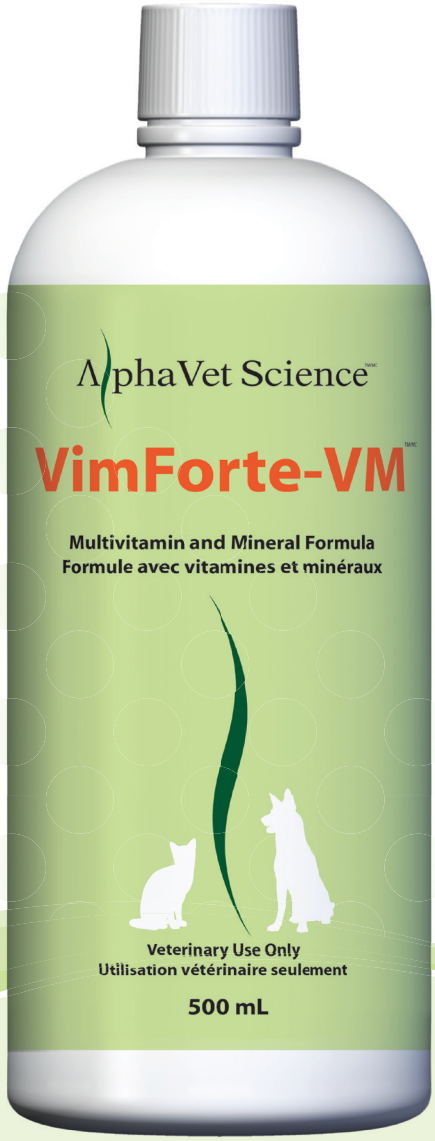
AlphaVet Science™/MC



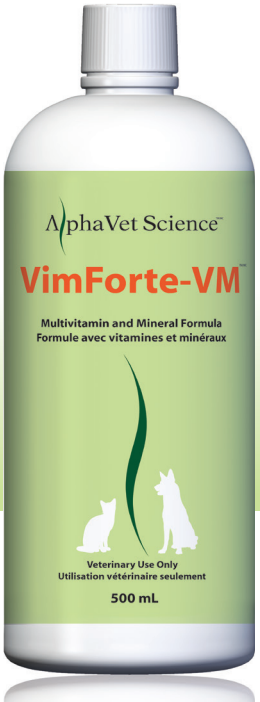
Just Natural Science™

La science au naturel, simplement™

AlphaVet Science™

VimForte-VM™

VimForte-VM™ is a nutritional supplement of macro-minerals, micro-minerals, fat-soluble vitamins, water-soluble vitamins and antioxidants essential for diverse biochemical functions.



INDICATIONS For the treatment and/or prevention of vitamin and mineral deficiencies associated with:

- Chronic diseases
- Convalescence
- Infections
- Malabsorption
- Postoperative
- Preoperative
- Restricted diets
- Stress

INGREDIENTS ACTIONS

- Antioxidant
- Enzyme Cofactors
- Growth
- Energetic
- Metabolic
- Restorative

ADMINISTRATION Oral

DOSAGE

1 - 20 lbs	1.25 ml (¼ teaspoon) daily.
21 - 50 lbs	2.5 ml (½ teaspoon) daily.
51 - 100 lbs	5 ml (1 teaspoon) daily.
> 100 lbs	10 ml (2 teaspoons) daily.

STORAGE Refrigerate after opening. Keep bottle cap tightly closed when not in use. Keep out of reach of children.

PACKAGING 500 mL/bottle

VimForte-VM™ FORMULA

1 teaspoon (5 mL) contains:

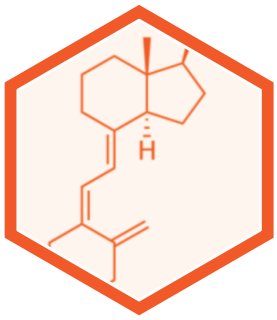
Cholecalciferol	(Vitamin D3)	200 IU	**Calcium**	(Citrate)	50 mg
d-alpha-Tocopherol	(Vitamin E)	50 IU	**Magnesium**	(Citrate)	30 mg
beta-Carotene		2500 IU	**Boron**	(Sodium Borate)	500 mcg
Thiamine Hydrochloride	(Vitamin B1)	2 mg	**Chromium**	(Polynicotinate)	10 mcg
Riboflavin	(Vitamin B2)	2 mg	**Copper**	(Gluconate)	0.5 mg
Niacinamide	(Vitamin B3)	15 mg	**Manganese**	(Sulphate)	2 mg
Calcium Pantothenate	(Vitamin B5)	5 mg	**Selenium**	(Sodium Selenite)	25 mcg
Pyridoxine Hydrochloride	(Vitamin B6)	1 mg	**Silicon**	(Sodium Metasilicate)	5 mg
Biotin	(Vitamin B7)	25 mcg	**Zinc**	(Citrate)	5 mg
Folic Acid	(Vitamin B9)	100 mcg	**Choline Bitartrate**		10 mg
Cyanocobalamin	(Vitamin B12)	25 mcg	**Inositol**		35 mg
Ascorbic Acid	(Vitamin C)	50 mg	**Lecithin**		25 mg

NON-MEDICINAL INGREDIENTS

Stevia, Citric acid, Potassium sorbate, Purified water, Sodium benzoate.

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

PHARMACOLOGICAL ACTIVITIES - TOXICOLOGY - DRUG INTERACTIONS



Cholecalciferol [Vitamin D_3] ($C_{27}H_{44}O$)

Dogs and cats may have limited ability to use UVB light for cutaneous biogenesis of vitamin D (Kleiman *et al.*, 2010). For this reason, it is important that vitamin D_3 be introduced directly into the diet (Kleiman *et al.*, 2010; Schenck, 2010). Vitamin D_3 regulates calcium:phosphorous balance in the body and it stimulates the kidney's retention of calcium, which is vitally important to bone formation, nerve and muscle control. Osteomalacia occurs when insufficient calcium and/or phosphorus is available for mineralization of newly formed osteoid (Ettinger & Feldman, 2000b).

