kg BW produced a transient fall in blood pressure. The lethal dose is approximately 350 mg/kg BW (NRC, 2006).

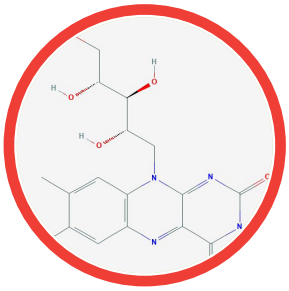
DRUG INTERACTIONS

Sulfites used as a preservative in food and medications, can cleave the thiamine molecule at the methyl bridge and make it inactive. Thiamine deficiency associated with the feeding of meat preserved with sulfur dioxide has been reported in dogs and cats (NRC, 2006).

Thiamine can be depleted by long-term use of the following prescription drugs: phenytoin, penicillin, cephalosporin, aminoglycosides, tetracycline derivatives, loop diuretics, fluoroquinolones, sulfonamide derivatives, and trimethoprim (AMR, 2003).

Note: All B complex vitamins can interfere with the absorption and effectiveness of the antibiotic, tetracycline (Penn State Hershey Medical Center, 2020).

Riboflavin (Vitamin B2) [$C_{17}H_{20}N_4O_6$]



- The major function of riboflavin is to serve as a precursor of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) [NRC, 2006] which contribute to cellular growth, enzyme function, and energy production (Groff et al., 1995). Flavins are used as cofactors by about 50 enzymes in mammals (Brody, 1998).
- Riboflavin deficiency results in anorexia, weight loss, decreased activity, hypothermia, periauricular alopecia with epidermal atrophy, cataracts, fatty liver, testicular atrophy, decreased respiratory rate, progressive weakness, ataxia, sudden collapse to a semi-comatose state, and death (NRC, 2006).
- Riboflavin is associated with bone mineral density and risk of fracture (Yazdanpanah et al., 2008).
- Glutathione (GSH), an important intracellular antioxidant, requires cysteine as a rate-limiting amino acid for its synthesis and riboflavin for its regeneration (Kannampuzha et al., 2010).

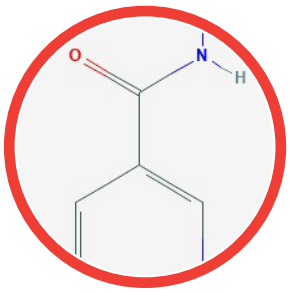
TOXICOLOGY

Toxicity for riboflavin has not been documented in dogs and cats when administered orally in therapeutic doses.

Oral LD50 of vitamin B2 is >10 g/kg in rat (NRC, 1987).

DRUG INTERACTIONS

Riboflavin levels are decreased by interactions with tricyclic antidepressants, phenothiazine, oral contraceptives, and anti-malarial drugs. Probenecid decreases the absorption of riboflavin in the gut (AMR, 2008).



Niacinamide (Vitamin B3) [$C_6H_6N_2O$]

- Niacinamide (aka nicotinamide or nicotinic acid amide) is derived from niacin. Niacinamide has the same biological activity as niacin because it can be converted into each other within the organism (Gehring, 2004; NRC, 2006).
- Dogs are able to synthesize nicotinamide endogenously from tryptophan but cats do not produce any measurable amounts. Cats have all the enzymes of the pathway of niacin synthesis, but the activity of picolinic carboxylase is extremely high which prevents the synthesis of niacin (NRC, 2006), so niacin is an absolute essential dietary nutrient for cats (Ettinger & Feldman, 2000).
- Niacinamide is a component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) which are required by approximately 200 metabolic enzymes. Most of these enzymes are involved in many intracellular oxidation-reduction reactions (Groff et al., 1995).
- It improves joint flexibility and reduces inflammation in osteoarthritis (Jonas et al., 1996).
- Acts as an antioxidant by preventing NAD depletion during DNA repair (AMR, 2002).
- Clinical signs of niacin deficiency include anorexia, weight loss, reddening of the inside of the upper lip that progresses into inflammation and ulceration of the buccal and pharyngeal mucosa, profuse salivation with blood-stained saliva drooling from the mouth, bloody diarrhea, neuronal degeneration of the spinal cord, dehydration, emaciation, and death (NRC, 2006).

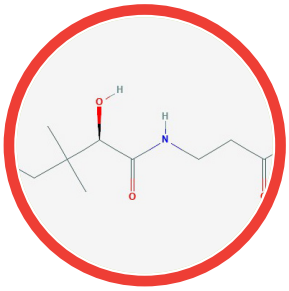
TOXICOLOGY

Repeated oral doses of 2 g of nicotinic acid per day produced bloody feces in dogs followed by convulsions and death (NRC, 2006). Dietary intakes of nicotinic acid in excess of 350 mg/kg BW are toxic to animals in general (NRC, 1987).

DRUG INTERACTIONS

Niacinamide inhibits the metabolism of antiepileptic drugs such as primidone and carbamazepine in humans (Bourgeois et al., 1982). In addition, concomitant use of niacinamide (250 mg/kg) and carbamazepine, diazepam, and sodium valproate potentiate the anticonvulsant action of these drugs (Kryzhanovskiĭ & Shandra, 1985).

D-Pantothenic acid (Vitamin B5) [$C_9H_{17}NO_5$]



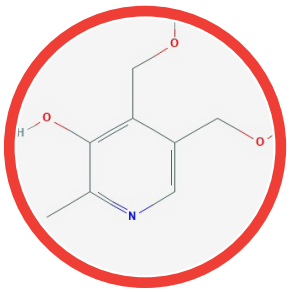
- Pantothenic acid is an integral component of coenzyme A (CoA). As a component of CoA, pantothenic acid becomes essential for the production of energy, fat, and protein - the synthesis and oxidation of fatty acids, and the oxidation of pyruvate in the citric acid cycle (Groff et al., 1995; NRC, 2006).
- Coenzyme A ingested in foods is hydrolyzed in the intestines to pantothenic acid and absorbed by the enterocyte (NRC, 2006).
- Increases the biosynthesis of glutathione (Slyshenkov et al., 2004).
- Pantothenic acid may have an antioxidant effect on the inflammatory process (Jung et al., 2017).
- Pantothenic acid will affect both the structure and the function of the adrenal cortex. Impaired adrenocortical function in pantothenate deficiency is provided by the abnormal response of animals to various types of stress stimuli (Ralli & Dumm, 1953)
- Signs of pantothenic acid deficiency include erratic food intake, failure to grow, sudden prostration or coma, rapid respiratory and heart rates, convulsions, and gastrointestinal signs including gastritis, enteritis, and intussusception causing an intestinal obstruction (NRC, 2006).

TOXICOLOGY

Toxicity for pantothenic acid has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Pantothenic acid may increase the effects of cholinesterase inhibitors such as donepezil, memantine hydrochloride, galantamine, and rivastigmine (Penn State Hershey Medical Center, 2020).



Pyridoxine hydrochloride (Vitamin B6) [$C_8H_{12}ClNO_3$]

- The coenzyme form of vitamin B6, pyridoxal-5′-phosphate (PLP), is essential to over 100 enzymes, the majority of which are involved with amino acid metabolism. PLP plays a role in a wide range of physiological processes including gluconeogenesis, erythrocyte function, niacin synthesis, nervous system function, immune response, lipid metabolism, hormone modulation, and gene expression (Groff et al., 1995; Brody, 1998; NRC, 2006).
- Pyridoxal participates in the allysine formation which is considered as the first step of collagen maturation (Tane et al., 1976) and functions as a cofactor for lysyl oxidase, an enzyme initiating cross-link formation in collagen and elastin (Carrington et al., 1984).
- Increases the resistance of cartilage against mechanical degeneration (Kurz et al., 2002).
- Acts as a substrate of alkaline phosphatase in bone formation (Fedde et al., 1988) and pyridoxal deficiency could affect the mechanical property of the bone (Dai & Koh, 2015).
- Clinical signs of vitamin B6 deficiency include convulsions, muscle twitching, microcytic hypochromic anemia anorexia, ataxia, cardiac dilation and hypertrophy, kidney lesions, congestion of various tissues, demyelination of peripheral nerves, and weight loss (NRC, 2006).

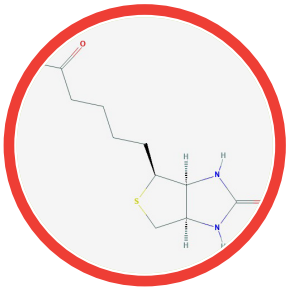
TOXICOLOGY

Toxicity for pyridoxal-5′-phosphate has not been documented in dogs and cats when administered orally in therapeutic doses. Pyridoxine at 1,000 mg/kg BW of diet for less than 60 days, or less than 500 mg/kg BW of diet for more than 60 days, appears to be safe for dogs (NRC, 1987).

DRUG INTERACTIONS

Medications that can form complexes and limit the bioavailability of pyridoxine include cyclosporine, hydralazine, isoniazid, penicillamine, theophylline, monoamine oxidase inhibitors (MAOIs) such as phenelzine and tranylcypromine, and erythropoietin therapy. Pyridoxine reduces the effectiveness of levodopa and phenytoin (Clayton, 2006). Long-term use of NSAIDs such as celecoxib and naproxen may also impair vitamin B6 metabolism (Chang et al., 2013).

Biotin (Vitamin B7) [$C_{10}H_{16}N_2O_3S$]



- Biotin serves as an essential cofactor in 4 carboxylase reactions in mammals that catalyze the incorporation of bicarbonate as a carboxyl group into substrates. Pyruvate carboxylase, propionyl-CoA-carboxylase, and β- methylcrotonyl-CoA carboxylase are mitochondrial enzymes whereas acetyl-CoA-carboxylase occurs both in mitochondria and cytosol (NRC, 2006). These 4 biotin-dependent enzymes are necessary for gluconeogenesis, metabolism of some amino acids, catabolism of leucine, and fatty acid synthesis (Groff et al., 1995).
- Clinical signs of biotin deficiency include accumulation of salivary, nasal, and lachrymal secretions, progressive alopecia, achromotrichia, dermatitis, weight loss, and diarrhea (NRC, 2006).
- Biotin deficiency can enhance pro-inflammatory cytokine responses (Agrawal et al., 2016).

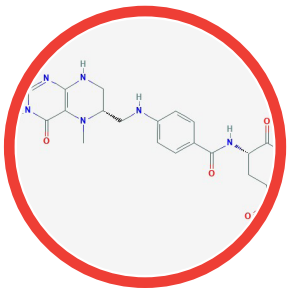
TOXICOLOGY

Toxicity for biotin has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Several studies have shown long-term therapy with anticonvulsants such as phenobarbital, phenytoin, carbamazepine, and primidone can lower biotin levels in the body. The use of the anticonvulsant valproic acid in children has resulted in hair loss reversed by biotin supplementation (AMR, 2007).

L-Methylfolate (Vitamin B9) [$C_{20}H_{25}N_7O_6$]



- Folates are used as cofactors and serve as donors and acceptors of one-carbon units in a variety of reactions such as amino acid metabolism, nucleotide metabolism, disposal of one-carbon units, and mitochondrial protein synthesis (NRC, 2006).
- Folate is critical in the metabolism of nucleic acid precursors and several amino acids, as well as in methylation reactions in the metabolism of homocysteine (Groff et al., 1995).
- Hyperhomocysteinemia may induce a tissue-specific accumulation of homocysteine in the bone through its binding to collagen in the extracellular matrix that could adversely reduce bone formation and bone strength (Dai & Koh, 2015).
- Folate deficiency causes marked impairment in collagen synthesis (Hautvast & Barnes, 1974).
- The deficiency of folate increases the resorption activity of osteoclasts (Herrmann et al., 2007).
- A significant relationship exists between increased folate intake/level and increased bone mineral density or reduced fracture risk (van Wijngaarden et al., 2013; Dai & Koh, 2015).
- Erythrocytes contain higher concentrations of folate than plasma in both dogs and cats. In the tissues, folate is present in both the cytosol and the mitochondria (NRC, 2006).
- Ascorbic acid, with its reducing capability, has been shown to protect folate from oxidative destruction. A synergistic relationship exists between folate and vitamin B12 (Groff et al., 1995).
- Deficiency of folate results in a decrease in growth rate, weight loss, decline in the hemoglobin concentration of blood, lowered hematocrit, increase in plasma iron concentration, megaloblastic anemia, and cleft palate (NRC, 2006).

