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(54) Title: ORAL FELINE FEED AND METHODS FOR CONTROLLING FLEA INFESTATIONS IN A FELINE

(57) Abstract: An oral feline feed and a method of controlling fleas in a feline in need thereof by orally administering to the feline a daily feed comprising an effective amount of a isoxazoline for an effective time to thereby cause the amount of isoxazoline in the feline's blood to rise to and maintain at a therapeutically effective level for controlling fleas.



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ORAL FELINE FEED AND METHODS FOR CONTROLLING FLEA INFESTATIONS IN A FELINE

TECHNICAL FIELD

[0001] The teachings of this disclosure generally relate to an isoxazoline, a feline feed that includes the isoxazoline and a method of administering the isoxazoline in a feed to control flea infestations in felines.

BACKGROUND AND SUMMARY

[0002] Fleas are the most common of all external feline parasites, the most common of which is the cat flea, or *Ctenocephalides felis*. A flea infestation is usually terribly uncomfortable for most cats and can be the source of deadly disease. Flea bites can cause itching, and the consequent scratching by the cat may cause skin wounds that are vulnerable to infection. Further, the fleas themselves often carry infectious agents. For example, the cat flea can carry the larval stage of the tapeworm *Dipylidium caninum* and cats can become infected by ingesting fleas during self-grooming.

[0003] Further, fleas are instrumental in the transmission of “cat scratch disease” to humans. This is an infection with the bacterium *Bartonella hensellae* and is spread when fleas feed on blood. Cat scratch disease causes symptoms in humans that are unpleasant and can include, among other things, bumps or blisters at the scratch site, swollen lymph nodes, fatigue, headache, fever and body aches. One of the recommended ways to control human risk from fleas is to control the risk of infestation in cats.

[0004] Treatments currently available for controlling flea infestations in felines achieve varying degrees of success. Many treatments involve chemicals applied to indoor and outdoor surfaces, as well as to the feline. The chemicals used include a variety of carbamates, pyrethrins and pyrethroids, certain macrocyclic lactones, insect growth regulators (including chitin synthesis inhibitors, juvenile hormone analogs, and juvenile hormones), nitromethylenes, neonicotinoids, pyridines and pyrazoles or fiproles. These compounds often have toxic side effects that are a problem for both the feline and its owner. In addition, there is evidence that the use of these chemicals may be ineffective due to insecticide resistance and treatment deficiencies. [M. K. Rust, The Biology and Ecology

of Cat Fleas and Advancements in Their Pest Management: A Review, Insects 2017, 8 118.].

[0005] Topical treatments are a well-known method for controlling flea infestations in felines. While there are numerous ways to deliver these therapeutic agents to the haircoats and skins of felines, many of these methods are either ineffective and/or present safety risks to the feline or user during or after the dispensing activity. More particularly, because a physical connection at the skin level must be achieved between the applicator tip of the drug delivery device when the applicator tip is installed thereon, there is inherently a risk that the connection will be inadequate, thereby permitting some of the therapeutic agent to leak out of the device and into physical contact with the user. For example, in the case of uncooperative felines, it may be difficult to maneuver the dispenser with one hand and maintain the feline in place with the other hand, resulting in some, if not all, of the substance being spilled on the floor or on the person applying it instead of reaching the feline's skin. Not only is this leakage wasteful and messy, it also places the user at a heightened risk of suffering from a skin irritation or other such health concern, particularly if the user comes into direct contact with the agent.

[0006] Oral treatments are also available. However, to be effective, the feline owner must administer a treatment once every 30-90 days, for example. The extended time between treatments creates compliance issues when owners forget to administer doses.

[0007] Despite the availability of effective treatments, a recent study by The Harris Poll found that 33% of pet owners do not routinely protect their pets against fleas at all. Another study found that pet owners purchased, on average, only 4 months of flea prevention products per year per pet, despite being told that pets needed to be given flea prevention treatments year-round. Thus, there continues to be a need for relatively safe, effective agents for controlling flea infestations on felines that is easier for owners to remember to use.

[0008] Surprisingly, it has been discovered by the inventors that isoxazolines can provide improved control over flea infestations in felines when orally administered in smaller, more frequent/chronic doses. The administration is discussed below as being combined with feed. However, it is also contemplated that the isoxazoline may be administered by

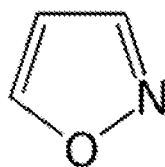
itself or in a dosage form other than feed, such as a chew, tablet, liquid, gel or other suitable form for oral administration. Advantageously, by using smaller, more frequent doses, less total isoxazoline is required over the same time period to control flea infestations. Assume, for example, that 24 mg of isoxazoline/kg of feline body weight is needed for a single dose in a 30-day (1-month) period according to the prior art approach to reach and maintain a therapeutically effective concentration of isoxazoline in the feline's blood for continued flea control. With the inventive approach of smaller and more frequent doses, as little as 0.1-0.72 mg of isoxazoline/kg of feline body weight may be needed per day, or 3-21.6 mg of isoxazoline/kg of feline body weight cumulative over the same 30-day period.

[0009] Advantageously, the total amount of isoxazoline required for a therapeutically effective once-monthly dose can be reduced by 10-87.5% by converting to daily administration. However, from a practical perspective, at least two problems arise: (1) creating a homogenous feed; and (2) analytical control testing for a very small dose of isoxazoline may be difficult to accomplish. The analytical matrix from feeds can be quite complex and difficult to assay. Assays will be in the parts per million to billion range for some needed dose and feed concentrations. Thus, it is possible that one of skill in the art may opt to increase the daily dose such that the total of the daily doses over the course of one month equals the prior art once-monthly dose or is even higher, for example, 200% of the prior art once-monthly dose. This may be done to help ensure homogeneity as well as increase assay accuracy and decrease analytical variability when administering the dose as part of a feed.

[0010] The method and composition taught herein have the further advantage of encouraging compliance because the smaller doses of an isoxazoline can be incorporated into a feed. Since owners naturally follow a daily feeding regimen in any event, this makes it less likely that owners will forget or neglect to administer the isoxazoline. Thus, this disclosure provides a method for prolonged control of fleas in a safer and more effective manner than that achieved with previously known treatment methodologies. All the owner need remember is to feed their pet as they normally would.

[0011] Further, the bioavailability of certain isoxazolines can be improved by administering them with feed. Thus, this disclosure provides a method for prolonged control of fleas in a safer and more effective manner than that achieved with previously known treatments.

[0012] Isoxazolines are a class of five-membered heterocyclic chemical compounds, containing one atom each of oxygen and nitrogen which are located adjacent to one another.



[0013] Isoxazolines are all derivatives of isoxazole. They are structural isomers of the more common oxazolines and exist in three different isomers depending on the location of the double bond.

[0014] Isoxazoline derivatives are known. For example, WO2007/105814, WO2008/122375, and WO2009/035004 disclose certain alkylene linked amides. WO2010/032437 discloses that the benzyl amide can be moved to the position ortho to the isoxazoline. WO2007/075459 discloses phenyl isoxazolines substituted with 5- to 6-membered heterocycles, and WO2010/084067 and WO2010/025998 disclose phenyl isoxazolines substituted with 10- to 11-membered fused aryl and heteroaryls. Chiral processes for manufacturing isoxazolines are disclosed in WO2011/104089 and WO2009/063910.

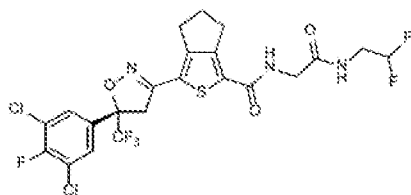
[0015] A number of isoxazolines compounds are known, including but not limited to 4-(5-methyl-5-substituted pyrrolyl-4,5-dihydroisoxazole-3-yl) benzoic acid amide derivatives; 4-(5-substituted carbamoylmethyl-4,5-dihydroisoxazole-3-yl) benzoic acid amide derivatives; 3-(5-substituted carbamoylmethyl-5-substituted alkyl-4,5-dihydroisoxazole-3-yl) benzoic acid amide derivatives; 4-(5-substituted carbamoylmethyl-4,5-dihydroisoxazole-3-yl) benzamidine derivatives; 4-(5-substituted-5-substituted aryl-4,5-dihydroisoxazole-3-yl)benzoic acid amide compounds; 3-(4-substituted phenyl)-4,5-dihydroisoxazole derivatives; 5-substituted alkyl-3,5-bis substituted phenyl-4,5-

dihydroisoxazole derivatives; 3-alkoxyphenyl-5-substituted-5-phenyl-4,5-dihydroisoxazole derivatives; 3-alkoxyphenyl-5-substituted alkyl-5-substituted carbamoyl-4,5-dihydroisoxazole derivatives; 3-(4-halophenyl)-5-substituted-5-substituted phenyl-4,5-dihydroisoxazole derivatives; 3-(4-nitrophenyl)-5-substituted-5-substituted phenyl-4,5-dihydroisoxazole derivatives; 4-hydroxyiminomethyl benzoic acid amide derivatives; 4-hydroxyiminomethyl-N,N-dimethyl benzoic acid amide; 4-hydroxyiminomethyl benzoyl piperidine derivatives; 4-hydroxyiminomethyl-N-bicycloalkyl benzoic acid amide derivatives; 6-(hydroxyiminomethyl) pyridine-2-carboxamide derivatives; haloalkenylbenzene derivatives, such as substituted 3,3,3-trifluoro-2-propenylbenzene derivatives; 4-(isoxazoliny)-benzamides, such as substituted 4-(5-(halomethyl)-5-phenyl-isoxazolin-3-yl)-benzamides; 4-(isoxazoliny)-benzothioamides, such as substituted 4-(5-(halomethyl)-5-phenyl-isoxazolin-3-yl)-benzothioamides; dihydroisoxazole compounds; and spirocyclic substituted isoxazolines.