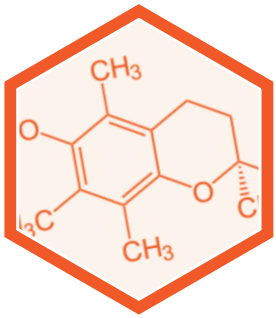
TOXICOLOGY

Several factors, such as the chemical form (vitamin D_2 or Vitamin D_3), 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). Intraperitoneal LD_{50} of vitamin D_3 is 135.4 mg/kg of body weight in male mice (Hatch & Laflamme, 1989). Published human cases of vitamin D_3 toxicity, for which serum levels and dose are known, all involve intake of > or = 40,000 IU (1,000 mcg) per day (Vieth, 1999).

DRUG INTERACTIONS

Due to a narrow therapeutic index, vitamin D analogs given in combination with each other or with pharmacologic doses of vitamin D (calcitriol, doxercalciferol, paricalcitol) may demonstrate additive effects resulting in toxicity manifested as hypercalcemia, hypercalciuria, and hyperphosphatemia (Drugs.com). Atorvastatin appears to increase 25-hydroxycholecalciferol (25[OH]D) concentrations, whereas concurrent vitamin D supplementation decreases concentrations of atorvastatin. Use of thiazide diuretics in combination with calcium and vitamin D supplements may cause hypercalcemia in humans or those with compromised renal function or hyperparathyroidism. Insufficient evidence is available to determine whether lipase inhibitors, antimicrobial agents, antiepileptic drugs, highly active antiretroviral agents, or H2 receptor antagonists alter serum 25(OH)D concentrations (Robien *et al.*, 2013).

alpha-Tocopherol [Vitamin E] ($C_{29}H_{50}O_2$)



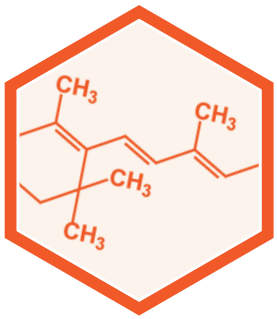
Vitamin E is a natural antioxidant that is important for maintaining stability of cell membranes. Vitamin E supplementation increases antioxidant capacity and can play a potential beneficial role in the prevention or treatment of several diseases in dogs (Raila *et al.*, 2011). Vitamin E deficiency may cause pathologic change in smooth muscle, central nervous system, skeletal muscle, and retina in dogs (Ettinger & Feldman, 2000b). Pansteatitis is associated with a vitamin E deficiency in cats that are habitually or exclusively fed high fat diets, particularly red tuna or other oily fish. Vitamin E supplementation is beneficial in the treatment of pansteatitis (Ettinger & Feldman, 2000a).

TOXICOLOGY

Toxicity for vitamin E has not been documented in dogs and cats when administered orally in therapeutic doses. Vitamin E is generally regarded as one of the least toxic fat-soluble vitamins. The oral LD_{50} alpha-tocopherol acetate for rats, mice and rabbits has been estimated to be >2 g/kg of body weight (NRC, 1987).

DRUG INTERACTIONS

Vitamin E might slow blood clotting. Taking vitamin E along with anticoagulant drugs, such as warfarin; antiplatelet drugs, such as clopidogrel and dipyridamole; and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and others might increase the chances of bruising and bleeding. Also, individuals on anticoagulant therapy or individuals who are vitamin K deficient should not take alpha-tocopherol supplements without close medical supervision because of the increased risk of hemorrhage (DRI, 2000). Vitamin E increases xenobiotic pathways that increase hepatic metabolism and excretion of all vitamin K forms (Traber, 2008). A number of medications may decrease the absorption of vitamin E, including cholestyramine, colestipol, isoniazid, mineral oil, orlistat, sucralfate, and the fat substitute, olestra. Anticonvulsant drugs, such as phenobarbital, phenytoin, or carbamazepine, may decrease plasma levels of vitamin E (DRI 2000; Hendler & Rorvik, 2001).



beta-Carotene ($C_{40}H_{56}$)

Many animals convert β-carotene to retinol to meet their vitamin A requirements. However, this pathway is inefficient in many carnivores including cats (Schweigert *et al.*, 2002). Although it has been shown that cats are capable of converting β-carotene to active vitamin A, it is inadequate to meet a cat's vitamin A requirement (Green *et al.*, 2011). Dietary supplements of vitamins E and C and beta-carotene reduce oxidative stress in cats with renal insufficiency (Yu & Paetau-Robinson, 2006). Dietary β-carotene stimulates cell-mediated and humoral immune responses in dogs (Chew *et al.*, 2000) and was found to restore immune responses in older dogs (Massimino *et al.*, 2003).

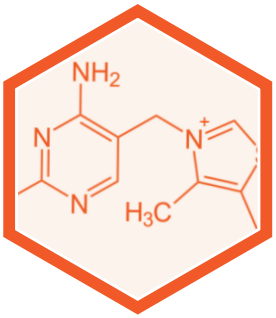
TOXICOLOGY

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

DRUG INTERACTIONS

Validated interactions studies do not exist for β-carotene preparations. However, β-carotene can interact with medication used for lowering cholesterol. Taking them together can lower the effectiveness of these medications and is considered only a moderate interaction (Web MD, 2012). Orlistat can reduce the absorption of β-carotene by as much as 30% (UMMC, 2012a). Bile acid sequestrants such as cholestyramine and colestipol and proton-pump inhibitors such as omeprazole can also decrease absorption of β-carotene (Meschino, 2012).