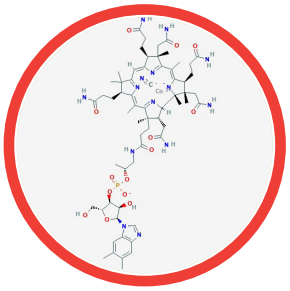
TOXICOLOGY

Toxicity for folic acid has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Cimetidine and antacids can reduce folate absorption and sulfasalazine interferes with folic acid absorption and conversion to the active form. Anticonvulsants, anti-tuberculosis drugs, oral contraceptives, and long-term use of NSAIDs depletes serum and tissue concentrations of folate (AMR, 2005). High doses of vitamin B12 can increase folate metabolism and hence lead to folate deficiency (Wee, 2016).

Cyanocobalamin (Vitamin B12) [$C_{63}H_{88}CoN_{14}O_{14}P$]



- Cobalamin (vitamin B12) forms 2 coenzymes, adenosylcobalamine and methylcobalamin, which participate in the functioning of more than a dozen enzyme systems but only adenosylcobalamin-dependent methylmalonyl CoA mutase and methylcobalamin-dependent methionine synthase are involved in dogs and cats (NRC, 2006).
- Studies have supported the protective role of vitamin B12 in preserving bone mass density and reducing fracture risk (Dai & Koh, 2015).
- Adequate vitamin B12 concentrations may lower pro-inflammatory cytokines (Al-Daghri et al., 2016).
- Cobalamin deficiency results in impairment in the activities of the B12-requiring enzymes (Brody, 1998). In bone tissue, deficiency of vitamin B12 increases the resorption activity of osteoclasts (Herrmann et al., 2007).
- Clinical signs of cobalamin deficiency include weight loss, diarrhea, vomiting, nausea, or thickened intestines, failure to thrive, neutropenia, megaloblastic changes of bone marrow, anemia, and homocysteinemia (NRC, 2006).

TOXICOLOGY

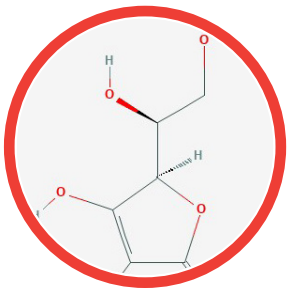
Toxicity for cyanocobalamin has not been documented in dogs and cats when administered orally in therapeutic doses.

However, subcutaneous doses of 2 to 33 µg/kg BW have been given to dogs, and have resulted in disturbances of reflex activity (NRC, 2006).

DRUG INTERACTIONS

Several drugs reduce the absorption of vitamin B12 including proton-pump inhibitors (e.g., omeprazole and lansoprazole), histamine2 (H2)-receptor antagonists (e.g., cimetidine, famotidine, and ranitidine), cholestyramine, and metformin. Nitrous oxide (anesthetic) oxidizes and inactivates vitamin B12. Large doses of folic acid (>1,000 µg/d) masks a vitamin B12 deficiency, a risk factor for developing irreversible neurologic damage (O'Leary & Samman, 2010).

L-Ascorbic acid (Vitamin C) [$C_6H_8O_6$]



- Dogs and cats can synthesize ascorbic acid from the metabolism of glucose. It functions as a catalyst in many biological reactions and as a redox cofactor and is involved in the synthesis of a number of hormones and in hormone activation (NRC, 2006).
- Ascorbic acid is a skeletal anabolic agent (Zhu et al., 2012).
- Essential for the metabolism of connective tissue substances especially collagen (van Robertson & Schwartz, 1953).
- A cofactor for hydroxylating enzymes required for the formation and synthesis of hydroxyproline and hydroxylysine, the essential elements of collagen (Murad et al., 1981; Pinnel et al., 1987; Nieves, 2005).
- Essential for the synthesis of muscle carnitine (Naidu, 2003).
- Ascorbic acid scavenges reactive oxygen and nitrogen species that are involved in the oxidative damage of lipids, proteins, and nucleic acids (NRC, 2006).
- Ascorbic acid, with its reducing capability, has been shown to protect folate from oxidative destruction. A synergistic relationship exists between folate and vitamin B12 (Groff et al., 1995).
- Deficiency of ascorbic acid may cause capillary fragility, petechial hemorrhages, bleeding, and delayed wound healing (NRC, 2006).

TOXICOLOGY

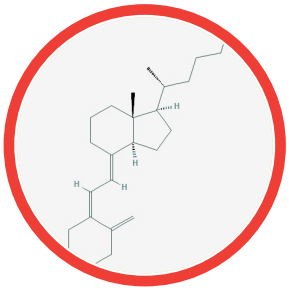
Toxicity for ascorbic acid has not been documented in dogs and cats when administered orally in therapeutic doses.

However, in humans, there is some concern that high ascorbic acid intake could increase the risk of calcium oxalate kidney stones because oxalate is a metabolite of ascorbic acid (Traxer et al., 2003). Ascorbic acid 1000 mg twice each day increased urinary oxalate and Tiselius Risk Index (TRI) for calcium oxalate kidney stones in 40% of participants, both stone-formers and non-stone-formers (Massey et al., 2005).

DRUG INTERACTIONS

Both aspirin and NSAIDs can lower the amount of ascorbic acid in the body and high doses of ascorbic acid can cause more of these drugs to stay in the body, raising the levels in the blood; Ascorbic acid can increase the amount of aluminum in the body from aluminum-containing antacid; and barbiturates may decrease the effects of ascorbic acid (Penn State Hershey Medical Center, 2020).

Cholecalciferol (Vitamin D3) [$C_{27}H_{44}O$]



- Exposure of dogs and cats to UV light results in inefficient synthesis of cholecalciferol. They are virtually entirely dependent on the diet for vitamin D. The skin of dogs and cats have low concentrations of 7-dehydrocholesterol. Administration of cholecalciferol is utilized more efficiently than ergocalciferol to maintain plasma concentration of 1-25-(OH)2 vitamin D3 (calcitriol) [NRC, 2006].
- Vitamin D3 is associated with skeletal growth and strong bones and plays an important in the synthesis of osteocalcin by stimulating osteoblasts (Groff et al., 1995).
- Vitamin D3 has an emerging role in regulating inflammation and chemokine production as well as an important role in immunomodulation. Evidence exists that vitamin D has a potential antimicrobial activity. It boosts innate immunity by modulating the production of anti-microbial peptides (AMPs) and cytokine response. Vitamin D activates B and T cells as well as promotes the activity of monocytes and macrophages which contribute to a potent systemic anti-microbial effect (Youssef et al., 2011).
- Vitamin D3 demonstrates the direct effects on muscle cells (Halfon et al., 2015) and is beneficial in repairing the muscles that are subject to inflammatory and proteolytic processes (Brennan-Speranza et al., 2017).
- Vitamin D3 has an interrelationship with calcium, phosphorus, and vitamin K. It is also speculated that iron deficiency decreases vitamin D absorption (Groff et al., 1995).
- Signs of vitamin D deficiency include lameness, loss of muscular tone, weakness, and lethargy (NRC, 2006).

TOXICOLOGY

Toxicity for cholecalciferol has not been documented in dogs and cats when administered orally in therapeutic doses.

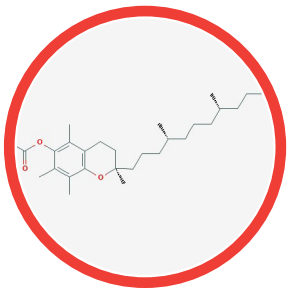
Note: Several factors, such as the chemical form (vitamin D2 or Vitamin D3), species, dietary intake of calcium and phosphorus, route of administration, and duration of treatment, can influence the maximum tolerable levels of vitamin D in the diet. Most animal species appear to be able to tolerate 10 times the level of vitamin D that they require for long periods of time (NRC, 1987).

In humans, vitamin D toxicity induces hypercalcemia, which could result in bone loss, kidney stones, and calcification of organs like the heart and kidneys if untreated over a long period of time. Hypercalcemia has been observed following daily doses of greater than 50,000 IU of vitamin D. However, doses of 10,000 IU of vitamin D3 per day for up to 5 months do not cause toxicity (Holick, 2007). Conditions such as primary hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma can increase the risk of hypercalcemia in response to increased vitamin D nutrition (Vieth, 1999).

DRUG INTERACTIONS

Cholestyramine, colestipol, orlistat, and mineral oil can decrease the intestinal absorption of vitamin D (Knodel & Talbert, 1987; McDuffie et al., 2002). Medications such as phenytoin, fosphenytoin, phenobarbital, carbamazepine, and rifampin increase the metabolism of vitamin D and may decrease serum 25-hydroxyvitamin D concentrations (Gröber et al., 2013). Ketoconazole reduces serum 1,25-dihydroxy vitamin D concentrations in normal subjects (Glass & Eli, 1986). Glucocorticoids and HIV treatment drugs can increase the catabolism of 25-hydroxy vitamin D (Holick et al., 2011).

d-alpha Tocopheryl acetate (Vitamin E) [$C_{31}H52O_3$]



- Vitamin E is the major lipid-soluble antioxidant present in plasma, erythrocytes, and tissues where it functions as a scavenger of free-radical or oxidative damage to polyunsaturated fatty acids (PUFAs) [NRC, 2006].
- Vitamin E protects against bones loss (Naina Mohamed et al., 2012), inhibits COX-2 and C-reactive protein which are involved in inflammatory reactions (Nazrun et al., 2012), and suppresses the production of pro-inflammatory mediators such as PGE2, TNFα, IL-1, and IL-6 that have been linked to increased bone loss (Nazrun et al., 2012; Feresin et al., 2013).
- Ascorbate is sometimes given to dogs under clinical conditions. High intake of ascorbate increases the requirements of vitamin E. No dietary requirement for L-ascorbic acid has been demonstrated in dogs (NRC, 2006).
- Requirements of vitamin E are a function of the total PUFAs in the diet. As cats frequently consume diets high in PUFAs, the requirement to prevent steatitis in cats is higher than that for dogs that are subjected to lower dietary inputs of PUFAs (Ettinger & Feldman, 2000).
- Clinical signs of Vitamin E deficiency include degeneration of skeletal muscle, muscular weakness, reproductive failure in both males and females, subcutaneous edema, anorexia, depression, dyspnea, and eventual coma (NRC, 2006).

TOXICOLOGY

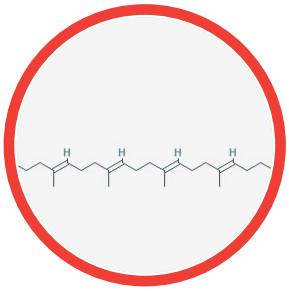
Toxicity for vitamin E has not been documented in dogs and cats when administered orally in therapeutic doses.

The oral LD50 alpha-tocopherol acetate for rats, mice, and rabbits has been estimated to be >2g/kg body weight (NRC, 1987).

DRUG INTERACTIONS

Vitamin E supplements may increase the risk of bleeding in individuals taking anticoagulant drugs such as heparin and the vitamin K antagonist, warfarin; antiplatelet drugs, such as clopidogrel, ticlopidine, tirofiban, and dipyridamole; and NSAIDs, including aspirin, ibuprofen, and others (Hendler & Rorvik, 2001; Pastori et al., 2013).