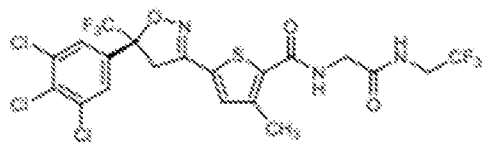
[0016] Isoxazolines of particular interest for controlling flea infestations in felines are afoxolaner (chemical names: (a) 1-Naphthalenecarboxamide, 4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-; or (b) 4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}-N-{2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl} naphthalene-1-carboxamide), fluralaner (chemical names: (a) Benzamide, 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-2-methyl-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-; or (b) 4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-2-methyl-N-{2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl} benzamide), sarolaner (chemical names: (a) Ethanone, 1-[5'-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]spiro[azetidine-3,1'(3'H)-isobenzofuran]-1-yl]-2-(methylsulfonyl)-; or (b) 1-[5'-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-3'-H-spiro[azetidine-3,1'-[2]benzofuran]-1-yl]-2-(methylsulfonyl)ethanone), lotilaner (chemical names: (a) 2-Thiophenecarboxamide, 5-[(5S)-4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-3-methyl-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-; or (b) 3-methyl-N-{2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}-5-[(5S)-5-(3,4,5-

trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]thiophene-2-carboxamide), esafoxolaner (chemical names: (a) 1-Naphthalenecarboxamide, 4-[(5S)-5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-; or (b) (S)-4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl)-1-naphthamide), tigolaner (chemical names: (a) Benzamide, 2-chloro-N-(1-cyanocyclopropyl)-5-[1'-methyl-3'-(1,1,2,2,2-pentafluoroethyl)-4'-(trifluoromethyl)[1,5'-bi-1H-pyrazol]-4-yl]-; or (b) 2-chloro-N-(1-cyanocyclopropyl)-5-[2'-methyl-5'-(pentafluoroethyl)-4'-(trifluoromethyl)-2'H-[1,3'-bipyrazol]-4-yl]benzamide), umifoxolaner (chemical names: (a) 1-Naphthalenecarboxamide, 4-[(5S)-5-[3-chloro-4-fluoro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-; or (b) 4-[(5S)-5-[3-chloro-4-fluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]naphthalene-1-carboxamide), modoflaner (chemical name: 6-fluoro-N-(2-fluoro-3-{[4-(heptafluoropropan-2-yl)-2-iodo-6-(trifluoromethyl)phenyl]carbonyl}phenyl)pyridine-3-carboxamide) and mivorilane/dihydroisoxazole (chemical names: (a) 4H-Cyclopenta[c]thiophene-1-carboxamide, 3-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-[(2,2-difluoroethyl)amino]-2-oxoethyl]-5,6-dihydro-; or (b) 3-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-N-[2-[(2,2-difluoroethyl)amino]-2-oxoethyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide).

[0017] More particularly, isoxazolines with the following structures are suitable for the methods and formulations of this disclosure:



[Mivorilane]



[0019]

[Lotilaner]

[0020] Isoxazolines can react to form salts that are also useful in the methods and formulations of this disclosure. The salts may be prepared using standard procedures for salt preparation. For example, suitable salts can be acid addition salts such as hydrohalogenated acids, e.g., hydrofluoric acid, hydrochloric acid, hydrobromic acid and hydroiodide, nitric acid, sulfuric acid, phosphoric acid, chloric acid, perchloric acid, salts of sulfonic acids, e.g., methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salts of carboxylic acids, e.g., valeric acids, formic acid, acetic acid, propionic acid, trifluoroacetic acid, fumaric acid, tartaric acid, oxalic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid, citric acid or salts of amino acids, e.g., glutamic acid and aspartic acid. Alternatively, metal salts are also suitable for the present disclosure. For example, alkali metal salts, e.g., lithium, sodium and potassium, and alkaline earth metals, e.g., calcium, barium and magnesium, or salts of aluminum.

[0021] The terms “isoxazoline” and “isoxazoline or a derivative thereof” as used herein refer to any isoxazoline, isoxazoline derivative, a salt thereof, a metabolite thereof, or a combination thereof.

[0022] Isoxazolines also provide advantages because they are very effective against fleas with post-treatment residual protection when orally administered in smaller, more frequent/chronic doses. Furthermore, isoxazolines have no known insecticidal cross-resistance to existing compounds. Thus, they are especially useful against flea populations on felines that have existing levels of resistance to currently used products. Isoxazolines, therefore, can be used in integrated pest management (IPM) programs to extend the life line of commonly used products where resistance is not well developed or has not yet developed.

[0023] Systemic efficacy (e.g., ingestion of blood containing isoxazolines by fleas) provides a different mode of exposure compared to topically applied formulations where

contact with the flea at the skin surface is the mode of exposure. The advantages of oral systemic treatments and killing of fleas from their ingestion of blood, compared to topical applications and contact killing, include:

- a) reduced exposure to the human applicator and children and objects in the feline's environment (e.g., flooring, carpets, furniture);
- b) no worry about loss from exposure of the feline to water (lakes, streams, bathing, etc.) or from loss due to rubbing;
- c) no concern about UV exposure and degradation;
- d) no problems with oxidation from oils on skin, etc.; and
- e) assurance that the entire dose is administered (compared to a topical application where some of the dose may drip off, rub off and/or remain in the dispensing tube immediately after treatment).

[0024] The formulations, or feeds, and methods of this disclosure may further include, in combination with the isoxazoline, one or more other active substances having therapeutic efficacy. Such active substances include agents efficacious against fleas. Active substances may include, for example, spinosyns, certain macrocyclic lactones, insect growth regulators (including chitin synthesis inhibitors, juvenile hormone analogs, and juvenile hormones), nitromethylenes, neonicotinoids, pyridines and pyrazoles or fiproles.

[0025] The methods of this disclosure are carried out by administering the isoxazoline to the feline in small, frequent doses. To facilitate routine dosing, the isoxazoline administration may be carried out using a feed or chew. A number of different feeds are envisioned, provided the manufacturing process(es) and feed compositions do not have deleterious effects related to efficacy, stability and safety on the isoxazoline and, if applicable, other active substances. For example, feeds and snacks, chews, treats or supplemental feeds in the broad categories of dry, semi-moist, canned-retorted feeds or fresh refrigerated feeds may be adapted for use with this disclosure. The feline receives a maintenance quantity of isoxazoline by consuming the feed product on a weekly, semi-weekly or daily basis.

[0026] By incorporating smaller doses of isoxazoline into an animal feed composition and administering it at an effective rate (most preferably daily), the blood level of

isoxazoline rises over time until it reaches an optimal steady state where it can be maintained by a daily or substantially daily dosage. By contrast, when isoxazoline is orally administered in larger doses at lower frequency, e.g., a single treatment of a large dose that is administered via “treat” once in a 30-day period, the level of isoxazoline in the blood spikes at the time of the dose and then falls until the next dose is administered. The administration of a large dose at low frequency means that the feline must consume more isoxazoline in each dose so that the blood level of isoxazoline does not fall below the necessary level for effective protection before the next dose.

[0027] All ratios, percentages, and parts discussed herein are “by weight” unless otherwise specified.

[0028] The term “controlling a flea infestation” refers to preventing, minimizing or eliminating an infestation by fleas on a feline.

[0029] The term “flea” refers to any member of the order Siphonaptera. The term “flea” includes the egg, larval, pupal, and adult stages of development.

[0030] The term “feline” refers to any member of the subfamily *Felidae*, which includes such species as the domestic cat, bobcats, wildcats, ocelots, members of the genus *lynx*, Pallas’s cat and cougars.

[0031] In carrying out the methods of this disclosure, a “feed” is an animal feed, snack, treat or other supplemental feed that may be administered daily or substantially daily. By using different forms of feed, e.g., kibble and treats, a pet owner may vary the feline’s meals and snacks from time to time while still conveniently administering a daily dose of isoxazoline.

[0032] The term “chew” refers to a treat that has flavor and aromatic properties that are appealing to a feline, but typically has no nutritional value. In carrying out the methods of this disclosure, a “feed” and/or a “chew” may be used interchangeably.

[0033] The term “effective time”, also referred to herein as “effective duration”, for the purposes of this disclosure includes at least the duration of feed administration needed to bring the level of isoxazoline in the feline’s blood to a sufficiently high level for controlling fleas, i.e., a “therapeutically effective” level. In some embodiments, the effective time may be as little as three days. In other instances, the effective time may be

seven days or fifteen days or longer. As discussed below, the effective time will vary based on how frequently the feed or isoxazoline is administered.