Thiamine Hydrochloride [Vitamin B_1] ($C_{12}H_{17}ClN_4OS.HCl$)



Thiamine (vitamin B_1) is an essential cofactor in the decarboxylation of pyruvate and alpha-ketoglutarate and these reactions are essential for aerobic metabolism. Deficiency of thiamine blocks CNS aerobic metabolic pathways. In cats, initial thiamine deficiency can develop into central vestibular disease, head tremor, mydriasis, and cervical ventroflexion, which may progress to opisthotonos, coma, and death. In dogs, ataxia, paresis, vestibular signs, and seizures have been observed (Ettinger & Feldman, 2000a).

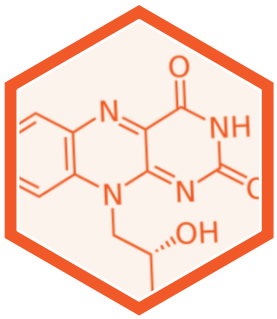
Cats are more susceptible to thiamine deficiency than dogs as they require about four times as much thiamine in the diet. Fish-based diets that contain active thiaminases before processing can destroy thiamine added to these diets and in the heat processing of dog and cat foods, large losses of thiamine can occur. Canned foods often contain gelling agents that increase the pH of the food and in combination with prolonged heat during retorting results in extensive inactivation of thiamine. Moreover, sulphites used for food preservation, cleave the thiamine molecule at the methylene bridge making thiamine inactive. Thiamine deficiency associated with the feeding of meat preserved with sulphur dioxide has been reported in cats and dogs (NRC, 2006).

TOXICOLOGY

Toxicity for vitamin B_1 has not been documented in dogs and cats when administered orally in therapeutic doses. Intravenous LD_{50} of vitamin B_1 is 50-125 mg/kg of body weight in dogs (NRC, 1987).

DRUG INTERACTIONS

Validated interactions studies do not exist for thiamine preparations. However, laboratory studies suggest that digoxin may reduce the ability of heart cells to absorb and utilize thiamine. Diuretics such as furosemide may reduce the levels of thiamine in the body (UMMC, 2012b).



Riboflavin [Vitamin B_2] ($C_{17}H_{20}N_4O_6$)

The major function of riboflavin is to serve as a precursor of the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Synthesis of the coenzymes from riboflavin is under the control of thyroid hormones. A deficiency of riboflavin impacts other vitamins because flavin coenzymes are involved in their metabolism. These vitamins include folic acid, pyridoxine, niacin, and vitamins K and D. Acute riboflavin deficiency in dogs and cats results in anorexia, body weight loss, decreased activity, hypothermia, decreased respiratory rate, progressive weakness, ataxia, sudden collapse to semicomatose state, and death. Chronic riboflavin deficiency has been associated with anorexia, body weight loss, muscular weakness, flaking dermatitis of the abdomen and medial surface of the hind legs, and ocular lesions (NRC, 2006).

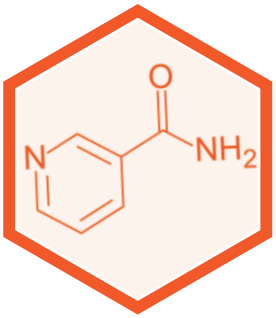
TOXICOLOGY

Toxicity for vitamin B_2 has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} of vitamin B_2 is >10 g/kg of body weight in rats (NRC, 1987).

DRUG INTERACTIONS

Validated interactions studies do not exist for riboflavin preparations. However, anticholinergic drugs and probenecid may decrease riboflavin absorption. Riboflavin can affect the absorption of tetracycline. Tricyclic antidepressants, phenothiazines, doxorubicin, and phenytoin may reduce levels of riboflavin in the body. Methotrexate can inhibit the utilization of riboflavin (UMMC, 2012c).

Niacinamide [Vitamin B_3] ($C_6H_6N_2O$)



Dogs and cats derive most of their energy from oxidation-reduction (redox) reactions, which are processes involving the transfer of electrons. As many as 200 enzymes require the niacin coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), mainly to accept or donate electrons for redox reactions. NAD functions most often in energy producing reactions involving the catabolism of carbohydrates, fats, proteins, and alcohol. NADP functions more often in anabolic reactions, such as in the synthesis of all macromolecules, including fatty acids and cholesterol (Brody, 1999).

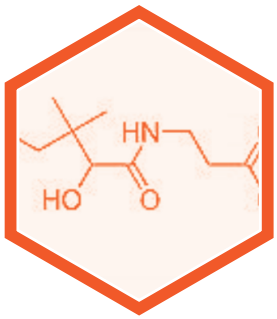
A vitamin B_3 deficiency is characterized by loss of appetite, fatigue, apathy and mouth ulcers, diarrhoea, emaciation and pruritic dermatitis of the hind legs and ventral abdomen. Cats need more niacin than dogs. Dogs are able to synthesize nicotinamide endogenously from tryptophan; cats do not produce any measurable quantities. Cats possess all the enzymes of the pathway of niacin synthesis, but the activity of picolinic carboxylase is extremely high, precluding any measurable synthesis of nicotinic acid (NRC, 2006; Ettinger & Feldman, 2000a).

TOXICOLOGY

Toxicity for vitamin B_3 has not been documented in dogs and cats when administered orally in therapeutic doses. However, it has been reported that repeated oral administration of 2 g/day of nicotinic acid produced bloody feces, convulsions and death in a few dogs (Chen *et al.*, 1938). Oral LD_{50} of niacinamide is 4.5-7 g/kg of body weight in rats (NRC, 1987).

DRUG INTERACTIONS

Validated interactions studies do not exist for niacinamide preparations. However, niacinamide inhibits metabolism of primidone in mice and metabolism of primidone and carbamazepine in humans. This probably occurs by inhibition of cytochrome P-450 by nicinamide (Bourgeois *et al.*, 1982).