Menaquinones (Vitamin K2) [$C_{46}H_{64}O_2$]



- Vitamin K2, is one of a series of vitamin K compounds with unsaturated side chains called multiprenyl menaquinones and synthesized by bacteria. It facilitates the carboxylation of the glutamic acid residues of proteins and these proteins form three groups: vitamin K-dependent clotting factors, vitamin K-dependent skeletal proteins, and other vitamin K-dependent proteins (Groff et al., 1995; NRC, 2006).
- Vitamin K exerts its anabolic effect on the bone turnover by promoting osteoblast differentiation, upregulating transcription of specific genes in osteoblasts, and activating the bone-associated vitamin k dependent proteins that play critical roles in extracellular bone matrix mineralization (Akbari & Rasouli-Ghahroudi, 2018). Epidemiological studies suggested that a lack of vitamin K is associated with several diseases, including osteoporosis and vascular calcification (Fusaro et al., 2017).
- Cats when fed with high-fish diets, have a prolongation of clotting time and require supplementation with vitamin K2 (Ettinger & Feldman, 2000).
- A number of clinical conditions such as hepatic lipidosis, inflammatory bowel disease, cholangiohepatitis, and enteritis, result in malabsorption of lipids and induce a secondary deficiency of vitamin K. Prolonged clotting times have been recorded in cats and dogs that have accidentally ingested dicumarol-based rodenticides (NRC, 2006).

TOXICOLOGY

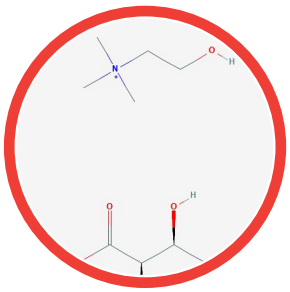
Toxicity for vitamin K2 (Menaquinones) has not been documented in dogs and cats when administered orally in therapeutic doses.

Menadione (vitamin K3) should not be given by the parenteral route because it causes hemolysis and toxicity in low doses (NRC, 2006).

DRUG INTERACTIONS

Dicumarol causes depletion of active vitamin K in the blood. Accidental ingestion by dogs of rodenticides containing analogs of dicumarol as anticoagulant has resulted in a decrease in prothrombin times to 10 percent of normal (NRC, 2006).

Cephalosporins, bile acid sequestrants, and orlistat can reduce the absorption of vitamin K; Vitamin K blocks the effects of the blood-thinning medication warfarin; and phenytoin interferes with the body's ability to use vitamin K (Penn State Hershey Medical Center, 2020).



Choline (Choline bitartrate) [$C_9H_{19}NO_7$]

- Choline is usually grouped with the vitamin B complex due to the interconnection between choline and the other B vitamins, such as folate, pyridoxal, and cobalamin (Niculescu & Zeisel, 2002). Choline supplies liable methyl groups and a lack of methyl groups in the diet leads to the fatty liver because of an inability to mobilize hepatic fat (Ettinger & Feldman, 2000).
- Choline is an integral component of phospholipid phosphatidylcholine or lecithin. The major role of choline is as a donor of methyl groups for methylation reactions. Choline is required in cholinergic neurons for acetylcholine synthesis which is essential for normal neurologic function. It is also a structural element in membranes and a required component of very low-density lipoproteins (VLDLs) [Groff et al., 1995; NRC, 2006].
- Choline lowers the levels of several inflammatory markers including C-reactive protein, IL-6, and TNF (Detopoulou et al., 2008).
- Choline deficiency diminishes the capacity of the liver to synthesize phosphatidylcholine which results in the accumulations of lipids. Deficiency of choline is also associated with weight loss, vomiting, fatty liver, and death (NRC, 2006). Low plasma choline is associated with low bone mass density and increased the risk of hip fracture in humans (Øyen et al., 2014).

TOXICOLOGY

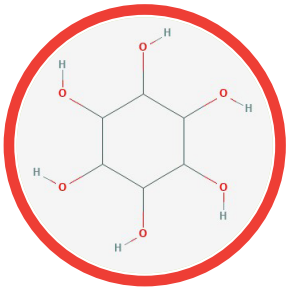
Toxicity for choline has not been documented in dogs and cats when administered orally in therapeutic doses.

Excess of choline in the diet can cause anemia. Maximum intake of choline is 2000 mg/kg BW (NRC, 1987).

DRUG INTERACTIONS

Validated interactions studies do not exist for choline preparations. Clinical interactions with other drugs have not been reported.

Inositol (Myo-inositol) [$C_6H_{12}O6$]



- Inositol is an essential nutrient for some bacteria and can be beneficial at specific stages of growth. Inositol, like choline, is a constituent of phospholipids (NRC, 2006).
- Myo-inositol is a prominent component of membrane-incorporated phosphatidylinositol. It participates in a multitude of cellular processes, including ion channel permeability, metabolic homeostasis, mRNA export and translation, cytoskeleton remodeling, stress response (Bizzarri et al., 2016).
- Inhibits oxygen radical generation, increases enzymatic antioxidant capacity and prevents oxidative damage (Jiang et al., 2009). Inositol also improves metabolism (Pizzo et al., 2014) and promotes muscle glucose uptake (Chukwuma et al., 2016).
- Deficiency of inositol can cause accumulation of lipid in the liver or intestine in some animals but no deficiencies of inositol have been documented in either dogs or cats (NRC, 2006).

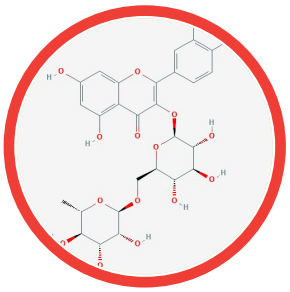
TOXICOLOGY

Toxicity for inositol has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Inositol can counteract the actions of mood-stabilizing drugs such as lithium, carbamazepine and valproic acid (Williams et al., 2002).

Rutin (Vitamin P) [$C_{27}H_{30}O_{16}$]



- Rutin, also known as vitamin P or rutoside, is a flavonol, abundantly found in plants, such as passion flower, buckwheat, tea, and apple. It has demonstrated a number of pharmacological effects including antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective, hepatoprotective, anti-fatigue, immunomodulatory, and cardioprotective activities. In experimental models, rutin was found beneficial in arthritis, osteoporosis, cataracts, hypercholesterolemia, neuro-inflammation, and wound healing (Ganeshpurkar & Saluja, 2017).

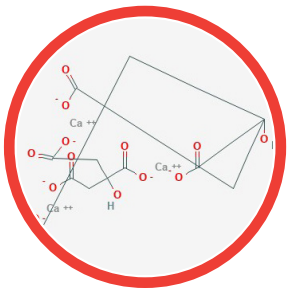
TOXICOLOGY

Toxicity for rutin has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for rutin preparations. Clinical interactions with other drugs have not been reported.

MINERALS



Calcium (Calcium citrate) [$C_{12}H_{10}Ca_3O_{14}$]

- Calcium is found in greatest abundance in mammals including dogs and cats. The active period of formation of bones and teeth increases the need for calcium. It plays essential roles in blood coagulation, nerve impulse transmission, excitation-contraction coupling, and muscular contractions, and it serves as a second messenger in a host of intracellular reactions (NRC, 2006).
- Calcium intake is necessary for mineralization of the skeleton and attainment of peak bone mass (Brown et al., 2006).
- Calcium intake is tied directly to the calcium-phosphorus ratio (1.5:1) in the body. A diet high in calcium and low in phosphorus may lead to problems metabolizing the calcium. It will cause bone deformities and hip dysplasia. Calcium deficiency in kittens demonstrated bone rarefaction, especially in the lumbar vertebrae which tended to curve and collapse, and in the pelvis (NRC, 2006).
- Deficiency of calcium results in bone pain which proceeds to pathological fractures (NRC, 2006).

TOXICOLOGY

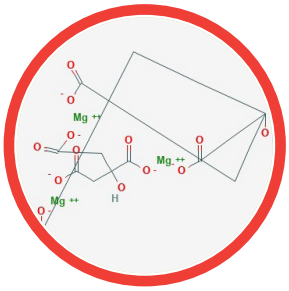
Toxicity for calcium citrate has not been documented in dogs and cats when administered orally in therapeutic doses.

However, in humans, supplementation with calcium (0.6 g/day-2 g/day for two to five years) has been associated with a higher risk of adverse gastrointestinal events like constipation, cramping, bloating, pain, diarrhea (Lewis et al., 2012). Elevated calcium concentrations in the blood (hypercalcemia) can cause malignancy and primary hyperparathyroidism (Moe, 2008).

DRUG INTERACTIONS

Significant interactions have been observed between calcium and certain antibiotics namely tetracyclines and fluoroquinolones (Pfizer, 1990; Bayer, 2002). Calcium decreases the bioavailability of levothyroxine (Abbott, 2002). Combining calcium with thiazide diuretics increases the risk of developing hypercalcemia. High doses of supplemental calcium could increase the likelihood of abnormal heart rhythms in people taking digitalis for heart failure (Vella et al., 1999). Intravenous calcium salts can prevent hypotension associated with intravenous verapamil (Moser et al., 2000). Calcium citrate when taken with aluminum-containing antacids, the amount of aluminum absorbed into the blood may be increased significantly. Bile acid sequestrants such as cholestyramine, colestipol, and colesevelam may interfere with calcium absorption and increase the loss of calcium in the urine (UMMC, 2012a).

Magnesium (Magnesium citrate) [$C_{12}H_{10}Mg_3O_{14}$]



- Between 50 to 65% of magnesium in the body is found associated with bone. Magnesium is the second most abundant intracellular cation, after potassium, and is involved in more than 300 metabolic processes. As a cofactor in enzyme function, it is essential for binding phosphate groups in ATP, DNA and RNA metabolism, protein synthesis, stability of muscle and nerve cell membranes, cell-to-cell adhesion, extracellular matrix communication, calcium channel regulation in cardiac tissue, lymphocyte proliferation, platelet activation, and secretion and function of hormones (Groff et al., 1995; NRC, 2006).
- Magnesium is involved in bone and mineral homeostasis and is important in bone crystal growth and stabilization (Prentice, 2004) and the intake of magnesium is associated with higher bone mineral density (Nieves, 2005).
- Hypomagnesemia promotes inflammation as TNFα, IL-1, and IL-6 are increased both in serum and in the bone marrow microenvironment and a relationship exists between inflammation and bone loss (Castiglioni et al., 2013).
- Low extracellular magnesium inhibits osteoblast growth by increasing the release of nitric oxide through the upregulation of inducible nitric oxide synthase, while it increases the number of osteoclasts generated from bone marrow precursors (Castiglioni et al., 2013).
- In dogs and cats, deficiency of magnesium can cause anorexia, weight loss, poor growth rate, hyperextension of carpal joints, muscular twitching and convulsions, posterior ataxia, and lameness (NRC, 2006).

TOXICOLOGY

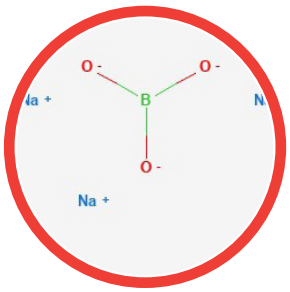
Toxicity for magnesium citrate has not been documented in dogs and cats when administered orally in therapeutic doses.

LD50 for magnesium sulphate in dogs is considered to be >1,200 mg/kg BW (infused at 200 mg/kg/hr) [Mochizuki et al., 1998].

DRUG INTERACTIONS

The absorption of quinolone antibiotics, such as ciprofloxacin and moxifloxacin, tetracycline antibiotics, including tetracycline, doxycycline, and minocycline, and nitrofurantoin, may be diminished when taking magnesium supplements. Magnesium may potentiate the side effects such as dizziness, nausea, and fluid retention associated with calcium channel blockers. High doses of furosemide and some thiazide diuretics, if taken for extended periods, may result in magnesium depletion (Hendler & Rorvik, 2001; UMMC, 2012b). Digoxin can lead to increased loss of magnesium in the urine and it is important that normal levels of magnesium be maintained while taking digoxin because low blood levels of magnesium can increase adverse effects from this drug, including heart palpitations and nausea (UMMC, 2012b).

Boron (Sodium borate) [$Na_2B_4O_7$]



- Boron acts directly or indirectly to influence the composition, structure, and strength of bones (Groff et al., 1995). It may prevent arthritis and osteoporosis by increasing the production of steroid hormones (Devirian & Volpe, 2003).
- Boron is an essential nutrient for animals. It influences parathormone activity thereby enhances the metabolism of calcium, phosphorus, magnesium, and vitamin D. Hence, boron is of importance in calcium homeostasis and bone metabolism. Boron also has an effect on brain electrical activity (NRC, 2006).
- Boron reduces the risk of arthritis and beneficial in the treatment of osteoarthritis (Newnham, 1994; Travers et al., 2009; Nielsen & Meacham, 2011).