[0034] As just alluded, the “effective time” will vary as a function of the frequency at which the feed is administered. The term “effective frequency” as used herein means the number of feedings over a given time that produce a therapeutically effective concentration of isoxazoline in the feline’s blood. In all events, the term “effective frequency” as used herein contemplates multiple feedings including the isoxazoline per month. One of skill in the art will appreciate that the isoxazoline may be administered in a range of frequencies. For example, the isoxazoline may be administered at a frequency of daily, every other day, every third day, once per week or even at inconsistent time intervals.

[0035] Further, as discussed above, the effective frequency may affect the duration required to obtain a therapeutically effective level of isoxazoline in the feline’s blood. By way of example, if the feline were being fed an isoxazoline composition daily, the duration of feed administration required to achieve a therapeutically effective level of isoxazoline in the feline’s blood, and thus the “effective time”, would be comparatively less than if the feline were being fed the isoxazoline composition only once or twice per week.

[0036] Further, the effective frequency is influenced by the amount of the daily dose in mg/kg of body weight of the feline. Particularly, at slightly higher daily doses, missed doses have less of an impact on efficacy.

[0037] Further, the effective frequency is influenced by the duration of treatment. In the initial stages, e.g., before the amount of isoxazoline in the feline’s blood has reached a therapeutically effective level, the animal feed may need to be administered more often than would be necessary after a longer period of use, i.e., once a therapeutically effective level is obtained.

[0038] For purposes of this disclosure, “substantially daily” means a sufficiently regular basis such that the isoxazoline concentration in the feline’s blood rises to and remains at a therapeutically effective level. For example, the disclosed feed composition can preferably be fed to a feline every day indefinitely. However, as a practical matter, there are many reasons why days may be missed or skipped periodically. For example, the feline may be ill or the owner may run out of the medicated feed composition. The disclosed method is

robust enough that the feline has a significant level of protection from fleas even with occasional interruptions in daily feeding of the medicated animal feed composition. In carrying out the method of this disclosure, the term “substantially daily” includes at least 10 days per month, more preferably at least 15 days per month, still more preferably at least 20 days per month. All of these feeding frequencies, whether they be, e.g., three times per week, every other day or daily, fit under the umbrella of substantially daily provided that they promote the isoxazoline reaching and maintaining a therapeutically effective level of the isoxazoline in the feline’s blood.

[0039] The term “therapeutically effective” means that the dose or blood level of isoxazoline is sufficient to control the flea infestation better than if no drug were present. The isoxazoline may be present on its own or with one or more additional active substances. Preferably it controls the flea infestation at around at least 50% better than if no drug were present, and more preferably it controls the flea infestation at about at least 90% better than if no drug were present.

[0040] In carrying out the methods of this disclosure, an effective or therapeutically effective amount of an isoxazoline is administered orally to the feline. The term “effective amount” or “therapeutically effective amount” refers to the amount needed to control the flea infestation. As those in the art will understand, this amount will vary depending upon a number of factors. These factors include, for example, the type of feline being treated and its weight and general physical condition.

[0041] Isoxazolines vary in potency. Thus, the effective amount of isoxazoline must be calculated for each particular isoxazoline used in the method according to this disclosure. In general, the effective amount for a daily dose of an isoxazoline will be in the range of about 12.5%-90% of the approved label dose for said isoxazoline divided by length of the dosing/retreatment interval (e.g., the dosage divided by 30 for a product administered once per month). One of skill in the art will recognize that a higher dose of, e.g., 90%-200% of the approved label dose for said isoxazoline may be selected for reasons such as, but not limited to, manufacturability, ease of testing and analysis, etc. The particular dose selected may be sufficient to raise the feline’s blood concentration of said isoxazoline to a therapeutically effective level within about 7 days of substantially daily administrations,

more preferably within about 5 days of substantially daily administrations, most preferably within about 3 days of substantially daily administrations.

[0042] While this disclosure describes concentrations of isoxazoline in terms of feeds such as kibble, it also contemplates administration using other dosage forms, such as treats or chews. It is also contemplated that the isoxazoline may be administered by itself or in a tablet, liquid, gel or other suitable form for oral administration. One of skill in the art will appreciate that the concentration of isoxazoline will vary according to the particular dosage form. For example, where the animal feed is a treat, the concentration of isoxazoline in the treat will be greater than, e.g., the concentration of isoxazoline in a kibble. For example, if the daily dose of isoxazoline based on the weight of the feline is 20 mg, then a typical 5 g treat may contain about 0.4 percent isoxazoline (by weight). Since the amount of kibble consumed in a day is more than 5 g, the percent isoxazoline in kibble will be smaller.

[0043] For example, an effective amount of mivorilaner may be a dose of from about 0.06 to about 5 mg of mivorilaner/kg of body weight of the feline. More preferably, an effective amount of mivorilaner may be a dose of from about 0.1 to about 2.25 mg of mivorilaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.06 to about 1.875 mg/kg of body weight of the feline.

[0044] Animal feeds will typically contain from about 0.0002 to about 0.12 percent of mivorilaner (by weight) in the feed; preferably between about 0.0003 to about 0.075 percent of mivorilaner (by weight) in the feed; most preferably between about 0.0009 to about 0.045 percent of mivorilaner component or components (by weight) in the feed.

[0045] In another example, an effective amount of lotilaner may be a dose of from about 0.026 to about 2 mg of lotilaner/kg of body weight of the feline. More preferably, an effective amount of lotilaner may be a dose of from about 0.04 to about 0.9 mg of lotilaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.026 to about 0.75 mg/kg of body weight of the feline.

[0046] Animal feeds will typically contain from about 0.00006 to about 0.045 percent of lotilaner (by weight) in the feed; preferably between about 0.00012 to about 0.03 percent of lotilaner (by weight) in the feed; most preferably between about 0.0003 to about 0.0015 percent of lotilaner component or components (by weight) in the feed.

[0047] In another example, an effective amount of afoxolaner may be a dose of from about 0.003 to about 0.25 mg of afoxolaner/kg of body weight of the feline. More preferably, an effective amount of afoxolaner may be a dose of from about 0.0045 to about 0.113 mg of afoxolaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.003 to about 0.094 mg/kg of body weight of the feline.

[0048] Animal feeds will typically contain from about 0.0000075 to about 0.045 percent of afoxolaner (by weight) in the feed; preferably between about 0.000015 to about 0.03 percent of afoxolaner (by weight) in the feed; most preferably between about 0.000045 to about 0.0018 percent of afoxolaner component or components (by weight) in the feed.

[0049] In another example, an effective amount of sarolaner may be a dose of from about 0.0015 to about 0.12 mg of sarolaner/kg of body weight of the feline. More preferably, an effective amount of sarolaner may be a dose of from about 0.0024 to about 0.054 mg of sarolaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.0015 to about 0.045 mg/kg of body weight of the feline.

[0050] Animal feeds will typically contain from about 0.000003 to about 0.045 percent of sarolaner (by weight) in the feed; preferably between about 0.000006 to about 0.03 percent of sarolaner (by weight) in the feed; most preferably between about 0.00045 to about 0.0009 percent of sarolaner component or components (by weight) in the feed.

[0051] In another example, an effective amount of fluralaner may be a dose of from about 0.012 to about 1 mg of fluralaner/kg of body weight of the feline. More preferably, an effective amount of fluralaner may be a dose of from about 0.019 to about 0.45 mg of fluralaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.012 to about 0.375 mg/kg of body weight of the feline.

[0052] Animal feeds will typically contain from about 0.00003 to about 0.045 percent of fluralaner (by weight) in the feed; preferably between about 0.00006 to about 0.03 percent of fluralaner (by weight) in the feed; most preferably between about 0.00015 to about 0.009 percent of fluralaner component or components (by weight) in the feed.

[0053] In another example, an effective amount of umifoxolaner may be a dose of from about 0.0015 to about 0.12 mg of umifoxolaner/kg of body weight of the feline. More preferably, an effective amount of umifoxolaner may be a dose of from about 0.0025 to

about 0.06 mg of umifoxolaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.0015 to about 0.047 mg/kg of body weight of the feline.

[0054] Animal feeds will typically contain from about 0.000003 to about 0.045 percent of umifoxolaner (by weight) in the feed; preferably between about 0.0000075 to about 0.03 percent of umifoxolaner (by weight) in the feed; most preferably between about 0.000015 to about 0.0009 percent of umifoxolaner component or components (by weight) in the feed.

[0055] In another example, an effective amount of esafoxolaner may be a dose of from about 0.0015 to about 0.12 mg of esafoxolaner/kg of body weight of the feline. More preferably, an effective amount of esafoxolaner may be a dose of from about 0.0025 to about 0.06 mg of esafoxolaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.0015 to about 0.047 mg/kg of body weight of the feline.

[0056] Animal feeds will typically contain from about 0.000003 to about 0.045 percent of esafoxolaner (by weight) in the feed; preferably between about 0.0000075 to about 0.03 percent of esafoxolaner (by weight) in the feed; most preferably between about 0.000015 to about 0.0009 percent of esafoxolaner component or components (by weight) in the feed.

[0057] In another example, an effective amount of tigolaner may be a dose of from about 0.0015 to about 0.12 mg of tigolaner/kg of body weight of the feline. More preferably, an effective amount of tigolaner may be a dose of from about 0.0025 to about 0.06 mg of tigolaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.0015 to about 0.047 mg/kg of body weight of the feline.