Calcium Pantothenate [Vitamin B_5] ($C_{18}H_{32}CaN_2O_{10}$)

Pantothenic acid is found throughout living cells in the form of coenzyme A (CoA), a vital coenzyme in numerous chemical reactions (Tahiliani & Beinlich, 1991). CoA is required for chemical reactions that generate energy from fat, carbohydrates, and proteins. The synthesis of essential fats, cholesterol, and steroid hormones requires CoA, as does the synthesis of melatonin and the neurotransmitter, acetylcholine. Heme requires succinyl-CoA for its synthesis and the metabolism of a number of drugs and toxins by the liver requires CoA (Brody, 1999). Failure to grow and histological changes are the main signs of pantothenate deficiency in cats (NRC, 2006).

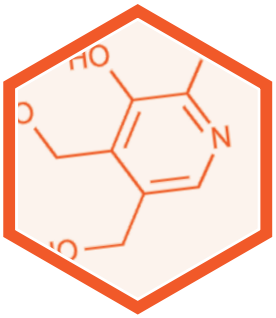
TOXICOLOGY

Toxicity for vitamin B_5 has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} of calcium pantothenate is 10 g/kg of body weight in mice (Unna & Greslin, 1941)

DRUG INTERACTIONS

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

Pyridoxine Hydrochloride [Vitamin B_6] ($C_8H_{11}NO_3 \cdot HCl$)



The liver is the primary organ for metabolism of vitamin B_6, and it releases the active form pyridoxal-5-phosphate (PLP) into the circulation to supply other tissues. Low riboflavin status leads to a reduction in circulating PLP (NRC, 2006). PLP plays a vital role in the function of approximately 100 enzymes that catalyze essential chemical reactions in the body. PLP functions as a coenzyme for glycogen phosphorylase, an enzyme that catalyzes the release of glucose from stored glycogen. Much of the PLP in the body is found in muscle bound to glycogen phosphorylase. PLP is also a coenzyme for reactions used to generate glucose from amino acids, a process known as gluconeogenesis (Shils *et al.*, 2006).

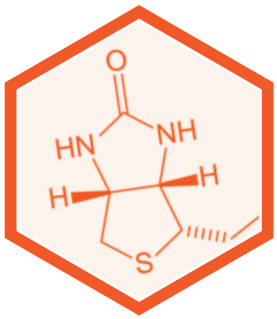
Vitamin B_6 deficiency can result in growth depression, a mild microcytic hypochromic anemia with elevated serum iron; convulsive seizures, and irreversible kidney lesions consisting of tubular atrophy and dilation, fibrosis, and intratubular deposits of birefringent crystals (NRC, 1986). It may also cause a dull, waxy, unkempt coat with fine scales and patchy alopecia (Watson, 1998).

TOXICOLOGY

Toxicity for vitamin B_6 has not been documented in dogs and cats when administered orally in therapeutic doses. However, studies have suggested that probably 1,000 times the nutritional requirements would have to be included in diets in order to produce signs of toxicity. The LD_{50} for vitamin B_6 in dogs is 1 g/kg of body weight. According to another report, dogs can tolerate up to 1 g of pyridoxine/kg of body weight for a short duration of time, but over longer periods can cause ataxia, muscle weakness and neurological damage (Friedrich, 1988). In another study dogs administered 50 mg of pyridoxine hydrochloride/kg of body weight reported no signs of toxicity (Phillips *et al.*, 1978). Levels of pyridoxine of 1,000 mg/kg of diet for less than 60 days, or less than 500 mg/kg of diet for more than 60 days, appear to be safe for dogs (NRC, 1987).

DRUG INTERACTIONS

Pyridoxine deficiency can occur with medications such as isoniazid, cycloserine, and penicillamine. High doses of pyridoxine may decrease the efficacy of phenobarbital and phenytoin (Shils *et al.*, 2006; Bender, 1999). Pyridoxine 10-25 mg may be enough to inhibit levodopa (Leon *et al.*, 1971).



Biotin [Vitamin B_7] ($C_{10}H_{16}N_2O_3S$)

Biotin is attached at the active site of five mammalian enzymes known as carboxylases. Acetyl-CoA carboxylase I and II catalyze the binding of bicarbonate to acetyl-CoA to form malonyl-CoA which is required for the synthesis of fatty acids. Pyruvate carboxylase is a critical enzyme in gluconeogenesis – the formation of glucose from sources other than carbohydrates. Methylcrotonyl-CoA carboxylase catalyzes an essential step in the catabolism of leucine, an essential amino acid. Propionyl-CoA carboxylase catalyzes essential steps in the metabolism of certain amino acids, cholesterol, and odd chain fatty acids (Chapman-Smith & Cronan, 1999; Zempleni & Mock, 1999). Symptoms of biotin deficiency include dried secretions around the eyes, nose and the angle of the mouth, scaly dermatitis, alopecia, hypersalivation, bloody diarrhea, anorexia, and emaciation (NRC, 1986).

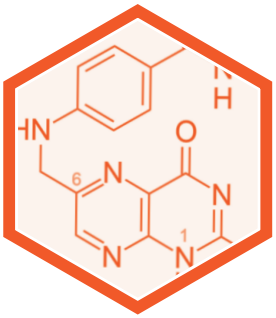
TOXICOLOGY

Toxicity for biotin has not been documented in dogs and cats when administered orally in therapeutic doses. The LD_{50} for repeated (10 day) oral administration in rats was found to be >350 mg/day (EVM, 2002).

DRUG INTERACTIONS

Anticonvulsant drugs such as primidone and carbamazepine inhibit biotin absorption in the small intestine. Use of valproic acid has been associated with decreased biotinidase activity (Schulpis *et al.*, 2001; Bowman & Russel, 2006).