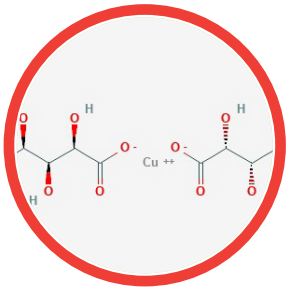
TOXICOLOGY

Toxicity for magnesium citrate has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for boron preparations. Clinical interactions with other drugs have not been reported.

Copper (Cupric gluconate) [$C_{12}H_{22}CuO_{14}$]



- Copper is an integral component of enzymes that catalyze oxidation reactions such as monoamine oxidase (catalyzes the oxidation and inactivation of monoamine neurotransmitters), lysyl oxidase (connective tissue formation), ferroxidase also known as ceruloplasmin (iron metabolism, hematopoiesis, melanin pigment formation), cytochrome C oxidase (myelin formation), and as a cofactor for superoxide dismutase (antioxidant) [Groff et al., 1995; NRC, 2006].
- Copper is an essential cofactor for enzymes involved in the synthesis of various bone matrix constituents and plays a particularly important role in the regulation of bone deposition and resorption (Lowe et al., 2002).
- Many animal studies, including some dogs and cats, have demonstrated that cupric oxide is only very slightly bioavailable and therefore should not be used (NRC, 2006).
- Deficiency of copper can result in loss of hair pigmentation, hyperextension in distal phalanges, hind-limb ataxia, and weight loss (NRC, 2006). Copper deficiency is also associated with bone fragility (Jonas et al., 1993) and skeletal abnormalities (Lowe et al., 2002).

Note: In cats and dogs, observations indicate that the availability of copper in diets containing high portions of plant products is compromised (Ettinger & Feldman, 2000).

TOXICOLOGY

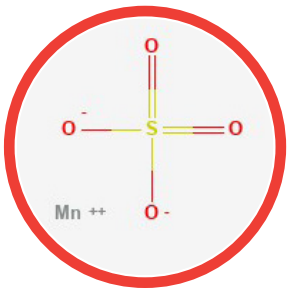
An acute oral dose of 165 mg/kg BW of copper sulfate to dogs resulted in vomiting and death within four hours (NRC, 2006).

There is a considerable body of evidence on copper toxicosis in several breeds of dogs with hereditary defect resulting in excessive accumulation of copper in the liver, including Bedlington terriers, West Highland white terriers, and Sky terriers. This copper toxicosis is similar to Wilson's disease in humans. Acute poisoning is usually seen after the accidental administration of excessive amounts of soluble copper salts (NRC, 2006; Kahn & Line, 2010).

DRUG INTERACTIONS

Antacids containing bismuth, aluminum, silica, magnesium, and sodium inhibit copper absorption (Groff et al., 1995). Zinc is a potent inhibitor of copper bioavailability by virtue of its stimulation of the formation of metal-binding metallothionein proteins in enterocytes, which have higher binding affinity for copper than for zinc (NRC, 2006). Penicillamine dramatically increases the urinary excretion of copper; individuals taking the medication for reasons other than copper overload may have an increased copper requirement (Shils et al., 2006).

Manganese (Manganese sulfate) [$MnSO_4$]



- Manganese functions mainly as an essential structural component in metalloenzymes such as arginase, pyruvate carboxylase, and manganese superoxide dismutase. Manganese also functions as an enzyme activator of hydrolases, decarboxylases, kinases, and transferases (Groff et al., 1995; NRC, 2006).
- Manganese is needed for the biosynthesis of mucopolysaccharides in the bone matrix formation and is a cofactor for several enzymes in bone tissue (Leach & Muenster, 1962; Palacios, 2006).
- Modulates receptor activator of nuclear factor-kappaB ligand (RANKL)/ osteoprotegerin (OPG) ratio in the process of bone formation, determining the thickness of the trabecular bone area and increasing trabecular number (Zofkova et al., 2017).
- Required in the synthesis of chondroitin sulfate (Leach et al., 1969).
- Signs of manganese deficiency include retarded bone growth and shortening and bowing of the forelegs, lameness and/or enlarged joints, poor locomotor function, and ataxia. Manganese deficiency has also been reported to have profound negative effects on reproduction, including delayed estrus, poor conception, increased abortion rates, stillbirths, and low birth rates (NRC, 2006).

TOXICOLOGY

Toxicity for manganese sulfate has not been documented in dogs and cats when administered orally in therapeutic doses.

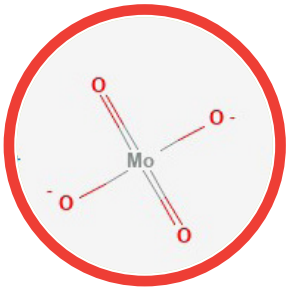
However, a study in Beagle dogs, intravenous infusion of manganese chloride 16 mg/kg/day (3-5 times the daily dose of manganese) caused severe hepatotoxicity (Khan et al., 1997).

DRUG INTERACTIONS

Validated interactions studies do not exist for manganese sulfate preparations. Clinical interactions with other drugs have not been reported.

However, there are some reports that magnesium-containing antacids, laxatives, and the antibiotic tetracycline, may decrease the absorption of manganese if taken together with manganese-containing foods or supplements (Hendler & Rorvik, 2001).

Molybdenum (Sodium molybdate) [Na_2MoO_4]



- Molybdenum is essential as a cofactor for metalloenzymes such as xanthine dehydrogenase, xanthine oxidase, aldehyde oxidase, and sulfite oxidase, all of which catalyze oxidation and reduction reactions (Groff et al., 1995; NRC, 2006).
- Xanthine dehydrogenase is found in a variety of tissues, including the liver, lungs, kidneys, intestine, and thyroid cells. Xanthine oxidase is found in the intestine and thyroid cells. These enzymes are capable of hydroxylating various nitrogen-containing compounds such as purines, pteridines, and pyrimidines (Groff et al., 1995; NRC, 2006).
- Sulfite oxidase is involved in making sulfate and taurine, both of which are involved in detoxification (Moss, 1995).
- Bone retains molybdenum longer than any other tissue (Novotny, 2011). Reduces pain and supplemental molybdenum is beneficial in arthritis (Moss, 1995).
- Deficiency of molybdenum results in decreased rates of conception and increased rates of abortions, as well as poor growth and increased mortality rate (NRC, 2006).

TOXICOLOGY

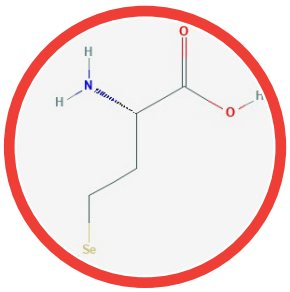
Toxicity for molybdenum has not been documented in dogs and cats when administered orally in therapeutic doses.

However, elevated dietary intake of molybdenum can cause copper deficiency (NRC, 2006).

DRUG INTERACTIONS

Validated interactions studies do not exist for molybdenum preparations. Clinical interactions with other drugs have not been reported.

Selenium (L-Selenomethionine) [$C_5H_{11}NO_2Se$]



- Selenium is a non-metal mineral that is widely distributed in animal tissue found in the highest concentrations in the liver, kidney, and muscle. One of the major functions of selenium is its role in the selenium-containing enzyme glutathione peroxidase, an important antioxidant that protects the body against free-radical and other oxidative damage. Some of the less defined roles include its involvement in the maintenance or induction of the cytochrome P450 system, in DNA repair and enzyme activation, in immune system function, and in detoxification of heavy metals (Groff et al., 1995; NRC, 2006).
- Selenium is an essential nutrient involved with selenoproteins (antioxidant enzymes) that participate in maintaining cellular redox balance, which is important in the regulation of inflammation and bone cell proliferation/differentiation. (Zeng et al., 2013; Zofkova et al., 2017).
- Plasma selenoprotein P concentrations have been found to be positively correlated with bone mineral density. Selenium transport to the bone relies on selenoprotein P (Zhang et al., 2014). Vitamins/selenium supplementation reduces the mechanical induction of articular cartilage degeneration and increases the expression of antioxidant enzymes in the knee joint (Kurz et al., 2002).
- Clinical signs of selenium deficiency include anorexia, muscular degeneration depression, dyspnea, and coma (NRC, 2006). The inadequacy of selenium can retard growth and change bone metabolism (Zeng et al., 2013).

TOXICOLOGY

Toxicity for selenium has not been documented in dogs and cats when administered orally in therapeutic doses.

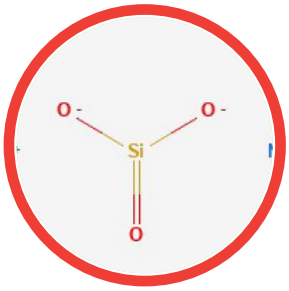
However, it has been reported that a dietary selenium concentration of 5 mg/kg BW resulted in selenium toxicity in dogs (NRC, 2006).

Parenteral selenium products are also quite toxic, especially to young animals, and have caused deaths in baby pigs, calves, and dogs at doses as low as 1.0 mg/kg BW (Kahn & Line, 2010).

DRUG INTERACTIONS

The anticonvulsant medication valproic acid has been found to decrease plasma selenium levels. Animal studies have found that supplemental sodium selenite decreases the toxicities of the antibiotic nitrofurantoin (Flodin, 1990). Vitamin E exhibits a protective effect on selenium intoxication (Berschneider et al., 1976).

Silicon (Sodium metasilicate) [Na_2SiO_3]



- The physiologic role of silicon is of normal development of the bone, connective tissue, and cartilage, functioning both in metabolic and structural capacity. Studies in experimental animals demonstrate that silicon is an essential nutrient that plays a role in the calcification and maturation bone. Silicon is also a cofactor in prolyl hydrase activity, which is involved in collagen synthesis (Groff et al., 1995; NRC, 2006).
- Stimulates osteoblasts and osteoblast-like cells to secrete type I collagen and other markers involved in bone cell maturation and bone formation (Reffitt et al., 2003). Silicon increases mechanical strength and reduces bone-related injuries (Jugdaohsingh, 2007).
- Signs of silicon deficiency are related to the poor structural development of connective tissue and bone (NRC, 2006).

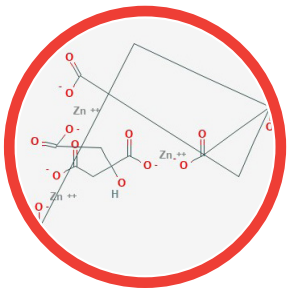
TOXICOLOGY

Toxicity for silicon has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for silicon preparations. Clinical interactions with other drugs have not been reported.

Zinc (Zinc citrate) [$C_{12}H_{10}O_{14}Zn_3$]



- Zinc acts as a cofactor or catalyst in some 200 zinc-containing enzymes that are involved in cell growth, cell replication, carbohydrate and protein metabolism, bone formation, cell-mediated immunity, skin integrity, and wound healing. Zinc also plays a role in the structure and function of biological membranes as well as in the stabilization of DNA and RNA. Zinc is a part of more enzyme systems than the rest of the trace minerals combined (Groff et al., 1995; NRC, 2006).
- Zinc positively influences the strength, flexibility, and architecture of the skeleton (Zofkova et al., 2017) and is implicated as an activator for bone formation (Osredkar & Sustar, 2011). Zinc is needed for the osteoblastic activity, collagen synthesis, and alkaline phosphatase activity (Palacios, 2006).
- Collagenase is a zinc-dependent metalloenzyme, essential for bone resorption and remodeling (Beattie & Avenell, 1992).
- Clinical signs of zinc deficiency include power growth rate, skeletal abnormalities, defective collagen synthesis or cross-linking, weight loss, skin lesions, poor wound healing, dermatitis, and impaired immune function (Groff et al., 1995; NRC, 2006).