[0058] Animal feeds will typically contain from about 0.000003 to about 0.045 percent of tigolaner (by weight) in the feed; preferably between about 0.0000075 to about 0.03 percent of tigolaner (by weight) in the feed; most preferably between about 0.000015 to about 0.0009 percent of tigolaner component or components (by weight) in the feed.

[0059] In another example, an effective amount of modolaner may be a dose of from about 0.003 to about 0.25 mg of modolaner/kg of body weight of the feline. More preferably, an effective amount of modolaner may be a dose of from about 0.0045 to about 0.113 mg of modolaner/kg of body weight of the feline. More commonly, the effective amount is from about 0.003 to about 0.094 mg/kg of body weight of the feline.

[0060] Animal feeds will typically contain from about 0.0000075 to about 0.045 percent of modolaner (by weight) in the feed; preferably between about 0.000015 to about 0.03 percent of modolaner (by weight) in the feed; most preferably between about 0.000045 to about 0.0018 percent of modolaner component or components (by weight) in the feed.

[0061] In one aspect, this disclosure relates to a method of controlling a flea infestation in a feline by administering a systemically active oral composition including isoxazoline and animal feed or a chew at least once per week, more preferably three times per week, most preferably substantially daily.

[0062] In another aspect, this disclosure relates to a systemically active oral composition that includes an isoxazoline and animal feed or a chew.

[0063] This disclosure also relates to the use of an isoxazoline for the manufacture of an animal feed or a chew for controlling a flea infestation on a feline.

[0064] This disclosure also relates to a method of controlling a flea infestation on a feline for a prolonged time, comprising orally administering daily or substantially daily doses of an effective amount of an isoxazoline to the feline. This method is especially useful for controlling fleas on a feline for a prolonged time comprising orally administering substantially daily doses of an effective amount of an isoxazoline to the feline.

[0065] An aspect of this disclosure is the oral administration of an amount of isoxazoline which is, in and of itself, ineffective or sub-optimal for controlling a flea infestation in a feline when administered in a single dose once per month, but over time with repeated administrations, as described herein, results in efficacious control of flea infestations. Ineffective or sub-optimal means that a single dosing, as well as several dosings, results in less than a 50% reduction in the flea infestation, including no, or substantially no, reduction, as compared to no drug administration at all. This reflects the chronic, rather than acute, administration aspect disclosed herein.

[0066] Embodiment 1: A method of controlling a flea infestation in a feline in need thereof, comprising orally administering to said feline an effective amount of an isoxazoline for an effective time at a frequency of at least four times per month.

[0067] Embodiment 2: The method of embodiment 1, wherein said feline is a domestic cat.

[0068] Embodiment 3: The method of any of embodiment 1 or 2, wherein said isoxazoline is mivorilaner, or a salt thereof.

[0069] Embodiment 4: The method of embodiment 3, wherein said mivorilaner is provided in a feed in an amount selected from the group consisting of between about 0.0002 to about 0.12 percent by weight of the feed and between about 0.0003 to about 0.075 percent by weight of the feed.

[0070] Embodiment 5: The method of any of embodiments 3-4, wherein said mivorilaner is administered to said feline in an amount selected from the group consisting of between about 0.06 mg/kg and about 5 mg/kg of body weight of said feline and between about 0.1 mg/kg and about 2.25 mg/kg of body weight of said feline.

[0071] Embodiment 6: The method of any of embodiments 3-5, wherein said administration provides a concentration of mivorilaner of more than about 60 ng/mL and less than about 18,000 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0072] Embodiment 7: The method of any of embodiment 1 or 2, wherein said isoxazoline is fluralaner, or a salt thereof.

[0073] Embodiment 8: The method of embodiment 7, wherein said fluralaner is provided in a feed in an amount selected from the group consisting of between about 0.00003 to about 0.045 percent by weight of the feed and between about 0.00006 to about 0.03 percent by weight of the feed.

[0074] Embodiment 9: The method of any of embodiments 7-8, wherein said fluralaner is administered to said feline in an amount selected from the group consisting of between about 0.012 mg/kg and about 1 mg/kg of body weight of said feline, and between about 0.019 mg/kg and about 0.45 mg/kg of body weight of said feline.

[0075] Embodiment 10: The method of any of embodiments 7-9, wherein said administration provides a concentration of fluralaner of more than about 6 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0076] Embodiment 11: The method of any of embodiment 1 or 2, wherein said isoxazoline is sarolaner, or a salt thereof.

[0077] Embodiment 12: The method of embodiment 12, wherein said sarolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed, and between about 0.000006 to about 0.03 percent by weight of the feed.

[0078] Embodiment 13: The method of any of embodiments 11-12, wherein said sarolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline, and between about 0.0024 mg/kg and about 0.054 mg/kg of body weight of said feline.

[0079] Embodiment 14: The method of any of embodiments 11-13, wherein said administration provides a concentration of sarolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0080] Embodiment 15: The method of any of embodiment 1 or 2, wherein said isoxazoline is afoxolaner, or a salt thereof.

[0081] Embodiment 16: The method of embodiment 15, wherein said afoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of they feed, and between about 0.000015 to about 0.03 percent by weight of the feed.

[0082] Embodiment 17: The method of any of embodiments 15-16, wherein said afoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.

[0083] Embodiment 18: The method of any of embodiments 15-17, wherein said administration provides a concentration of afoxolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0084] Embodiment 19: The method of any of embodiment 1 or 2, wherein said isoxazoline is lotilaner, or a salt thereof.

[0085] Embodiment 20: The method of embodiment 19, wherein said lotilaner is provided in a feed in an amount selected from the group consisting of between about

0.00006 to about 0.045 percent by weight of the feed and between about 0.00012 to about 0.03 percent by weight of the feed.

[0086] Embodiment 21: The method of any of embodiments 19-20, wherein said lotilaner is administered to said feline in an amount selected from the group consisting of between about 0.026 mg/kg and about 2 mg/kg of body weight of said feline and between about 0.04 mg/kg and about 0.9 mg/kg of body weight of said feline.

[0087] Embodiment 22: The method of any of embodiments 19-21, wherein said administration provides a concentration of lotilaner of more than about 12 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0088] Embodiment 23: The method of any of embodiments 1-22, wherein said isoxazoline is administered as a component of a feed.

[0089] Embodiment 24: The method of embodiment 23, wherein said feed is dry cat food.

[0090] Embodiment 25: The method of embodiment 23, wherein said feed is wet cat food.

[0091] Embodiment 26: The method of any of embodiments 1-22, wherein said isoxazoline is administered as a component of a chew.

[0092] Embodiment 27: The method of any of embodiments 1-26, wherein said frequency is selected from the group consisting of at least 3 times per week, substantially daily and daily.

[0093] Embodiment 28: The method of any of embodiments 1-27, wherein said effective time comprises administering the isoxazoline for a period of time selected from the group consisting of at least one week and at least two weeks.

[0094] Embodiment 29: The method of any of embodiments 1-28, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood within a period of time selected from the group consisting of one week of the first administration of said isoxazoline and two days of the first administration of said isoxazoline.

[0095] Embodiment 30: The method of any of embodiments 1-29, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood for a period of time selected from the group consisting of at least 30 days, at least 60 days, at least 90 days, at least 180 days and at least 365 days.

[0096] Embodiment 31: The method of any of embodiments 1-30, wherein said isoxazoline is administered for a period of time selected from the group consisting of at least 15 out of 30 days, and at least 20 out of 30 days.

[0097] Embodiment 32: The method of any of embodiments 1-31, wherein said isoxazoline is administered as a component of a feed that comprises one or more other active substances.

[0098] Embodiment 33: The method of any of embodiments 1-32, further comprising discontinuing the administration of the isoxazoline for a period of time selected from the group consisting of at least 3 days and at least 7 days, wherein the feline's blood concentration of isoxazoline is maintained at a therapeutically effective level.

[0099] Embodiment 34: The method of embodiment 33, further comprising resuming the administration of the isoxazoline after the discontinuing of the administration of the isoxazoline and thereby maintaining the feline's blood concentration of isoxazoline at the therapeutically effective level.

[00100] Embodiment 35: An isoxazoline for use in controlling fleas on a feline in need thereof, said isoxazoline, or salt thereof, being administered in an effective amount to said feline for an effective time at a frequency of at least 4 times per month.

[00101] Embodiment 36: The isoxazoline of embodiment 35, wherein said feline is a domestic cat.

[0102] Embodiment 37: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is mivorilaner, or a salt thereof.

[0103] Embodiment 38: The isoxazoline of embodiment 37, wherein said mivorilaner is provided in a feed in an amount selected from the group consisting of between about 0.0002 to about 0.12 percent by weight of the feed and between about 0.0003 to about 0.075 percent by weight of the feed.

[0104] Embodiment 39: The isoxazoline of any of embodiments 37-38, wherein said mivorilaner is administered to said feline in an amount selected from the group consisting of between about 0.06 mg/kg and about 5 mg/kg of body weight of said feline and between about 0.1 mg/kg and about 2.25 mg/kg of body weight of said feline.

[0105] Embodiment 40: The isoxazoline of any of embodiments 37-39, wherein said administration provides a concentration of mivorilaner of more than about 60 ng/mL and less than about 18,000 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0106] Embodiment 41: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is fluralaner, or a salt thereof.