Folic Acid [Vitamin B_9] ($C_{19}H_{19}N_7O_6$)



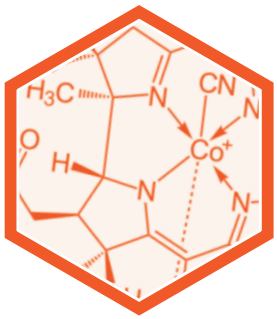
The terms folic acid and folate are often used interchangeably, folic acid, the more stable form, occurs rarely in foods. The function of folate coenzymes in the body is to mediate the transfer of one-carbon units (Choi & Mason, 2000). Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids (Bailey & Gregory, 1999). Deficiency of folic acid can cause macrocytic anemia, megaloblastic anemia, leucopenia, elevated plasma iron concentration, and weight loss (NRC, 1986).

TOXICOLOGY

Toxicity for folic acid has not been documented in dogs and cats when administered orally in therapeutic doses. The Registry of toxic effects of chemical substances (US Department of Health and Human Services, 1979) gives two LD_{50} values for folic acid in mice, intraperitoneal 100 mg/kg of body weight and intravenous 239 mg/kg of body weight (Parchure *et al.*, 1985).

DRUG INTERACTIONS

NSAIDs such as aspirin or ibuprofen may interfere with folate metabolism when taken in very large therapeutic dosages. Phenytoin, has been shown to inhibit the intestinal absorption of folate, and several studies have associated decreased folate status with long-term use of the anticonvulsants, phenytoin, phenobarbital, and primidone (Lewis *et al.*, 1995; Apeland *et al.*, 2001). Taking folic acid at the same time as the cholesterol-lowering agents such as cholestyramine and colestipol, may decrease the absorption of folic acid (Hendler & Rorvik, 2001). A number of other medications have been shown to have antifolate activity, including tetracycline, trimethoprim, pyrimethamine, triamterene, and sulfasalazine (UMMC, 2012d).



Cyanocobalamin [Vitamin B_{12}] ($C_{63}H_{88}CoN_{14}O_{14}P$)

Vitamin B_{12} has the largest and most complex chemical structure of all the vitamins. It is unique among vitamins in that it contains a metal ion, cobalt. In mammals, cobalamin is a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-CoA mutase (Shils *et al.*, 2006). A deficiency of cobalamin can cause a clinical and hematologic picture identical to that of folate deficiency (Ettinger & Feldman, 2000b). There are a number of clinical reports of cobalamin deficiency in dogs and these reports relate to either deficiencies induced by bacterial overgrowth of the intestine resulting in decreased availability of cobalamin or genetic abnormalities of cobalamin metabolism (NRC, 2006).

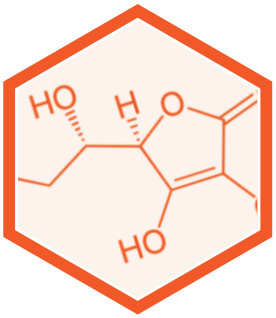
TOXICOLOGY

Toxicity for vitamin B_{12} has not been documented in dogs and cats when administered orally in therapeutic doses. However, subcutaneous doses of 2 to 33 µg/kg of body weight have been given to dogs, and have resulted in disturbances of reflex activity (NRC, 2006). Oral LD_{50} for cyanocobalamin is 13,500 mg/kg of body weight in rats and 22,000 mg/kg of body weight in mice (USP, 2007).

DRUG INTERACTIONS

Medications that reduce levels of vitamin B_{12} in the body include proton pump inhibitors such as esomeprazole, lansprazole, omeprazole and rabeprazole (Kasper, 1999); H_2 blockers including cimetidine, famotidine, and ranitidine (Termanini *et al.*, 1998); anti-seizure medications such as phenytoin, phenobarbital, and primidone; anti-diabetic medication metformin; bile acid sequestrants including colestipol, cholestyramine, and colsevelam (UMMC, 2012e).

Ascorbic Acid [Vitamin C] ($C_6H_8O_6$)



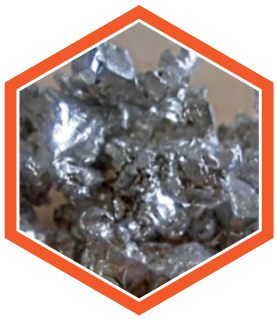
Vitamin C is required for the synthesis of collagen, an important structural component of blood vessels, tendons, ligaments, and bone. Vitamin C also plays an important role in the synthesis of the neurotransmitter, norepinephrine. Vitamin C deficiency can slow healing and increase susceptibility to disease. In dogs and cats supplementation of vitamin C may be beneficial, particularly in times of stress. Studies have shown a slight depression in serum vitamin C concentration in response to some conditions and diseases, and supplementation can increase serum levels in healthy animals (NRC, 2006).

TOXICOLOGY

Toxicity for vitamin C has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} for ascorbic acid is 11,900 mg/kg in rat and 3,367 mg/kg of body weight in mice (ACROS, 2008).

DRUG INTERACTIONS

Estrogen-containing contraceptives and aspirin can lower vitamin C levels in plasma and white blood cells (Basu, 1982). High doses of vitamin C have been found to interfere with the interpretation of certain laboratory tests such as serum bilirubin, serum creatinine, and the guaiac assay for occult blood (Hendler & Rorvik, 2001).



Calcium (Citrate)

Calcium is a major structural element in bones and teeth. The amount of calcium absorption in dogs ranges from 25 to 90 percent, depending on the amount of intake and the age of the animal (Ettinger & Feldman, 2000a). Calcium deficiency in dogs is characterized by rickets in normal dogs, milk fever syndrome in pregnant or lactating dogs and a condition known as nutritional secondary hyperparathyroidism (NSHP). Chronic dietary calcium deficiency causes major decreases in bone material content, which can result in significant skeletal abnormalities including fractures. 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).