TOXICOLOGY

Toxicity for zinc has not been documented in dogs and cats when administered orally in therapeutic doses.

However, zinc toxicosis caused by ingestion of foreign materials such as galvanized metal and pennies has been reported in dogs, but it has not been described in cats. Clinical signs include acute gastroenteritis, hemolytic anemia, and lethargy (Hardy et al., 2003; NRC, 2006).

DRUG INTERACTIONS

Both quinolone antibiotics and tetracycline antibiotics interact with zinc in the gastrointestinal tract, inhibiting the absorption of both zinc and the antibiotic (Lomaestro et al., 1995; Penttilä et al., 1975). Zinc can reduce the absorption and action of penicillamine, a drug used to treat rheumatoid arthritis (Brewer et al. 1993). Thiazide diuretics such as chlorthalidone and hydrochlorothiazide increase urinary zinc excretion by as much as 60% (Wester, 1980).

Note: In cats and dogs, observations indicate that the availability of zinc in diets containing high portions of plant products is compromised (Ettinger & Feldman, 2000).

PHYTONUTRIENTS

Boswellia serrata (Frankincence Resin)

- Gummi Boswellii consists of the dried gum resin of *Boswellia serrata* (Burseraceae). Preparations from Gummi Boswellii have been used as a traditional remedy in Ayurvedic medicine for the treatment of inflammatory diseases. Supported by clinical data and described in pharmacopeias, Gummi Boswellii is used orally for the management of arthritis and rheumatism (WHO, 2009).
- The pentacyclic triterpenic acids (β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and acetyl-11-keto-β-boswellic acid) isolated from Gummi Boswellii are collectively called as boswellic acids that are found to exert potent anti-inflammatory effects (Ammon, 2002; Siddiqui, 2011).
- A systematic review of 47 RCTs indicated that Gummi Boswellii extracts were clinically effective and no serious safety issues were noted. The included trials related to rheumatoid arthritis, osteoarthritis, and other inflammatory conditions (Ernst, 2008).
- The mechanism of action is due to boswellic acids, the active constituents of Gummi Boswellii. It is different from that of NSAIDs and is related to components of the immune system. The most evident action is the inhibition of 5-lipoxygenase. However, other factors such as cytokines (interleukins and TNF-α) and the complement system are also candidates. In addition, leukocyte elastase and oxygen radicals are targets (Ammon, 2006). Gummi Boswellii has been shown to reduce the destruction of glycosaminoglycans (Reddy et al., 1989).

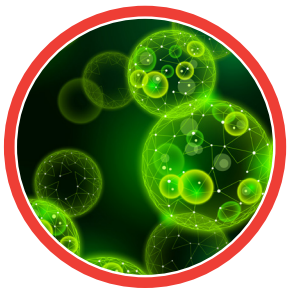
TOXICOLOGY

Toxicity for *Gummi Boswellii* has not been documented in humans when administered orally in therapeutic doses. However, minor gastrointestinal side-effects have been reported in the clinical trials (WHO, 2009).

DRUG INTERACTIONS

Validated interactions studies do not exist for *Gummi Boswellii* preparations. Clinical interactions with other drugs have not been reported.

Chlorella vulgaris (Chlorella Broken Cell)



- *Chlorella vulgaris*, a unicellular green alga, has been shown to have many positive effects in human and animal studies in Japan and in the United States. *Chlorella vulgaris* is a microscopic, unicellular freshwater green alga that contains highly nutritious substances such as proteins, nucleic acids, carbohydrates, vitamins, and minerals (Saad et al., 2006). This micro alga contains very high concentrations of chlorophyll including both chlorophylls a and b. It also a rich source of β-carotene, lutein, ascorbic acid, tocopherol, riboflavin, and retinol (Kitada et al., 2009; Safi et al., 2014).
- In experimental studies, *Chlorella vulgaris* improves the regenerative capacity of young and senescent myoblasts and promotes myoblast differentiation, indicating its potential in promoting muscle regeneration. It may also act as an antiaging agent, as shown by its effects on delaying replicative senescence in myoblast cells (Zainul Azlan et al., 2019).
- Various studies have reported on the beneficial effects of *Chlorella vulgaris*, such as its hypolipidemic action due to the modulation of lipid metabolism and increased fecal excretion of lipid (Lee et al., 2008) and its effects against diabetes by improving insulin sensitivity (Jeong et al., 2009). Another study also reported that glucose and insulin resistance were increased and triglyceride, cholesterol, and free fatty acid levels were decreased in high-fat diet-induced insulin-resistant obese mice treated with *Chlorella vulgaris* (Vecina et al., 2014).
- Evaluation of side effects in 18 patients chronically infected with the hepatitis C virus showed that Chlorella was well tolerated. Quality of life (QOL) assessment showed that 76.9% of the participants reported an improvement in their energy levels and 46.1% reported an improvement in their perception of general health (Azocar & Diaz, 2013). In a self-control, randomized, and open-label clinical trial in 45 female patients with breast cancer, chlorella supplementation improved QOL and vitality (Noguchi et al., 2014).

Note: *Chlorella vulgaris* cell-wall is very rigid and has been reported to be a trilaminar sheath composed of an outermost toughest layer of sporopollenin (a highly resistant biopolymer) with an underlying secondary wall rich in mannose and chitin-like polysaccharides heterogeneously arranged. The methods of breaking or disruption of the cell-wall include chemical, physical, physicochemical, and biological (Kim et al., 2016).

TOXICOLOGY

Toxicity for *Chlorella vulgaris* has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for *Chlorella vulgaris* preparations. Clinical interactions with other drugs have not been reported.

Curcuma longa (Turmeric Rhizome)

- Rhizoma Curcumae Longae is the dried rhizome of *Curcuma longa* which has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions (WHO, 1999). Curcumin has received worldwide attention for its multiple health benefits, which appear to act primarily through its anti-oxidant and anti-inflammatory mechanisms (Hewlings & Kalman, 2017).
- The anti-inflammatory activity of Rhizoma Curcumae Longae has been demonstrated in animal models (WHO, 1999). In a clinical study, the administration of curcumin to obese cats improved the obesity-related inflammatory state which could be attributed to anti-inflammatory properties of curcumin (Leray et al., 2011). The anti-inflammatory activity of curcumin may be due to its ability to scavenge oxygen radicals (Kunchandy & Rao, 1990) and in the regulation of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and IL-6 (Zhou et al., 2011).
- The active constituent of Rhizoma Curcumae Longae, curcumin, presents great potential for treating osteoarthritis and has been categorized as having preclinical evidence of efficacy (Henrotin et al., 2013). Research suggests that curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. It may also help in the management of exercise-induced inflammation and muscle soreness, thus enhancing recovery and subsequent performance. In addition, a relatively low dose can provide health benefits for individuals who do not have diagnosed health conditions (Hewlings & Kalman, 2017).

TOXICOLOGY

Toxicity for Rhizoma Curcumae Longae has not been documented in dogs and cats when administered orally in therapeutic doses. Feeding pups with Rhizoma Curcumae Longae 500 mg/kg BW for 3 months was found to be safe with no toxicity (WHO, 1980).

DRUG INTERACTIONS

In animal studies, pre-treatment with curcumin, a major active component of Rhizoma Curcumae Longae resulted in increased plasma elimination half-life of the broad-spectrum antibacterial agent norfloxacin, thereby reducing the dosage of the drug (Pavithra et al., 2009); Curcumin has been shown to down-regulate intestinal P-Glycoprotein levels, thereby increasing the concentration of celiprolol (beta-blocker) and midazolam (benzodiazepine) in rats (Zhang et al., 2007); Curcumin may enhance the effect and decrease the toxicity of the antifungal drug amphotericin B *in vitro* (Kudva et al., 2011); and curcumin could enhance the effects of the chemotherapeutic agents such as mitomycin C (Ko et al., 2011) and cisplatin (Tsai et al., 2011) *in vitro.*

Harpagophytum procumbens (Devil's Claw Root)

- Radix Harpagophyti consists of the dried, tuberous, secondary roots of Harpagophytum procumbens (Fam. Pedaliaceae). Radix Harpagophyti is documented as a supportive treatment of degenerative rheumatism, painful arthrosis, and tendonitis (WHO, 2007). European Medicines Agency recommends Radix Harpagophyti for the relief of minor articular pain, for the relief of mild digestive disorders such as bloating and flatulence, and where there is a temporary loss of appetite (EMA, 2016).
- Research conducted on Radix Harpagophyti in the early seventies indicated that the anti-arthritic activity of Radix Harpagophyti was due to the redox potential of the iridoid glycosides (Beresford, 2002). Radix Harpagophyti is chondroprotective, possibly due to inhibition of inflammatory mediators, including cyclooxygenase-2 (COX-2), leukotrienes, nitric oxide, TNF-α, and IL-1β (Occhiuto et al., 1985).
- The analgesic action of Radix Harpagophyti may be due to a complex interaction between various active principles, suggesting that these, especially harpagoside interfere with the mechanisms which regulate calcium in the cells (Occhiuto et al., 1985). Radix Harpagophyti also demonstrates antioxidant effects by scavenging both superoxide and peroxyl free radicals in a dose-dependent manner (Langmead et al., 2002).

TOXICOLOGY

Toxicity for Radix Harpagophyti has not been documented in dogs and cats when administered orally in therapeutic doses.

In male Wistar rats, no significant hematological or gross pathological findings were evident following 21 days of sub-acute oral treatment with 7.5 g/kg BW of Radix Harpagophyti (EMEA, 2009). In male and female Swiss Webster mice the acute oral LD50 of Radix Harpagophyti was >13.5 g/kg of body weight (ESCOP, 2009).

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Harpagophyti preparations. Clinical interactions with other drugs have not been reported.

Moringa oleifera (Drumstick Tree)

- Known as "Miracle Tree", *Moringa oleifera* is a multi-purpose herbal plant used as human food and an alternative for medicinal purposes worldwide. It is a storehouse of important nutrients: the leaves are ricin minerals like calcium, potassium, zinc, magnesium, iron, and copper. Vitamins like β-carotene, vitamin B such as folic acid, pyridoxine, and nicotinic acid, vitamin C, D and E also present in *Moringa oleifera*. Immature pods (seed) contain around 46.78% fiber and around 20.66% protein content. Pods have 30% of amino acid content, the leaves have 44% and flowers have 31%. The immature pods and flowers showed similar amounts of palmitic, linolenic, linoleic and oleic acids (Abdull Razis et al., 2014; Gopalakrishnan et al., 2016).
- The leaves, seed and immature pods of *Moringa oleifera* act as cardiac and circulatory stimulants, possess antitumor, antipyretic, antiepileptic, anti-inflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol-lowering, antioxidant, antidiabetic, hepatoprotective, antibacterial and antifungal activities (Anwar et al., 2007).
- Phenolic glucosides isolated from seed and immature pods of *Moringa oleifera* have demonstrated anti-inflammatory activity by inhibiting the production of nitric oxide, tumor necrosis factor-alpha, and interleukin-2 which may benefit in the management of arthritis (Cheenpracha et al., 2010; Sashidhara et al., 2009).

TOXICOLOGY

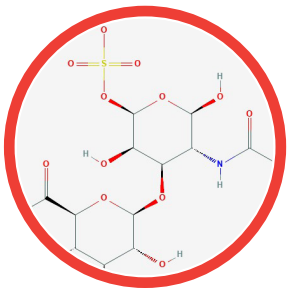
Toxicity for *Moringa oleifera* has not been documented in dogs and cats when administered orally in therapeutic doses.

Acute toxicity studies in rats for Folium Moringae (leaves) aqueous extract showed no toxicity or mortality at 2,000 mg/kg BW oral dose (Adedapo et al., 2009).

DRUG INTERACTIONS

In a pre-clinical study, isolated fractions of Semen Moringae (seed) inhibited cytochrome P-450 and increased the bioavailability of rifampicin (Pal et al., 2011).