[0107] Embodiment 42: The isoxazoline of embodiment 41, wherein said fluralaner is provided in a feed in an amount selected from the group consisting of between about 0.00003 to about 0.045 percent by weight of the feed and about 0.00006 to about 0.03 percent by weight of the feed.

[0108] Embodiment 43: The isoxazoline of any of embodiments 41-42, wherein said fluralaner is administered to said feline in an amount selected from the group consisting of between about 0.012 mg/kg and about 1 mg/kg of body weight of said feline and between about 0.019 mg/kg and about 0.45 mg/kg of body weight of said feline.

[0109] Embodiment 44: The isoxazoline of any of embodiments 41-43, wherein said administration provides a concentration of fluralaner of more than about 6 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0110] Embodiment 45: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is sarolaner, or a salt thereof.

[0111] Embodiment 46: The isoxazoline of embodiment 45, wherein said sarolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.000006 to about 0.03 percent by weight of the feed.

[0112] Embodiment 47: The isoxazoline of any of embodiments 45-46, wherein said sarolaner is administered to said feline in an amount selected from the group consisting of

between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0024 mg/kg and about 0.054 mg/kg of body weight of said feline.

[0113] Embodiment 48: The isoxazoline of any of embodiments 45-47, wherein said administration provides a concentration of sarolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0114] Embodiment 49: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is afoxolaner, or a salt thereof.

[0115] Embodiment 50: The isoxazoline of embodiment 49, wherein said afoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of the feed and between about 0.000015 to about 0.03 percent by weight of the feed.

[0116] Embodiment 51: The isoxazoline of any of embodiments 49-50, wherein said afoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.

[0117] Embodiment 52: The isoxazoline of any of embodiments 49-51, wherein said administration provides a concentration of afoxolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0118] Embodiment 53: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is lotilaner, or a salt thereof.

[0119] Embodiment 54: The isoxazoline of embodiment 53, wherein said lotilaner is provided in a feed in an amount selected from the group consisting of between about 0.00006 to about 0.045 percent by weight of the feed and between about 0.00012 to about 0.03 percent by weight of the feed.

[0120] Embodiment 55: The isoxazoline of any of embodiments 53-54, wherein said lotilaner is administered to said feline in an amount selected from the group consisting of between about 0.026 mg/kg and about 2 mg/kg of body weight of said feline and between about 0.04 mg/kg and about 0.9 mg/kg of body weight of said feline.

[0121] Embodiment 56: The isoxazoline of any of embodiments 53-55, wherein said administration provides a concentration of lotilaner of more than about 12 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0122] Embodiment 57: The isoxazoline of any of embodiments 35-56, wherein said isoxazoline is administered as a component of a feed.

[0123] Embodiment 58: The isoxazoline of embodiment 57, wherein said feed is dry cat food.

[0124] Embodiment 59: The isoxazoline of embodiment 57, wherein said feed is wet cat food.

[0125] Embodiment 60: The isoxazoline of any of embodiments 35-56, wherein said isoxazoline is administered as a component of a chew

[0126] Embodiment 61: The isoxazoline of any of embodiments 35-60, wherein said feeding frequency is selected from the group consisting of at least 3 times per week, substantially daily and daily.

[0127] Embodiment 62: The isoxazoline of any of embodiments 35-61, wherein said effective time comprises administering the isoxazoline for a period of time selected from the group consisting of at least one week and at least two weeks.

[0128] Embodiment 63: The isoxazoline of any of embodiments 35-62, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood within a period of time selected from the group consisting of one week of the first administration of said isoxazoline and two days of the first administration of said isoxazoline.

[0129] Embodiment 64: The isoxazoline of any of embodiments 35-63, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood for a period of time selected from the group consisting of at least 30 days, at least 60 days, at least 90 days, at least 180 days and at least 365 days.

[0130] Embodiment 65: The isoxazoline of any of embodiments 35-64, wherein said isoxazoline is administered at a frequency selected from the group consisting of at least 15 out of 30 days and at least 20 out of 30 days.

[0131] Embodiment 66: The isoxazoline of any of embodiments 35-65, wherein said isoxazoline is administered as a component of a feed that comprises one or more other active substances.

[0132] Embodiment 67: The isoxazoline of any of embodiments 35-66, further comprising discontinuing the administration of the isoxazoline for a period of time selected from the group consisting of at least 3 days and at least 7 days, wherein the feline's blood concentration of isoxazoline is maintained at a therapeutically effective level.

[0133] Embodiment 68: The isoxazoline of embodiment 67, further comprising resuming the administration of the isoxazoline after the discontinuing of the administration of the isoxazoline and thereby maintaining the feline's blood concentration of isoxazoline at the therapeutically effective level.

[0134] Embodiment 69: A feed or chew for controlling fleas in a feline, comprising an effective amount of an isoxazoline when administered to said feline for an effective time at a frequency of at least four times per month.

[0135] Embodiment 70: The feed or chew of embodiment 69, wherein said feline is a domestic cat.

[0136] Embodiment 71: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is mivorilane, or a salt thereof.

[0137] Embodiment 72: The feed or chew of embodiment 71, wherein said mivorilane is provided in a feed in an amount selected from the group consisting of between about 0.0002 to about 0.12 percent by weight of the feed and between about 0.0003 to about 0.075 percent by weight of the feed.

[0138] Embodiment 73: The feed or chew of any of embodiments 71-72, wherein said mivorilane is administered to said feline in an amount selected from the group consisting of between about 0.06 mg/kg and about 5 mg/kg of body weight of said feline and between about 1 mg/kg and about 2.25 mg/kg of body weight of said feline.

[0139] Embodiment 74: The feed or chew of any of embodiments 71-73, wherein said administration provides a concentration of mivorilane of more than about 60 ng/mL and less than about 18,000 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0140] Embodiment 75: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is fluralaner, or a salt thereof.

[0141] Embodiment 76: The feed or chew of embodiment 75, wherein said fluralaner is provided in a feed in an amount selected from the group consisting of between about 0.00003 to about 0.045 percent by weight of the feed and between about 0.00006 to about 0.03 percent by weight of the feed.

[0142] Embodiment 77: The feed or chew of any of embodiments 75-76, wherein said fluralaner is administered to said feline in an amount selected from the group consisting of between about 0.012 mg/kg and about 1 mg/kg of body weight of said feline and between about 0.019 mg/kg and about 0.45 mg/kg of body weight of said feline.

[0143] Embodiment 78: The feed or chew of any of embodiments 75-77, wherein said administration provides a concentration of fluralaner of more than about 6 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0144] Embodiment 79: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is sarolaner, or a salt thereof.

[0145] Embodiment 80: The feed or chew of embodiment 79, wherein said sarolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.000006 to about 0.03 percent by weight of the feed.

[0146] Embodiment 81: The feed or chew of any of embodiments 79-80, wherein said sarolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0024 mg/kg and about 0.054 mg/kg of body weight of said feline.

[0147] Embodiment 82: The feed or chew of any of embodiments 79-81, wherein said administration provides a concentration of sarolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0148] Embodiment 83: The feed or chew of any of embodiment 69 or 70 wherein said isoxazoline is afoxolaner, or a salt thereof.

[0149] Embodiment 84: The feed or chew of embodiment 83, wherein said afoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of the feed and between about 0.000015 to about 0.03 percent by weight of the feed.

[0150] Embodiment 85: The feed or chew of any of embodiments 83-84, wherein said afoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.

[0151] Embodiment 86: The feed or chew of any of embodiments 83-85, wherein said administration provides a concentration of afoxolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0152] Embodiment 87: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is lotilaner, or a salt thereof.

[0153] Embodiment 88: The feed or chew of embodiment 87, wherein said lotilaner is provided in a feed in an amount selected from the group consisting of between about 0.00006 to about 0.045 percent by weight of the feed and between about 0.00012 to about 0.03 percent by weight of the feed.

[0154] Embodiment 89: The feed or chew of any of embodiments 87-88, wherein said lotilaner is administered to said feline in an amount selected from the group consisting of between about 0.026 mg/kg and about 2 mg/kg of body weight of said feline and between about 0.04 mg/kg and about 0.9 mg/kg of body weight of said feline.

[0155] Embodiment 90: The feed or chew of any of embodiments 87-89, wherein said administration provides a concentration of lotilaner of more than about 12 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0156] Embodiment 91: The feed or chew of any of embodiments 69-90, wherein said feed is dry cat food.

[0157] Embodiment 92: The feed or chew of any of embodiments 69-90, wherein said feed is wet cat food.

[0158] Embodiment 93: The feed or chew of any of embodiments 69-92, wherein said frequency is selected from the group consisting of at least 3 times per week, substantially daily and daily.

[0159] Embodiment 94: The feed or chew of any of embodiments 69-93, wherein said effective time comprises administering the feed or chew for a period of time selected from the group consisting of at least one week and at least two weeks.

[0160] Embodiment 95: The feed or chew of any of embodiments 69-94, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood within a period of time selected from the group consisting of one week of the first administration of said feed or chew and two days of the first administration of said feed or chew.