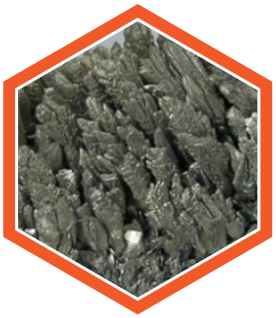
TOXICOLOGY

Toxicity for calcium citrate has not been documented in dogs and cats when administered orally in therapeutic doses. LD_{50} of calcium citrate is not documented. Oral LD_{50} for calcium carbonate is 6,450 mg/kg of body weight in rats (Sciencelab, 2010a).

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, 2012f).

Magnesium (Citrate)



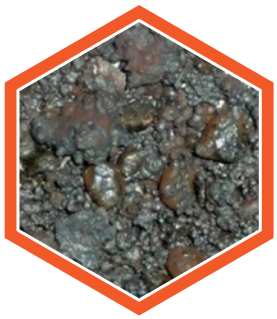
Magnesium is involved in more than 300 essential metabolic reactions such as energy production, synthesis of essential molecules (nucleic acid, enzymes, and glutathione), structural roles (cell membranes, chromosomes), and ion transport across cell membranes, cell signalling, and cell migration (Shils *et al.*, 2006). Magnesium deficiency in dogs can cause anorexia, weight loss, hyperextension of the carpal joints and hind-leg paralysis. Magnesium deficiency in cats can cause poor growth rate and overextension of the metacarpi followed by muscular twitching and convulsions (NRC, 2006).

TOXICOLOGY

Toxicity for magnesium citrate has not been documented in dogs and cats when administered orally in therapeutic doses. LD_{50} for magnesium sulphate in dogs is considered to be >1,200 mg/kg of body weight [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, 2012). 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, 2012g).



Boron (Sodium Borate)

Boron acts directly or indirectly to influence the composition, structure and strength of bones. Experiments in animals indicate that boron may influence calcium, phosphorus, magnesium, and cholecalciferol metabolism. A vitamin D deficiency enhances the need for boron, and boron normalizes abnormalities associated with a magnesium deficiency. Boron also has an effect on brain electrical activity (Groff *et al.*, 1995; NRC, 2006). The signs of boron deficiency in animals include depressed growth and in humans, a low-boron diet is associated with increased urinary calcium and magnesium excretion and with alteration in steroid hormone metabolism (Groff *et al.*, 1995).

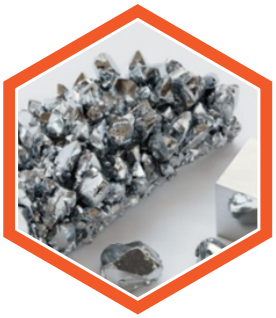
TOXICOLOGY

Toxicity for boron has not been documented in dogs and cats when administered orally in therapeutic doses. A study found that daily doses of 3 g of boric acid, 5 g of borax for 8-10 days had no physiological or pharmacological effect in adult dogs weighing 8 to 12 kg (NRC, 2005). Oral LD_{50} for sodium borate is 4.5 g/kg of body weight and 4.98 g/kg of body weight in male and female rats respectively (Weir & Fisher, 1999).

DRUG INTERACTIONS

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

Chromium (Polynicotinate)



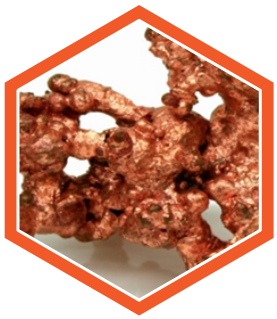
Chromium is an essential dietary trace mineral involved in carbohydrate and lipid metabolism. Chromium is required for cellular uptake of glucose, and chromium deficiency causes insulin resistance. Chromium supplementation may improve insulin sensitivity and has been used as adjunct treatment of diabetes mellitus in humans. Chromium supplementation in diabetic dogs at a level of 2.5-7.5 µg/kg for several months was found to be safe (Schachter *et al.*, 2001). Chromium has also been shown to be involved in protein synthesis, and nucleic acid metabolism (NRC, 2006). Signs of chromium deficiency in humans and several animal species have been found to include impaired glucose tolerance, elevated plasma insulin, hyperglycemia, impaired growth, elevated plasma triglycerides, neuropathy, encephalopathy, corneal lesions and decreased fertility and sperm count.

TOXICOLOGY

Toxicity for chromium polynicotinate has not been documented in dogs and cats when administered orally in therapeutic doses. Hexavalent chromium or chromium (Cr^{+6}) is a recognized carcinogen. In contrast, there is little evidence that trivalent chromium (Cr^{+3}) is toxic to humans (FNB & IOB, 2001b). Intravenous LD_{50} for nicotinic acid bound chromium complexes is approximately 1 g/kg of body weight in rats (EFSA, 2008).

DRUG INTERACTIONS

Validated interactions studies do not exist for chromium preparations. Clinical interactions with other drugs have not been reported. However, large doses of calcium carbonate or magnesium hydroxide-containing antacids decreased chromium absorption in rats. In contrast, aspirin and indomethacin both increased chromium absorption in rats (Shils *et al.*, 2006).



Copper (Gluconate)

Copper is an essential trace element for humans and animals. In the body, copper shifts between the cuprous (Cu^{1+}) and cupric (Cu^{2+}) forms, though the majority of the body's copper is in the Cu^{2+} form. Copper is a critical functional component of a number of essential enzymes known as cuproenzymes. Some of the physiologic functions known to be copper-dependent include energy production, regulation of gene expression (Uauy *et al.*, 1998), formation of connective tissue, the pigment melanin and maintenance of myelin sheath (Shils *et al.*, 2006), iron metabolism, synthesis of the neurotransmitter norepinephrine (O'Dell & Sunde, 1997), metabolism of neurotransmitters norepinephrine, epinephrine, dopamine and serotonin (FNB & IOB, 2001), antioxidant functions such as copper dependent superoxide dismutase and ceruloplasmin (Johnson *et al.*, 1992). In dogs copper deficiency can cause lameness and bone fragility, loss of hair pigmentation, and hyperextension in the distal phalanges (Ettinger & Feldman, 2000b; NRC, 2006).