ACCESSORY NUTRIENTS



D-Chondroitin sulphate (CS) [$C_{13}H_{21}NO_{15}S$]

- Chondroitin increases proteoglycan synthesis by chondrocytes, the viscosity of the synovial fluid, bone mineralization, and repair. In addition, chondroitin inhibits pro-inflammatory cytokines and collagenase that lead to the premature breakdown of cartilage in OA (Das & Hammad, 2000; Huskisson, 2008).
- Chondroitin sulfate (CS) increases the hyaluronan production by synovial cells, which has a beneficial effect on maintaining viscosity in the synovial fluid. It has been shown that chondroitin sulfate stimulates the chondrocyte metabolism, leading to the synthesis of collagen and proteoglycan, the basic components of new cartilage. In addition, CS inhibits the enzyme leukocyte elastase and hyaluronidase, which are found in high concentrations in the synovial fluid of patients with rheumatic diseases (Jerosch, 2011).
- The main rationale behind the use of CS in clinical practice is the reduction of NSAIDs in the overall drug management of osteoarthritis and therefore consequently to limit the very significant risks of upper gastrointestinal tract erosions, ulcers with bleeding and/or deleterious renal effects. In addition, oral CS supported the comparison with NSAIDs in a medium/long-term clinical study in patients with knee osteoarthritis (Uebelhart, 2008).

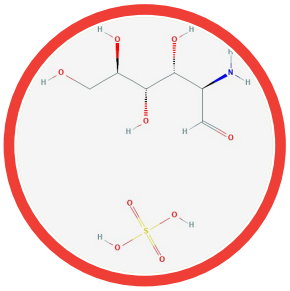
TOXICOLOGY

Toxicity for chondroitin sulfate has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for chondroitin sulfate preparations. Clinical interactions with other drugs have not been reported.

D-Glucosamine sulfate ($C_6H_{15}NO_9S$)



- Glucosamine is a major constituent of extracellular matrix macromolecules such as glycosaminoglycans (GAGs), glycolipids, and glycoproteins in its acetylated form. It is present in high quantities in articular cartilage, intervertebral disc, and synovial fluid (Henrotin et al., 2014).
- Glucosamine reduces the destruction of cartilage. It exerts pharmacological effects on osteoarthritic cartilage and chondrocytes and improves articular cartilage health (Chiusaroli et al., 2011; Reginster et al., 2012; Rovati et al., 2012).
- Glucosamine inhibits gene expression of different inflammation and matrix degradation markers, mainly IL-1, by interfering with the NF-κB pathway (Chiusaroli et al., 2011; Rovati et al., 2012) and glucosamine has been shown to reduces prostaglandin E2 (PGE2) production (Reginster et al., 2012). These anti-inflammatory actions of glucosamine can delay many inflammation-induced catabolic processes in the cartilage (Jerosh, 2011). In a comparative study, the symptomatic anti-inflammatory action of glucosamine was compared to that of NSAIDs and glucosamine had the same success rate (Reginster et al., 2012).

TOXICOLOGY

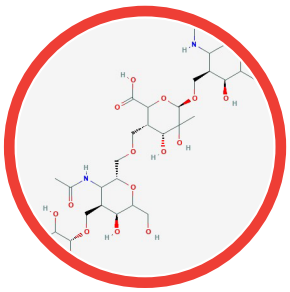
Toxicity for chondroitin sulfate has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for chondroitin sulfate preparations. Clinical interactions with other drugs have not been reported.

However, a potential interaction exists between the anticoagulant drug warfarin and glucosamine chondroitin that is associated with an increase in the international normalized ratio (INR) [Knudsen & Sokol, 2008].

Hyaluronic acid ($C_{33}H_{54}N_2O_{23}$)



- Hyaluronic acid, also known as hyaluronan or hyaluronate, is an anionic, non-sulfated glycosaminoglycan made up of alternating N-acetyl-D-glucosamine and D-glucuronic acid monosaccharide units (Saari et al., 1993). It is distributed widely throughout connective, epithelial, and neural tissues, and intracellular fluids including the aqueous and vitreous humor (Martindale, 1996).
- Found naturally in the synovial joints, it owns a key role in musculoskeletal structure as a cushioning and lubricating agent between joint surfaces against mechanical and chemical damage, while providing rigidity to vertebrae (Tsukasa, 2006).
- Hyaluronic acid has been used for more than four decades in the treatment of osteoarthritis in dogs, horses, and humans. Hyaluronic acid produces anti-arthritic effects via multiple mechanisms involving receptors, enzymes, and other metabolic pathways (Gupta et al., 2019).

TOXICOLOGY

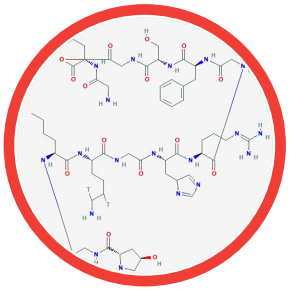
Toxicity for hyaluronic acid has not been documented in dogs and cats when administered orally in therapeutic doses.

Hyaluronic acid was not toxic in a wide range of acute animal toxicity studies, over several species and with different exposure routes (Becker et al., 2009).

DRUG INTERACTIONS

Validated interactions studies do not exist for oral hyaluronic acid preparations. Clinical interactions with other drugs have not been reported.

Hydrolyzed collagen (Marine Collagen) [$C_{57}H_{91}N_{19}O_{16}$]



- Collagen is mainly present in all connective tissues, including animal skin, bone, cartilage, tendon and blood vessels. Marine collagen has gained extensive recognition in the recent past as an appropriate alternative to mammalian collagen. Marine collagen has been extracted mainly from fish skin and it is a rich source of type I collagen (Silva et al., 2014; Blanco et al., 2017; Raman & Gopakumar, 2018).
- Type I collagen forms more than 90% of the organic mass of bone and is the most important collagen of tendons, skin, ligaments, cornea, and most interstitial connective tissues. It provides tensile stiffness for tendons and fascia in organs (Hashim et al., 2015).
- In clinical trials over the past decade, the beneficial effect of orally administered collagen in osteoarthritic dogs has demonstrated its effectiveness in decreasing lameness and increasing vitality in affected animals (Schunck et al., 2017).

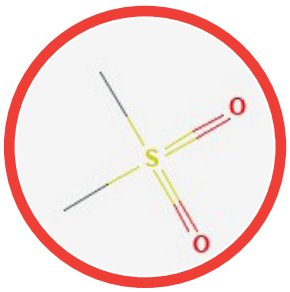
TOXICOLOGY

Toxicity for marine collagen has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral marine collagen preparations. Clinical interactions with other drugs have not been reported.

Methylsulfonylmethane (MSM) [$C_2H_6O_2S$]



- Methylsulfonylmethane (MSM), also known as dimethyl sulfone and methyl sulfone, is organic sulfur-containing compound that occurs naturally in a variety of fruits, vegetables, grains, and animals, including humans. MSM is popularly used for arthritic and rheumatic pain, often in combination with glucosamine and chondroitin sulfate. Because of MSM's sulfur content, it is used by the body to maintain normal connective tissues (Kim et al., 2006; Kim et al., 2009).
- MSM exhibits anti-inflammatory activities, chemopreventive properties, prostacyclin (PGI2) synthesis inhibition, anti-atherosclerotic action, salutary effect on eicosanoid metabolism, and free radical scavenging activity (Kim et al., 2006). Inhibits LPS-induced increases in NO and PGE2 production through suppression of iNOS and COX-2 expression. MSM also inhibits IL-6 and TNF-α products (Kim et al., 2009).
- As a 'Generally Recognized as Safe' (GRAS) approved substance, MSM is well-tolerated for arthritis and a number of other conditions related to inflammation, physical function, and performance (Butawan et al., 2017).

TOXICOLOGY

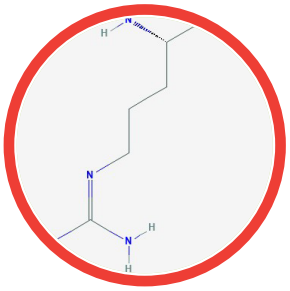
Toxicity for methylsulfonylmethane has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral methylsulfonylmethane preparations. Clinical interactions with other drugs have not been reported.

AMINO ACIDS

L-Arginine ($C_6H_{14}N_4O_2$)



- L-arginine is essential for both dogs and cats (NRC, 2006). L-arginine is one of the most versatile amino acids in animal cells, serving as a precursor for the synthesis not only of proteins but also of nitric oxide, urea, polyamines, proline, glutamate, creatine and agmatine (Wu & Morris, 1998). Also, L-arginine has been shown to elicit the release of several hormones and metabolic mediators including insulin, glucagon, and gastrin, and it is a precursor of biogenic amines, which are important in cell replication (NRC, 2006).
- L-arginine deficiency in the cat and dog results in a rapid onset of hyperammonemia with its associated symptoms of emesis, hypersalivation, ataxia, hyperesthesia, emprosthotonus, extended limbs, exposed claws, hypothermia and depression. The most severely affected animals go into a deep coma and have marked bradypnea and cyanosis, which may lead to death (Rogers & Phang, 1985; NRC, 2006).
- Cats can produce L-arginine in enterocytes and proximal renal tubular cells but limited amounts. Dietary intake remains the main source of arginine for cats (Dor et al., 2018). The recommendation of arginine as a therapeutic agent in dogs and cats is based on the need to minimize urinary orotic acid (NRC, 2006).

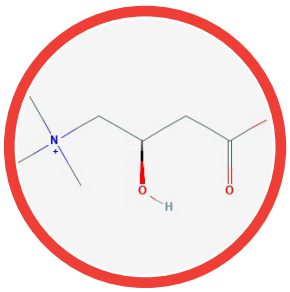
TOXICOLOGY

Toxicity for L-arginine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-arginine preparations. Clinical interactions with other drugs have not been reported.

L-Carnitine ($C_7H_{15}NO_3$)



- L-carnitine is critical for mitochondrial fatty acid β-oxidation. L-Carnitine plays a carrier role in the transportation of fatty acids from the cytosol into the mitochondria (NRC, 2006). L-Carnitine supplementation can stimulate erythropoiesis, activity intensity, body composition, reduce exercise-induced plasma lactate concentrations, and decrease post-exercise muscle damage (Epp et al., 2007; Varney et al., 2017).
- Some breeds of dogs have an autosomal recessive defect in carnitine biosynthesis pathway which leads to a deficiency. These breeds of dogs have neuronal ceroid lipofuscinoses (NCL) and cardiomyopathy. Evidence of NCL has been documented in over 20 canine breeds and in mixed-breed dogs. Supplementation with L-Carnitine in some cases leads to a reduction in clinical signs of the disease (NRC, 2006; Katz et al., 2017). In experimental feline hepatic lipidosis, L-carnitine supplementation protected the cats from ketosis and improved carnitine and lipid metabolism (Blanchard et al., 2002).

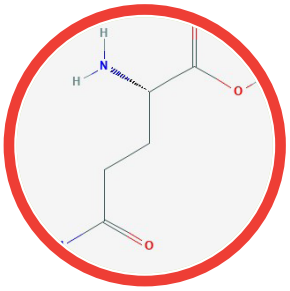
TOXICOLOGY

Toxicity for L-carnitine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Pivalic acid combines with L-carnitine and is excreted in the urine as pivaloylcarnitine, thereby increasing L-carnitine losses. Consequently, prolonged use of pivalic acid-containing antibiotics, including pivampicillin, pivmecillinam, pivcephalexin, and cefditoren pivoxil, can lead to secondary L-carnitine deficiency (Ohnishi et al., 2008; Todesco et al., 2009).

L-Glutamine ($C_5H_{10}N_2O_3$)



- L-glutamine is an amide of glutamic acid with amine as the functional group. L-glutamine has functions in the gastrointestinal tract such as attenuation of gut damage, support of intestinal barrier function and integrity, reduction in oxidative stress, restoration of mucosal immune homeostasis, and optimization of function by normalizing or reducing inflammatory cytokine secretion, and increasing immune regulatory cytokine concentrations (Rao & Samak, 2012).
- Physiologically, L-glutamine plays important roles in various metabolic processes: as an intermediary in energy metabolism, and as a substrate for the synthesis of peptides and non-peptides such as nucleotide bases, glutathione, and neurotransmitters. Additionally, L-glutamine contributes to the detoxification of ammonia and systemic acid-base balance (Kim & Kim, 2017).
- Several experiments in animals with irritable bowel disease (IBD) demonstrated that glutamine supplementation can protect the intestinal mucosa. Oral L-glutamine supplementation ameliorated abdominal radiation-induced mucosal injury and reduced bacterial translocation in gut mucosa of rats (Souba et al., 1990). In dextran sulfate sodium-induced rats, oral administration of glutamine reduced bleeding and diarrhea (Xue et al., 2011).