[0161] Embodiment 96: The feed or chew of any of embodiments 69-95, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood for a period of time selected from the group consisting of at least 30 days, at least 60 days, at least 90 days, at least 180 days and at least 365 days.

[0162] Embodiment 97: The feed or chew of any of embodiments 69-96, wherein said feed or chew is administered at a frequency selected from the group consisting of at least 15 out of 30 days and at least 20 out of 30 days.

[0163] Embodiment 98: The feed or chew of any of embodiments 69-97, wherein said feed or chew comprises one or more other active substances.

[0164] Embodiment 99: The feed or chew of any of embodiments 69-98, further comprising discontinuing the administration of the feed or chew for a period of time selected from the group consisting of at least 3 days and at least 7 days, wherein the feline's blood concentration of isoxazoline is maintained at a therapeutically effective level.

[0165] Embodiment 100: The feed or chew of embodiment 99, further comprising resuming the administration of the feed or chew after the discontinuing of the administration of the feed or chew and thereby maintaining the feline's blood concentration of isoxazoline at the therapeutically effective level.

[0166] Embodiment 101: The method of any of embodiment 1 or 2, wherein said isoxazoline is umifoxolaner, or a salt thereof.

[0167] Embodiment 102: The method of embodiment 101, wherein said umifoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0168] Embodiment 103: The method of any of embodiments 101-102, wherein said umifoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0169] Embodiment 104: The method of any of embodiments 101-103, wherein said administration provides a concentration of umifoxolaner of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0170] Embodiment 105: The method of any of embodiment 1 or 2, wherein said isoxazoline is esafoxolaner, or a salt thereof.

[0171] Embodiment 106: The method of embodiment 105, wherein said esafoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0172] Embodiment 107: The method of any of embodiments 105-106, wherein said esafoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0173] Embodiment 108: The method of any of embodiments 105-107, wherein said administration provides a concentration of esafoxolaner of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0174] Embodiment 109: The method of any of embodiment 1 or 2, wherein said isoxazoline is tigolaner, or a salt thereof.

[0175] Embodiment 110: The method of embodiment 109, wherein said tigolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0176] Embodiment 111: The method of any of embodiments 109-110, wherein said tigolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0177] Embodiment 112: The method of any of embodiments 109-111, wherein said administration provides a concentration of tigolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0178] Embodiment 113: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is umifoxolaner, or a salt thereof.

[0179] Embodiment 114: The isoxazoline of embodiment 113, wherein said umifoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0180] Embodiment 115: The isoxazoline of any of embodiments 113-114, wherein said umifoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0181] Embodiment 116: The isoxazoline of any of embodiments 113-115, wherein said administration provides a concentration of umifoxolaner of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0182] Embodiment 117: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is esafoxolaner, or a salt thereof.

[0183] Embodiment 118: The isoxazoline of embodiment 117, wherein said esafoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.45 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0184] Embodiment 119: The isoxazoline of any of embodiments 117-118, wherein said esafoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0185] Embodiment 120: The isoxazoline of any of embodiments 117-119, wherein said administration provides a concentration of esafoxolaner of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0186] Embodiment 121: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is tigolaner, or a salt thereof.

[0187] Embodiment 122: The isoxazoline of embodiment 121, wherein said tigolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0188] Embodiment 123: The isoxazoline of any of embodiments 121-122, wherein said tigolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0189] Embodiment 124: The isoxazoline of any of embodiments 121-123, wherein said administration provides a concentration of tigolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0190] Embodiment 125: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is umifoxolaner, or a salt thereof.

[0191] Embodiment 126: The feed or chew of embodiment 125, wherein said umifoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0192] Embodiment 127: The feed or chew of any of embodiments 125-126, wherein said umifoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0193] Embodiment 128: The feed or chew of any of embodiments 125-127, wherein said administration provides a concentration of umifoxolaner of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0194] Embodiment 129: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is esafoxolaner, or a salt thereof.

[0195] Embodiment 130: The feed or chew of embodiment 129, wherein said esafoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0196] Embodiment 131: The feed or chew of any of embodiments 129-130, wherein said esafoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0197] Embodiment 132: The feed or chew of any of embodiments 129-131, wherein said administration provides a concentration of esafoxolaner of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0198] Embodiment 133: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is tigolaner, or a salt thereof.

[0199] Embodiment 134: The feed or chew of embodiment 133, wherein said tigolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed and between about 0.0000075 to about 0.03 percent by weight of the feed.

[0200] Embodiment 135: The feed or chew of any of embodiments 133-134, wherein said tigolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline and between about 0.0025 mg/kg and about 0.06 mg/kg of body weight of said feline.

[0201] Embodiment 136: The feed or chew of any of embodiments 133-135, wherein said administration provides a concentration of tigolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0202] Embodiment 137: The method of any of embodiment 1 or 2, wherein said isoxazoline is modolaner, or a salt thereof.

[0203] Embodiment 138: The method of embodiment 137, wherein said modolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of the feed and between about 0.000015 to about 0.03 percent by weight of the feed.

[0204] Embodiment 139: The method of any of embodiments 137-138, wherein said modolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.

[0205] Embodiment 140: The method of any of embodiments 137-139, wherein said administration provides a concentration of modolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0206] Embodiment 141: The isoxazoline of any of embodiment 35 or 36, wherein said isoxazoline is modolaner, or a salt thereof.

[0207] Embodiment 142: The isoxazoline of embodiment 141, wherein said modolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of the feed and between about 0.000015 to about 0.03 percent by weight of the feed.

[0208] Embodiment 143: The isoxazoline of any of embodiments 141-142, wherein said modolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.

[0209] Embodiment 144: The isoxazoline of any of embodiments 141-143, wherein said administration provides a concentration of modolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0210] Embodiment 145: The feed or chew of any of embodiment 69 or 70, wherein said isoxazoline is modolaner, or a salt thereof.

[0211] Embodiment 146: The feed or chew of embodiment 145, wherein said modolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of the feed and between about 0.000015 to about 0.03 percent by weight of the feed.

[0212] Embodiment 147: The feed or chew of any of embodiments 145-146, wherein said modolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.

[0213] Embodiment 148: The feed or chew of any of embodiments 145-147, wherein said administration provides a concentration of modolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

[0214] In an aspect of any of the above embodiments, administration provides a therapeutically effective concentration of the particular isoxazoline in said feline's blood for at least 30 days. The precise concentration may vary according to the particular

isoxazoline. For example, administration of mivorilaner provides a concentration of isoxazoline of more than about 60 ng/mL and less than about 18,000 ng/mL in said feline's blood for at least 30 days. More preferably, administration of mivorilaner provides a concentration of isoxazoline of more than about 60 ng/mL and less than about 3750 ng/mL in said feline's blood for at least 30 days. In another example, afoxolaner provides a concentration of isoxazoline of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for at least 30 days. More preferably, afoxolaner provides a concentration of isoxazoline of more than about 3 ng/mL and less than about 900 ng/mL in said feline's blood for at least 30 days. In another example, fluralaner provides a concentration of isoxazoline of more than about 6 ng/mL and less than about 4500 ng/mL in said feline's blood for at least 30 days. More preferably, fluralaner provides a concentration of isoxazoline of more than about 6 ng/mL and less than about 2250 ng/mL in said feline's blood for at least 30 days. In another example, sarolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for at least 30 days. More preferably, sarolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 600 ng/mL in said feline's blood for at least 30 days. In another example, lotilaner provides a concentration of isoxazoline of more than about 12 ng/mL and less than about 4500 ng/mL in said feline's blood for at least 30 days. More preferably, lotilaner provides a concentration of isoxazoline of more than about 12 ng/mL and less than about 3000 ng/mL in said feline's blood for at least 30 days. In another example, tigolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for at least 30 days. More preferably, tigolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 450 ng/mL in said feline's blood for at least 30 days. In another example, umifoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for at least 30 days. More preferably, umifoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 450 ng/mL in said feline's blood for at least 30 days. In another example, esafoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 900 ng/mL

in said feline's blood for at least 30 days. More preferably, esafoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 450 ng/mL in said feline's blood for at least 30 days.

[0215] In an aspect of any of the above embodiments, administration provides a therapeutically effective concentration of the particular isoxazoline in said feline's blood for at least 365 days. The precise concentration may vary according to the particular isoxazoline. For example, administration of mivorilane provides a concentration of isoxazoline of more than about 60 ng/mL and less than about 18,000 ng/mL in said feline's blood for at least 365 days. More preferably, administration of mivorilane provides a concentration of isoxazoline of more than about 60 ng/mL and less than about 3750 ng/mL in said feline's blood for at least 365 days. In another example, afoxolaner provides a concentration of isoxazoline of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for at least 365 days. More preferably, afoxolaner provides a concentration of isoxazoline of more than about 3 ng/mL and less than about 900 ng/mL in said feline's blood for at least 365 days. In another example, fluralaner provides a concentration of isoxazoline of more than about 6 ng/mL and less than about 4500 ng/mL in said feline's blood for at least 365 days. More preferably, fluralaner provides a concentration of isoxazoline of more than about 6 ng/mL and less than about 2250 ng/mL in said feline's blood for at least 365 days. In another example, sarolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for at least 365 days. More preferably, sarolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 600 ng/mL in said feline's blood for at least 365 days. In another example, lotilaner provides a concentration of isoxazoline of more than about 12 ng/mL and less than about 4500 ng/mL in said feline's blood for at least 365 days. More preferably, lotilaner provides a concentration of isoxazoline of more than about 12 ng/mL and less than about 3000 ng/mL in said feline's blood for at least 365 days. In another example, tigolane provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for at least 365 days. More preferably, tigolane provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 450 ng/mL

in said feline's blood for at least 365 days. In another example, umifoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for at least 365 days. More preferably, umifoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 450 ng/mL in said feline's blood for at least 365 days. In another example, esafoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 900 ng/mL in said feline's blood for at least 365 days. More preferably, esafoxolaner provides a concentration of isoxazoline of more than about 1.5 ng/mL and less than about 450 ng/mL in said feline's blood for at least 365 days.