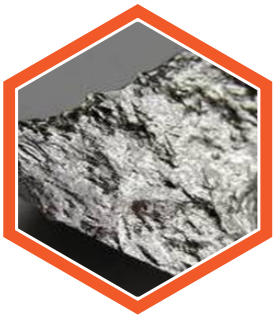
TOXICOLOGY

Toxicity for copper gluconate has not been documented in dogs and cats when administered orally in therapeutic doses. However, in various breeds of dogs, especially Bedlington Terriers, an inherited sensitivity to copper toxicosis similar to Wilson's disease in humans has been identified. Acute poisoning is usually seen after accidental administration of excessive amounts of soluble copper salts (Kahn & Line, 2010). Intradermal LD_{50} for copper salts is >1124 mg/kg of body weight in rats (EVM, 2000).

DRUG INTERACTIONS

Validated interactions studies do not exist for copper preparations. However, penicillamine dramatically increases the urinary excretion of copper; individuals taking the medication for reasons other than copper overload may have an increased copper requirement. Additionally, antacids may interfere with copper absorption when used in very high amounts (Shils et al., 2006).

Manganese (Sulphate)



Manganese plays an important role in a number of physiologic processes as a constituent of metalloenzymes and as an enzyme activator (Groff *et al.*, 1995). The functions of manganese include metabolism of carbohydrates, amino acids and cholesterol (FNB & IOB, 2001a), a component of manganese superoxide dismutase which is the principal antioxidant enzyme in the mitochondria (O'Dell & Sunde, 1997), formation of cartilage and bone (Ziegler & Filer, 1996; Ettinger & Feldman, 2000a), synthesis of glycosaminoglycan and production of collagen required in wound healing (Klimis-Tavantzis, 1994; Muszyńska *et al.*, 2000). Manganese deficiency is very rare in dogs and cats. Experimental dietary deficiency leads to disproportionate, shortened, and thickened long bones in different species; defective development of the skull; and formation of otoliths in the inner ear during gestation (Ettinger & Feldman, 2000a).

TOXICOLOGY

Toxicity for manganese sulphate has not been documented in dogs and cats when administered orally in therapeutic doses. However, in a study intravenous infusion of manganese chloride 16 mg/kg/day (3-5 times daily dose of manganese) to beagle dogs caused severe hepatotoxicity (Khan *et al.*, 1997). Oral LD_{50} for manganese sulphate is 2,150 mg/kg of body weight in rats (MDL, 2002).

DRUG INTERACTIONS

Validated interactions studies do not exist for manganese preparations. However, magnesium-containing antacids and laxatives and the antibiotic medication, tetracycline, may decrease the absorption of manganese if taken together with manganese-containing foods or supplements (Hendler & Rorvik, 2001).

Selenium (L-Selenomethionine)

Humans and animals require selenium for the function of a number of selenium-dependent enzymes, also known as selenoproteins. During selenoprotein synthesis, selenocysteine is incorporated into a very specific location in the amino acid sequence in order to form a functional protein. At least 25 selenoproteins have been identified, but the metabolic functions have been identified for only about one-half of them. The selenoproteins with an identified function include: glutathione peroxidises which are antioxidant enzymes (Gladyshev, 2006); thioredoxin reductase which participates in the regeneration of several antioxidants including vitamin C (Mustacich & Powis, 2000); iodothyronine deiodinases involved in the regulation of thyroid hormones (Hatfield *et al.*, 2006); selenoprotein P, associated with protection of vascular endothelial cells against reactive nitrogen species (Arteel *et al.*, 1999); selenoprotein W, thought to play a role in muscle growth and differentiation by protecting the developing myoblast from oxidative stress (Loflin *et al.* 2006); selenoprotein V functions in spermatogenesis; selenoprotein S is involved with inflammatory and immune responses; kDA selenoprotein has a redox function and is implicated in cancer prevention (Gladyshev, 2006). Animal studies indicate that selenium and vitamin E tend to spare one another and that selenium can prevent some of the damage resulting from vitamin E deficiency in models of oxidative stress (Sword *et al.*, 1991). Only one paper reports experimentally produced clinical signs of selenium deficiency in dogs; there are no reports for cats. Clinical signs include anorexia, depression, dyspnea, and coma (NRC, 2006).

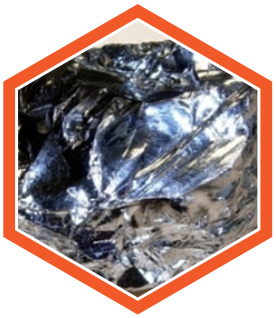
TOXICOLOGY

Toxicity for selenium has not been documented in dogs and cats when administered orally in therapeutic doses. However, a single acute oral dose of selenium in the range of 1-5 mg/kg of body weight is lethal in most animals. 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 of body weight (Kahn & Line, 2010). Oral LD_{50} for sodium selenite is 1.0 mg/kg in rabbits, 3.0 mg/kg of body weight in mice and 4.8-7.0 mg/kg of body weight in rats (EMEA, 1997). Vitamin E exhibits a protective effect on selenium intoxication (Berschneider *et al.*, 1976).

DRUG INTERACTIONS

Validated interactions studies do not exist for selenium preparations. However, 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).

Silicon (Sodium Metasilicate)



Silicon is an essential nutrient that plays a role in the calcification and maturation of bone. Silicon also appears to be a cofactor in prolyl hydrase activity, which is involved in collagen synthesis. Signs of silicon deficiency are related mainly to aberrant 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. No significant acute toxicity or mortality has been reported in animals given doses up to 3,000 mg/kg of body weight per day (NRC, 2005). Oral LD_{50} for sodium metasilicate is 1,280 mg/kg of body weight in rats and 2,400 mg/kg in mice (Haneke, 2002).