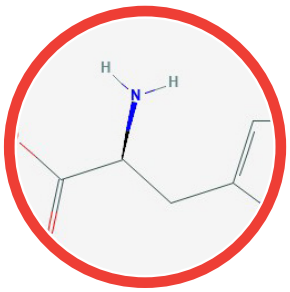
TOXICOLOGY

Toxicity for L-glutamine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-glutamine preparations. Clinical interactions with other drugs have not been reported.

L-Histidine ($C_6H_9N_3O_2$)



- L-histidine is essential for both dogs and cats (NRC, 2006). L-histidine is the most active and versatile member of amino acids that plays the multiple roles in protein interactions, often the key residue in enzyme catalytic reactions. It is essential as a precursor of neuroactive and regulatory compounds such as histamine, anserine, and carnosine, and is present in high concentrations in hemoglobin (NRC, 2006; Liao et al., 2013).
- L-histidine deficiency can result in weight loss, listless and reduced activity, negative nitrogen balance, decreases in plasma hemoglobin, and can result in cataracts (NRC, 2006).

Note: Cats had higher concentrations of the essential amino acids histidine, isoleucine, phenylalanine and valine, but lower concentrations of lysine, methionine and threonine compared with dogs (Hall et al., 2018).

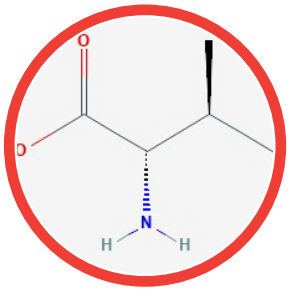
TOXICOLOGY

Toxicity for L-histidine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-histidine preparations. Clinical interactions with other drugs have not been reported.

L-Isoleucine ($C_6H_{13}NO_2$)



- L-isoleucine is essential for both dogs and cats (NRC, 2006). L-isoleucine is classified as branch-chain amino acid and is both ketogenic and glucogenic. It's only known essential function is as a constituted of proteins (NRC, 2006).
- L-isoleucine deficiency can result in loss of appetite, weight loss, negative nitrogen balance, and rough hair coat (NRC, 2006).

Note: L-leucine L-isoleucine, and L-valine are denoted as branched-chain amino acids (BCAA) are essential amino acids whose carbon structure is marked by a branch point. These three amino acids are critical to mammalian life and are particularly involved in stress, energy and muscle metabolism (NCBI, 2020). The BCAAs in addition to L-phenylalanine, is the most lipophilic of the amino acids (Brody, 1998). More recently, BCAA have been reported to participate in lipolysis, lipogenesis, glucose metabolism, glucose transportation, intestinal barrier function and absorption, milk quality, mammary health, embryo development, and immunity (Zhang et al., 2017).

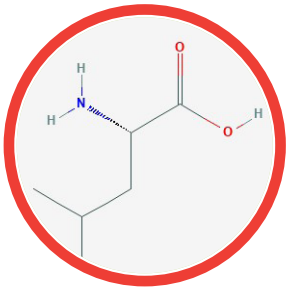
TOXICOLOGY

Toxicity for L-isoleucine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-isoleucine preparations. Clinical interactions with other drugs have not been reported.

L-Leucine ($C_6H_{13}NO_2$)



- L-leucine is essential for both dogs and cats. L-leucine is strongly ketogenic and the only structural role of L-leucine is as a constituent of proteins. L-leucine has a role in regulating the catabolism of all BCAAs. It has been reported that L-leucine enhances protein synthesis directly and indirectly by increasing plasma insulin and suppressing protein degradation in skeletal muscle (NRC, 2006).
- L-leucine is unique among the BCAAs in its ability to stimulate protein synthesis in the muscle of food-deprived rats (Anthony et al., 2000). When protein is ingested, L-leucine increases protein synthesis and decreases protein degradation, both of which increase the efficacy of utilization of all the essential amino acids including L-leucine for maintenance, growth, or reproduction (NRC, 2006).
- Proteinuria in dogs with kidney disease can contribute to protein-energy wasting and malnutrition. Dogs with protein-losing nephropathy had significantly lower concentrations of several essential amino acids including L-leucine (Parker et al., 2019).

TOXICOLOGY

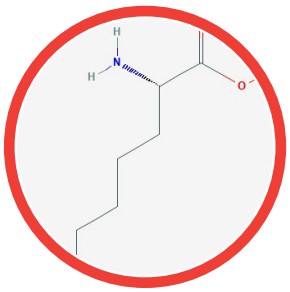
Toxicity for L-leucine has not been documented in dogs and cats when administered orally in therapeutic doses.

Note: L-leucine controls its own degradation and that of L-isoleucine and L-valine, this prevents potential toxicity from BCCAs at even high dietary concentrations (NRC, 2006).

DRUG INTERACTIONS

Fluoxetine is one of the most widely used antidepressants and it is also being used to manage obesity. Fluoxetine reduces L-leucine absorption by its action on the basolateral and apical membrane of the enterocyte (Urdaneta et al., 1998).

L-Lysine ($C_6H_{14}N_2O_2$)



- L-lysine is essential for both dogs and cats and is important for cross-linkages that occur in collagen (NRC, 2006). L-lysine is a necessary building block for all proteins in the body and plays a major role in calcium absorption, building muscle protein, recovering from surgery or injuries and the body's production of hormones, enzymes, and antibodies (Singh et al., 2011).
- L-lysine is clinically significant in the management of osteoporosis, anxiety and mood disturbances. Oral administration of lysine may be helpful in early treatment for FHV-1 infection by lessening the severity of disease (Stiles et al., 2002).
- L-lysine content in cat and dog diet can be severely affected by heat processing and storage for long periods of time. L-Lysine concentration is low in cereals as it readily forms Maillard reaction products (Maillard complex) with glucose and heat and it is often the limiting amino acid when low-protein, cereal-based diets are fed. The Maillard complex may be partially absorbed but cannot be utilized by the animal (NRC, 2006; Williams et al., 2006).
- Signs of L-lysine deficiency include anorexia, weight loss, and negative nitrogen balance (NRC, 2006).

TOXICOLOGY

Toxicity for L-lysine has not been documented in dogs and cats when administered orally in therapeutic doses.

However, 40 g excess lysine can cause growth depression and classical clinical signs of arginine deficiency including emesis, increased plasma ammonia, and orotic aciduria (NRC, 2006).

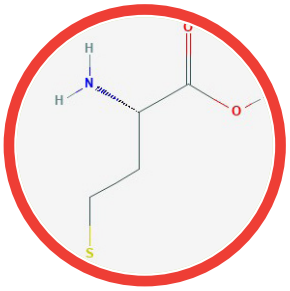
Several studies have demonstrated that L-lysine can affect NO production via competition for the shared intracellular transport protein. Therefore, it may be suggested that excess lysine may inhibit NO biosynthesis (Luiking & Deutz, 2007).

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-lysine preparations. Clinical interactions with other drugs have not been reported.

Note: L-lysine competes with arginine for intracellular transport and excess of lysine may indirectly affect arginine metabolism (Luiking & Deutz, 2007).

L-Methionine ($C_5H_{11}NO2S$)



- L-methionine is essential for both dogs and cats (NRC, 2006). L-methionine is generally the most limiting amino acid and it plays an important role in biological events such as methylation and antioxidant properties besides its function in protein synthesis (NRC, 2006; Zuo et al., 2019).
- L-methionine and L-cysteine may be considered to be the principal sulfur-containing amino acids in proteins. In animals, L-methionine metabolism mainly involves the following metabolic pathways: under the catalysis of methionine adenosyltransferases (MATs), L-methionine produces S-adenosylmethionine (SAM), which can be transmethylated to S-adenosylhomocysteine (SAH); SAM is an important methyl group donor for the synthesis of creatine, lecithin, and epinephrine and also can serve as a methylation source for the methylation of DNA, RNA, and proteins (Brosnan & Brosnan, 2006; Zuo et al., 2019).
- Signs of deficiency include a decrease in food intake, severe weight loss, swelling and reddening of the skin, dermatosis on the front footpads, pigmented gall stone, lethargy, and abnormal secretions from the eyes (NRC, 2006).

TOXICOLOGY

Oral administration of 1 g/kg BW of L-methionine every 4 hours for 24 hours caused no acute clinical signs in normal dogs but caused severe clinical signs similar to a hepatic coma in dogs with portocaval shunts. Cats given 1 g/kg BW/day of DL-methionine developed severe hemolytic anemia and a marked increase in methemoglobin concentration with Heinz body formation by 6days (NRC, 2006).

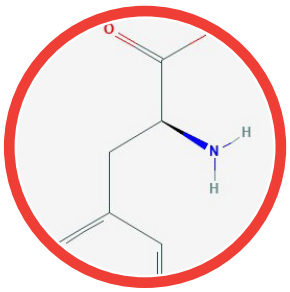
DL-methionine can be more toxic than L-form (NRC, 2006).

In infants, methionine intakes of 2-5 times normal resulted in impaired growth and extremely high plasma methionine levels. In another clinical study of rheumatoid polyarthritis patients, 5 or 10 g of L-methionine caused nausea, vomiting, constipation, and halitosis. Methionine can also to induce acidosis (Garlick, 2006).

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L- methionine preparations. Clinical interactions with other drugs have not been reported.

L-Phenylalanine ($C_9H_{11}NO2$)



- L-phenylalanine is essential for both dogs and cats and L-tyrosine can be synthesized in the body from L-phenylalanine by hydroxylation (NRC, 2006). The production of L-tyrosine is the terminal step in the normal metabolism of L-phenylalanine, catalyzed by phenylalanine hydroxylase (Sumaily & Mujamammi, 2017).
- In dogs and cats, the amount of phenylalanine required is the sum of phenylalanine plus tyrosine, provided the level of tyrosine in the diet is not higher than that of phenylalanine (NRC, 2006).
- Signs of deficiency include reduced food intake, weight loss, reddish-brown hair coat in black dogs and cats (NRC, 2006).

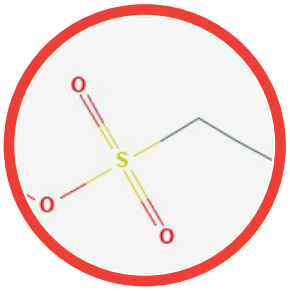
TOXICOLOGY

Toxicity for L-phenylalanine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-phenylalanine preparations. Clinical interactions with other drugs have not been reported.

L-Taurine ($C_2H_7NO_3S$)



- L-taurine (2-aminoethanesulfonic acid) is an essential dietary nutrient for cats but dispensable for dogs fed adequate quantities of sulfur-containing amino acids. L-taurine is one of the most abundant free amino acids in mammals, being particularly high in the brain, heart, and skeletal muscles. In cats, there is a gradual decrease (up to 75%) in L-taurine as they mature. The highest concentrations occur in the olfactory bulb and optic nerve (NRC, 2006).
- All ocular tissues contain L-taurine, and a quantitative analysis of ocular tissue extracts of the rat eye revealed that taurine was the most abundant amino acid in the retina, vitreous, lens, cornea, iris, and ciliary body. In the retina, taurine is critical for photoreceptor development and acts as a cytoprotectant against stress-related neuronal damage and other pathological conditions (Ripps & Shen, 2012).
- L-Taurine is involved in fetal development, growth, reproduction, neuromodulation, sight, hearing, heart function, osmoregulation, fat emulsification, neutrophil function, immune response, antioxidation, bile acid conjugation, detoxification, membrane stabilization, and modulation of cellular calcium levels (Birdsall, 1998; NRC, 2006; Ripps & Shen, 2012).
- Low levels of taurine are associated with various pathological lesions, including cardiomyopathy, retinal degeneration, and growth retardation, especially if a deficiency occurs during development (Birdsall, 1998). The landmark studies showing that taurine is an essential nutrient for cats focused on the link between taurine deficiency and the development of photoreceptor loss and retinal degeneration (Hayes et al., 1975; Schmidt et al., 1976). In cats, L-taurine not only causes pathology but it also shortens their lifespan (Schaffer & Kim, 2018). The most common sign of L-taurine deficiency in dogs has been dilated cardiomyopathy (NRC, 2006).