EXAMPLES

[0216] The following examples illustrate the methods of this disclosure. It shall be understood that two of the following three examples are prophetic examples, as that term is understood to one of skill in the art. In other words, two of the three examples that follow are based on predicted results rather than actual experiments. However, the predicted results are based on experiments done with other animals and are believed to be sufficient for one of skill in the art to practice this disclosure.

EXAMPLE 1

[0217] Efficacy of Isoxazoline Administered *per os*, i.e. by mouth, to Cats for the Treatment and Control of *Ctenocephalides felis*

[0218] Methods: A pool of 14 cats are to be preliminarily infested with ~ 100 unfed adult *C. felis* in order to identify cats that can suitably sustain a reliable infestation rate, defined as approximately 50% fleas being live at the end of a 48-hour period. The 12 cats with the highest live flea counts are to be selected for inclusion in the study. The cats are to be randomized and divided into a control group and a treatment group with 6 cats per group.

[0219] The cats are to be housed individually during the study period and are to be fed a commercial dry cat food ration with *ad libitum* access to water.

[0220] Each cat in the isoxazoline treatment group is to receive by mouth a liquid formulation of isoxazoline. The dosage of 1.125 mg/kg of isoxazoline is to be administered to the cats on each of days 0-29.

[0221] Cats in the control group are not to receive isoxazoline or any other flea control treatment. Each cat in the treatment group is to be offered its daily ration (dry food) and the individual doses of liquid formulation are to be administered after the individual cat has eaten at least 25% of its total daily ration. After receiving the dose of isoxazoline, the cats are to be allowed to continue eating. This mimics incorporating the isoxazoline in feed. Each cat in the treatment group and the control group is to be experimentally infested with 100 unfed adult fleas on test days -1, 5, 12, 20 and 35. Comb counts for live adult fleas are to be conducted on days 2, 7, 14, 22 and 37. The day 37 flea comb counts will be after an 8-day wash out period, approximately.

[0222] The expected result in such a study performed with various isoxazolines, for example, mivorilaner, is at least 95 percent reduction in live flea counts over the control group.

[0223] Using the same study method as described above, blood is to be drawn at 72, 168, 336, 504, 720 and 888 hours after the initial dose of isoxazoline is administered. The average concentration of isoxazoline in the blood can then be determined.

[0224] The average plasma concentration of isoxazoline in a feline's blood in such a study performed with various isoxazolines, for example, mivorilaner, at the 1.125 mg/kg

dosage level is expected to range between about 1011 ng/mL at 72 hours and about 4088 at 504 hours. Further, the average concentration is expected to decline to about 3025 ng/mL by 888 hours, approximately 8 days after the final dose is administered.

EXAMPLE 2

[0225] Efficacy of Various Doses of Isoxazoline Administered *per os*, i.e. by mouth, to Cats for the Treatment and Control of *Ctenocephalides felis*

[0226] Methods: A pool of 46 cats are to be preliminarily infested with ~ 100 unfed adult *C. felis* in order to identify cats that can suitably sustain a reliable infestation rate, defined as approximately 50% of fleas being live at the end of a 48-hour period. The 40 cats with the highest flea counts are to be selected for inclusion in the study. The cats are to be randomly assigned to a single control group and 4 treatment groups with 8 cats per group.

[0227] The cats are to be housed individually during the study period and are to be fed a commercial dry cat food ration with *ad libitum* access to water.

[0228] Each cat in a treatment group (test groups 2-5) is to receive by mouth a liquid formulation of isoxazoline. The dosage is to be administered to the cats on each of days 0-29 according to test groups in the table below:

Treatment Group	Daily Dose (mg/kg)	Route	Fed/Fasted State
1 (control)	0 mg/kg	n/a	n/a
2	0.1875 mg/kg daily for 29 consecutive days	Oral	Fed
3	0.375 mg/kg daily for 29 consecutive days	Oral	Fed
4	0.75 mg/kg daily for 29 consecutive days	Oral	Fed
5	1.5 mg/kg daily for 29 consecutive days	Oral	Fed

[0229] Cats in the control group are not to receive isoxazoline or any other flea control treatment. Each cat in each of the treatment groups 2 to 5 is to be offered its daily ration

(dry food) and the individual doses of liquid formulation are to be administered after the individual cat has eaten at least 25% of its total daily ration. After receiving the dose of isoxazoline, the cats are to be allowed to continue eating. This mimics incorporating the isoxazoline in feed. Each cat in the treatment group and the control group is to be experimentally infested with 100 unfed adult fleas on test days -1, 5, 12, 19, 28 and 35. Comb counts for live adult fleas are to be conducted on days 2, 7, 14, 21, 30 and 37. The day 37 flea comb counts will be after an 8-day wash out period, approximately.

[0230] The dosage level for treatment group 2 is expected to achieve 95% efficacy within 14 days. The dosage level for treatment group 3 is expected to achieve 95% efficacy within 7 days. The dosage levels for treatment groups 4 and 5 are expected to achieve 95% efficacy within 2 days.

[0231] Using the same study method as described above, blood is to be drawn at 0, 72, 120, 168, 336, 504, 720 and 888 hours after the initial dose of isoxazoline is administered. The average concentration of isoxazoline in the blood for different dosage levels can then be determined.

[0232] The average plasma concentration of isoxazoline in a feline's blood with substantially daily dosing at the dosage level for test group 2 would be expected to range between about 203 ng/ml at 72 hours and about 630 ng/ml at 720 hours. For test group 3, the expected range would be between about 424 ng/ml at 72 hours and about 1524 ng/ml at 720 hours. For test group 4, the expected range would be between about 711 ng/ml at 72 hours and about 2811 ng/ml at 720 hours. For test group 5, the expected range would be between about 1427 ng/ml at 72 hours and about 5635 ng/ml at 720 hours. At 888 hours, approximately 8 days after the final daily dose of isoxazoline on Day 29, the expected average plasma concentration of isoxazoline in a feline's blood for test group 2 would be approximately 500 ng/ml; for test group 3, the expected average plasma concentration of isoxazoline in a feline's blood would be approximately 1000 ng/ml; for test group 4, the expected average plasma concentration of isoxazoline in a feline's blood would be approximately 2000 ng/ml; and for test group 5, the expected average plasma concentration of isoxazoline in a feline's blood would be approximately 4000 ng/ml.

EXAMPLE 3

[0233] Efficacy of Various Liquid Formulations of Isoxazoline Administered *per os*, i.e. by mouth, to Cats for the Treatment and Control of *Ctenocephalides felis*

[0234] Methods: A pool of 36 cats are to be preliminarily infested with ~ 100 unfed adult *C. felis* in order to identify cats that can suitably sustain a reliable infestation rate, defined as approximately 50% of fleas being live at the end of a 48-hour period. The 30 cats with the highest live attached flea counts are to be selected for inclusion in the study. The cats are to be randomly assigned to a single control group and 4 treatment groups with 6 cats per group.

[0235] The cats are to be housed individually during the study period and are to be fed a commercial dry cat food ration with ad libitum access to water.

[0236] Each cat in a treatment group (test groups 2-5) is to receive by mouth a liquid formulation of isoxazoline. The dosage is to be administered to the cats on each of days 0-29 according to test groups:

Treatment Group	Treatment Description	Anticipated Oral Dose (mg/kg)	Formulation
1	Non-treated control	0 mg/kg	n/a
2	Afoxolaner	0.075 mg/kg daily (Days 0-29)	Afoxolaner liquid formulation
3	Afoxolaner	0.225 mg/kg daily (Days 0-29)	Afoxolaner liquid formulation
4	Fluralaner	0.125 mg/kg daily (Days 0-29)	Fluralaner liquid formulation
5	Fluralaner	0.375 mg/kg daily (Days 0-29)	Fluralaner liquid formulation

[0237] Cats in the control group are not to receive isoxazoline or any other flea control treatment. Each cat in the treatment group is to be offered its daily ration (dry food) and the individual doses of liquid formulation are to be administered after the individual cat has eaten at least 25% of its total daily ration. After receiving the dose of isoxazoline, the cats are to be allowed to continue eating. This mimics incorporating the isoxazoline in feed. Each cat in the treatment group and the control group is to be experimentally infested with 100 unfed adult fleas on test days -1, 5 and 28. Comb counts for live adult fleas are to be conducted on days 2, 7, and 30.

[0238] At the dosage levels described in this example, all treatment groups would be expected to reach greater than 95% efficacy by day 7.