DRUG INTERACTIONS

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

Zinc (Citrate)

Zinc plays important roles in growth and development, the immune response, neurological function, and reproduction. On the cellular level, the function of zinc can be divided into three categories: catalytic, structural, and regulatory (Bowman & Russell, 2006). Inadequate zinc supply, especially in growing animals, may lead to severe clinical signs within days, resulting in growth depression, skin defects, impaired immune function, and growth disorders of the skeleton (Ettinger & Feldman, 2000a). Zinc deficiency in the dog most commonly occurs as a skin condition called 'zinc responsive dermatosis' (Colombini, 1999; Campbell & Crow, 2010). The usual symptoms are hair loss, and scaling and crusting of the skin around the face, head, and legs. Lesions often encircle the mouth, chin, eyes, and ears. The foot pads may be scaly and the hair coats are dull and dry.

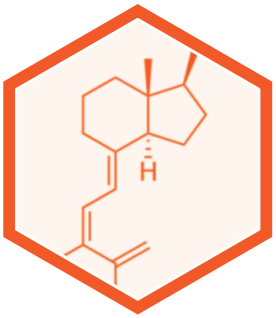
TOXICOLOGY

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 (Hardy *et al.*, 2003). No evidence of significant pathological effects were observed in rats following daily oral administration of zinc (as zinc citrate, zinc acetate, zinc oxide or zinc maleate) in doses up to 34 mg/kg of body weight for 35 to 53 weeks. Oral LD_{50} for zinc chloride is 350 mg/kg of body weight in rats and mice, 200-250 mg/kg of body weight in rabbits. Oral LD_{50} for zinc sulphate is 2,200 mg/kg of body weight in rats and 2,100 mg/kg of body weight in rabbits (EMEA, 1996).

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).

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



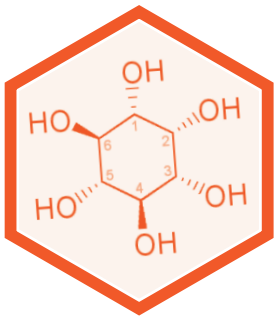
Although choline is not by strict definition a vitamin, it is an essential nutrient (Brody, 1999). The initial recognition of choline as a significant dietary factor depended on its capacity to reduce the fat content of the liver of diabetic dogs (Goodman & Gilman, 1996). The majority of the body's choline is found in specialized fat molecules known as phospholipids. Choline and its metabolites serve a number of vital biological functions such as structural integrity of cell membranes, cell signalling, nerve impulse transmission, lipid transport and metabolism (Groff *et al.*, 1995). Choline deficiency in animals can result in weight gain, fatty liver, liver cirrhosis and in severe cases, vomiting and death. Other effects of a choline deficiency include reduced plasma choline concentration, thymus atrophy, decreased growth rate, impaired reproduction, and hemorrhagic renal lesions. A chronic deficiency in dogs has been reported to cause anaemia, duodenal ulcers, liver damage and oedema (Lewis, 2005).

TOXICOLOGY

Toxicity for choline has not been documented in dogs and cats when administered orally in therapeutic doses. However, adverse effects have been reported for levels of choline chloride equivalent to 3 times the choline requirement (NRC, 1987). LD_{50} for choline bitartrate has not been documented. Oral LD_{50} for choline chloride is 3,900 mg/kg of body weight in mice (NRC, 1987).

DRUG INTERACTIONS

Validated interactions studies do not exist for choline preparations. Clinical interactions with other drugs have not been reported. However, in animal model, methotrexate administration has shown to deplete choline (Shils *et al.*, 2006).



Inositol ($C_6H_{12}O_6$)

Inositol and its isomers function as the basis for a number of signalling and secondary messenger molecules. They are involved in a number of biological processes, including insulin signal transduction (Larner, 2002), nerve transmission, intracellular calcium concentration control (Gerasimenko *et al.*, 2006), metabolism of fats and reducing blood cholesterol (Rapiejko *et al.*, 1986), cell membrane potential maintenance (Kukuljan *et al.*, 1997), serotonin activity modulation (Einat *et al.*, 2001), and gene expression, (Shen *et al.*, 2003; Steger *et al.*, 2003). No deficiencies of inositol have been documented in either dogs or cats (NRC, 2006).

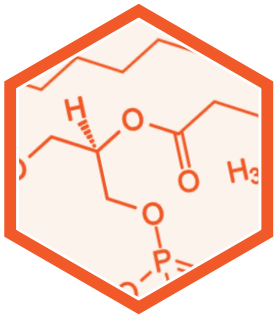
TOXICOLOGY

Toxicity for inositol has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} for inositol is 10 g/kg of body weight in mice (Sciencelab, 2010b).

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

Lecithin

Lecithin is a generic term to designate any group of yellow-brownish fatty substances occurring in animal and plant tissues, and in egg yolk, composed of phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides, and phospholipids. Phosphatidylcholine occurs in all cellular organisms, being one of the major components of the phospholipid portion of the cell membrane. Lecithin supplementation decreases hyperlipidemia, influences lipid metabolism, exhibits hepatoprotective (Lamireau *et al.*, 2007) and immunomodulatory (Miranda *et al.*, 2008) effects.



TOXICOLOGY

Toxicity for lecithin has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} for lecithin is >8 ml/kg of body weight in rats (Pfizer, 2009).

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

PRECAUTIONS

- An examination from a veterinarian is recommended prior to using this product.
- Safe use in pregnant animals or animals intended for breeding has not been proven.
- 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 incidence of gastrointestinal upset.
- Shake well before use.

WARNINGS

- To be used in dogs and cats only.
- Keep out of 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

- None documented.

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