Note: Rice bran increases the requirement for L-taurine in cats (NRC, 2006).

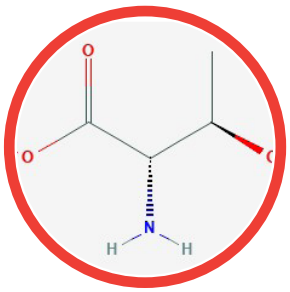
TOXICOLOGY

Toxicity for L-taurine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-taurine preparations. Clinical interactions with other drugs have not been reported.

L-Threonine ($C_4H_9NO_3$)



- L-threonine is essential for both dogs and cats and glucogenic amino acid (NRC, 2006). L-threonine plays a critical role in the maintenance of intestinal mucosal integrity and barrier function, which can be indicated by intestinal morphology, mucus production, transepithelial permeability, brush border enzyme activity, and growth performance (Mao et al., 2011).
- Dietary threonine restriction may decrease the production of digestive enzymes and increase mucosal paracellular permeability. A large proportion of dietary threonine is utilized for intestinal-mucosal protein synthesis, especially for mucin synthesis, and there is no oxidation of threonine by enterocytes. Because mucin proteins cannot be digested and reused, intestinal mucin secretion is a net loss of threonine from the body (Mao et al., 2011).
- Adequate L-threonine is needed to support optimum growth and immune function of animals, while threonine deficiency can reduce food intake, decrease growth rate, weight loss, and impaired immune function (NRC, 2006; Mao et al., 2011).

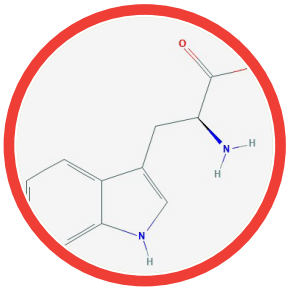
TOXICOLOGY

Toxicity for L-threonine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-threonine preparations. Clinical interactions with other drugs have not been reported.

L-Tryptophan ($C_{11}H_{12}N_2O_2$)



- L-tryptophan is essential for both dogs and cats (NRC, 2006). L-tryptophan has important precursor functions such as synthesis of niacin and protein synthesis. L-tryptophan is also the precursor of the neurotransmitters 5-hydroxytryptophan, serotonin, and melatonin (NRC, 2006; Richard et al., 2009).
- L-tryptophan plays a role as a substrate for the synthesis of the coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). It also exerts effects on other neurotransmitters and CNS compounds. Dopamine, norepinephrine, and beta-endorphin have been shown to increase following oral dosing of tryptophan. Through serotonin synthesis, L-tryptophan is also thought to be involved in the modulation of the endocrine system and cortisol, as well as prolactin and growth hormone (Richard et al., 2009).
- L-tryptophan is a precursor of niacin in dogs but cats cannot make significant quantities of niacin. The deficiency of L-tryptophan can decrease food intake and weight loss (NRC, 2006).

TOXICOLOGY

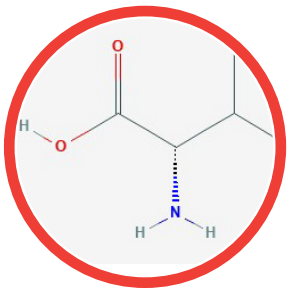
Toxicity for L-tryptophan has not been documented in dogs and cats when administered orally in therapeutic doses.

However, there are indications that dietary supplementation with high concentrations of L-tryptophan may have some neurobehavioral effects reduced aggression in dogs, presumably by increasing neurotransmitter synthesis (NRC, 2006).

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-tryptophan preparations. Clinical interactions with other drugs have not been reported.

L-Valine ($C_5H_{11}NO_2$)



- L-valine is essential for both dogs and cats. L-valine is glucogenic; it's only known essential role as a constituent of proteins (NRC, 2006). L-valine is a branched-chain amino acid (BCAA) and may function in improving health and preventing infectious diseases in animals and humans by regulating the immune system (Zhang et al., 2017).
- Signs of deficiency in dogs and cats include reduced food intake and weight loss (NRC, 2006).

TOXICOLOGY

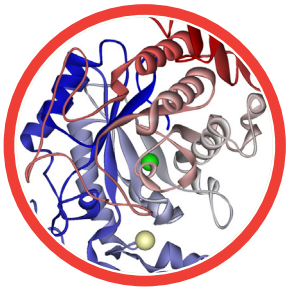
Toxicity for L-valine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral L-valine preparations. Clinical interactions with other drugs have not been reported.

ENZYMES

alpha-Amylase



- α-Amylase (1,4-α-D-glucan-glucanohydrolase) [EC.3.2.1.1] catalyzes the first step in the digestion of starch, the main source of carbohydrate (Butterworth et al., 2011). α-Amylase is a hydrolase enzyme that catalyzes the hydrolysis of internal α-1, 4-glycosidic linkages in starch, resulting in the production of maltose, maltotriose, glucose, and α-limit dextrins as the main products (Gupta et al., 2003).
- Most of the amylases are metalloenzyme requiring Ca+2 for their activity, structural integrity, and stabilization (Rameshkumar & Sivasudha, 2011; Saha et al., 2014) and also chloride is required for the activation of amylase (Levitzki & Steer, 1974).

TOXICOLOGY

Toxicity for α-amylase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral α-amylase preparations. Clinical interactions with other drugs have not been reported.

However, in vitro, α-amylase inhibitory effect of some clinically-used drugs include enalapril (99.9%), captopril (99.5%), tetracycline (97.9%), ketotifen (77.6%), naphazoline (13.6%), fluconazole (7.4%), diclofenac sodium (4.74%), ciprofloxacin (4.7%), Fluoxetine (4.7%), propranolol (4.6%), metronidazole (3.9%), timolol (3.9%), hydrochlorothiazide (3.8%), atenolol (3.5%), cloxacillin (3.5%), clarithromycin (3.13%), ampicillin (2.8%), azithromycin (2.75%), cephalexin (2.6%), orphinadrine citrate (2.6%), Astemizole (2.1%), and clindamycin (1.6%) [Hamdan II et al., 2004].

Cellulase

- Cellulase (4-(1,3;1,4)-beta-D-glucan 4-glucanohydrolase) [E.C.3.2.1.4] randomly cleave intramolecular β-1,4 glucosidic linkages and also acts on cellodextrins, the intermediate products of cellulose hydrolysis and converts them to cellobiase and glucose (White, 1982).
- Treating fruits and vegetables with cellulase enzyme can disrupt the cell wall and release carotenoids and anthocyanins (Sharada et al., 2014). Evidence suggests that absorption of biologically active phytochemicals such as anthocyanins and carotenoids occur in the stomach and small intestine (Yonekura & Nagao, 2007; He & Giusti, 2010).
- Bezoars, accumulations of foreign material in the stomach, have been known to occur in animals and man for centuries (Andrus & Ponsky, 1988). Phytobezoar, the most common type of bezoar, is composed of indigestible fruit and vegetable fibers, such as cellulose, hemicellulose, lignin, or tannins. The therapeutic options in the treatment of phytobezoars include treatment with cellulase and proteolytic enzymes. In a review of patients with phytobezoar, treatment with cellulase was successful in 100% of the patients and 87% with proteolytic enzymes (Walker-Renard, 1993).

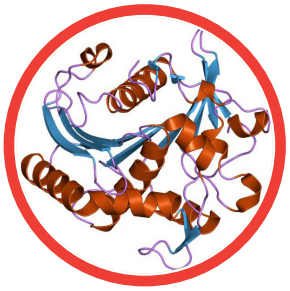
TOXICOLOGY

Toxicity for cellulase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral cellulase preparations. Clinical interactions with other drugs have not been reported.

Lipase



- Supplemental lipase enzyme (Triacylglycerol lipase) [EC.3.1.1.3] has been used in the treatment of gastrointestinal disturbances, dyspepsia, cutaneous manifestations of digestive allergies, and malignant tumors (Gurung et al., 2013).
- Oral digestive enzymes containing triacylglycerol lipase should be taken with meals to ensure adequate mixing with chyme (Toouli et al., 2010). In theory, supplementing with enzymes might improve the nutrient malabsorption that is often associated with inflammatory bowel disease (IBD). Treatment of steatorrhea by lipase supplementation therapy has become more successful in the last decade and bacterial lipase products show promising potential and offer future therapeutic alternatives (Layer & Keller, 2003)..

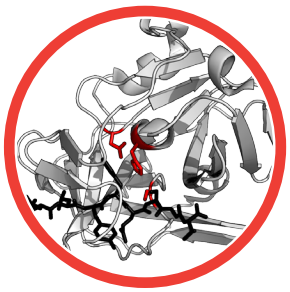
TOXICOLOGY

Toxicity for triacylglycerol lipase has not been documented in humans when administered orally in therapeutic doses.

DRUG INTERACTIONS

Orlistat inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract to decrease systemic absorption of dietary fat (Heck et al., 2000).

Protease



- Protease (E.C 3.4.23.18) performs proteolysis. Proteases regulate the fate, localization, and activity of many proteins, modulate protein-protein interactions, create new bioactive molecules, contribute to the processing of cellular information, and generate, transduce, and amplify molecular signals (López-Otín & Bond, 2008).
-
- Proteolytic enzymes, such as bromelain, papain, pancreatin, trypsin, and chymotrypsin, are essential regulators and modulators of the inflammatory response. Proteolytic enzymes modulate the inflammatory process by a variety of mechanisms, including reducing the swelling of mucous membranes, decreasing capillary permeability, and dissolving blood clot-forming fibrin deposits and micro-thrombi (Lenard et al., 2013).

TOXICOLOGY

Toxicity for protease has not been documented in humans when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interactions studies do not exist for oral protease preparations. Clinical interactions with other drugs have not been reported.

However, bromelain may affect the blood's ability to clot and could interfere with blood-thinning drugs.

SAFETY INFORMATION

PRECAUTIONS

- An examination from a veterinarian is recommended prior to using this product.
- Do not use in immature, pregnant or lactating animals.
- Do not use in animals with diabetes.
- Do no use in animals with gastrointestinal disease/ulceration.
- Do not use in animals receiving other drugs or certain dog breeds predisposed to copper toxicity, unless directed by a veterinarian.
- Do not exceed the recommended dose.
- Not for long term use unless directed by a veterinarian.
- If animal's condition worsens or does not improve, stop product administration and consult your veterinarian.
- Not to be used one week prior to surgery.
- Consult your veterinarian for potential drug interactions.
- Off-label use of this product in ruminants is not recommended.
- Oral use only.
- Administer during or after the animal has eaten to reduce the incidence of gastrointestinal upset.
- Shake well before use.
- Do not use if the security seal is broken.

WARNINGS

- To be used in dogs and cats only.
- Keep out of the reach of children and animals.
- In case of accidental overdose, contact a health professional immediately.

ADVERSE REACTIONS

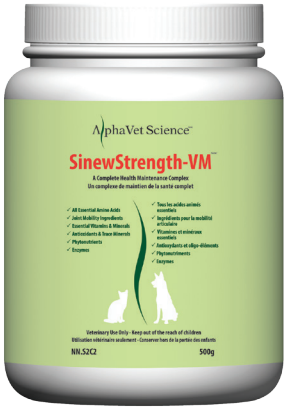
- Mild gastrointestinal discomfort may occur which is dose-dependent.

CONTRAINDICATIONS

- Contraindicated in pregnant and nursing dogs and cats.

AlphaVet Science™

Immunine-VM™



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