EXAMPLE 4

[0239] Plasma Concentration of Isoxazoline in Cats when Isoxazoline is Administered in a Medicated Feed Dosed at 1.5 mg/kg of the Cat's Weight

[0240] Methods: A pool of 30 cats are to be assigned to 5 groups by weight to minimize variation between and within the groups. Each group will be given a different feed formulation containing isoxazoline and the blood level of isoxazoline over the one month period following the single oral dose in medicated feed will be determined.

[0241] The cats are to be housed individually during the study period and are to have *ad libitum* access to water.

[0242] There is to be an initial acclimation period of at least 4 days during which cats are to be transitioned from a standard certified commercial feed to an unmedicated version of the daily feed. During the acclimation period, the cats are to be allowed 15 minutes/day to consume the feed.

[0243] Each medicated feed formulation should be able to deliver approximately 14.1 g/kg of daily feed containing isoxazoline. The amount of medicated feed for each cat is to be determined according to the most recent body weight of the cat prior to the first day (Day 0) of the study. Each medicated feed is to be provided for 15 minutes daily from Day 0 up to and including Day 30. Any uneaten medicated feed remaining after each daily 15 minute timed offering period is to be removed, weighed and the amount recorded. An amount of unmedicated feed equaling the amount of uneaten medicated feed is to be provided ten hours later, at the first blood sampling time.

[0244] Blood samples are to be taken at the following times: 0 hr (at the time the medicated feed is first provided), 0.25 hr, 0.5 hr, 1 hr, 3 hr, 6 hr, 10 hr, 1 day, 2 days, 4 days, 6 days, 9 days, 13 days, 20 days, 27 days and 31 days after the medicated feed is first provided on Day 0.

[0245] The mean plasma concentrations in such a study performed with various isoxazolines, for example, mivorilaner, would be expected to produce plasma

concentrations consistent with those achieved in Examples 1 and 2, above, irrespective of the different formulations of the feed.

EXAMPLE 5

[0246] Plasma Levels of Isoxazoline when Isoxazoline is Administered in a Medicated Feed for Different Dosage Levels

[0247] Methods: A pool of cats are to be randomly assigned to a single control group and 2 treatment groups with 6 cats per group.

[0248] The cats are to be housed individually during the study period and are to have *ad libitum* access to water.

[0249] Each cat in a treatment group (test groups 2 and 3) is to receive one of two medicated daily feeds from study days 0-14. The medicated daily feed is to be offered to the cats for 1 hour on each of days 0-14 according to test groups:

Treatment Group	# of Cats	Anticipated Daily Dose (mg/kg)
1	6	0
2	6	1
3	6	1

[0250] Blood is to be drawn at day 0 (day of the first administration of medicated feed) and days 2, 4, 7, 10, 14, 21 and 30 after the initial dose of isoxazoline is administered. The average concentration of isoxazoline in the blood for each of the medicated feed formulations (treatment groups 2 and 3) can then be determined.

[0251] The plasma concentrations of isoxazoline in such a study performed with various isoxazolines, for example, mivorilane, are expected to be consistent between treatment groups 2 and 3, regardless of the difference in feed formulations.

EXAMPLE 6

[0252] Efficacy of Isoxazoline when Isoxazoline is Administered in a Medicated Feed for the Treatment and Control of *Ctenocephalides felis*

[0253] Methods: A pool of cats are to be preliminarily infested with ~ 100 unfed adult *C. felis* fleas in order to produce cats that can suitably sustain a reliable infestation rate, defined as approximately 50% retention of live fleas at the end of a 48-hour period. The cats with the highest live flea counts are to be randomly assigned to a single control group (Group 1) and 2 medicated feed treatment groups (Groups 2 and 3) with 4 cats per group. The cats in groups 2 and 3 will receive Mivorilaner.

[0254] The cats are to be housed individually during the study period and are to have *ad libitum* access to water.

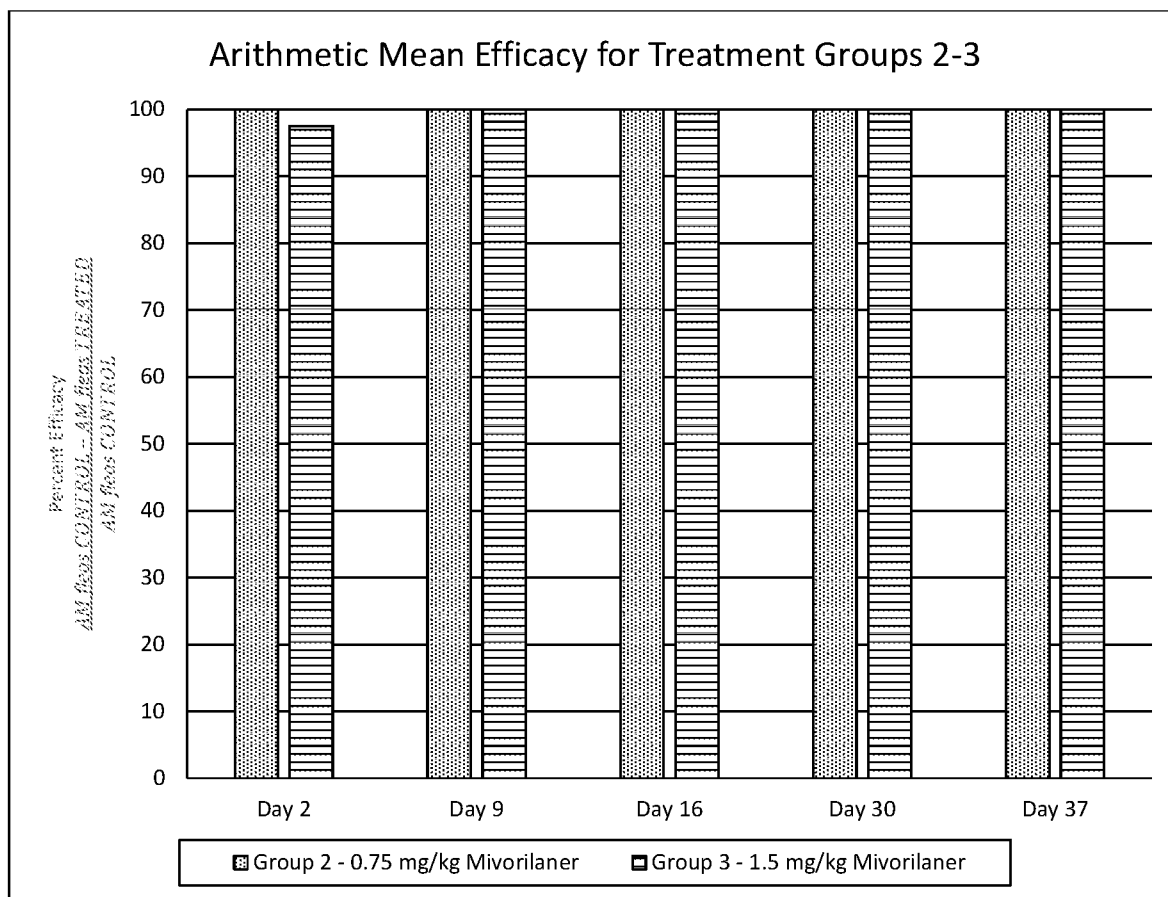
[0255] Each cat in a treatment group (Groups 2 and 3) is to receive a medicated daily feed from study days 0-29 according to the following table:

Treatment Group	# of Cats	Anticipated Daily Dose (mg/kg)	Infestation with fleas
1	4	0	Yes
2	4	0.75	Yes
3	4	1.5	Yes

[0256] The cats are to be fasted overnight prior to each daily treatment. The daily dose of Mivorilaner is to be mixed into a small portion (approximately 25% of the cat's daily dietary needs) of wet canned cat food. Approximately 4 hours after the medicated feed has been initially offered, the remaining medicated feed, if any, will be mixed with the 75% unmedicated daily feed for each cat. The resulting feed offering may be consumed by the cats until the feed bowls are removed for the daily overnight fast.

[0257] Cats in the control group are not to receive isoxazoline or any other flea control treatment. Each cat in treatment groups 2 and 3 and the control group is to be experimentally infested with 100 unfed adult *C. felis* on test days -1, 7, 14 and 28 during the treatment phase and on day 35 during the wash out period after the final feeding with the medicated daily feed. Comb counts for live and moribund fleas are to be conducted on days 2, 9, 16, 30 and 37.

[0258] Results: Percent reduction in live and moribund flea counts for treatment groups 2 and 3 according to this example are shown in the graph below:



[0259] While this invention has been described as having an exemplary design, the present invention may be further modified within the spirit and scope of this disclosure. This application is therefore intended to cover any variations, uses, or adaptations of the invention using its general principles.

WHAT IS CLAIMED IS:

1. A method of controlling a flea infestation in a feline in need thereof, comprising orally administering to said feline an effective amount of an isoxazoline for an effective time at a frequency of at least four times per month.
2. The method of claim 1, wherein said feline is a domestic cat.
3. The method of claim 1, wherein said isoxazoline is mivorilaner, or a salt thereof.
4. The method of claim 3, wherein said mivorilaner is provided in a feed in an amount selected from the group consisting of between about 0.0002 to about 0.12 percent by weight of the feed and between about 0.0003 to about 0.075 percent by weight of the feed.
5. The method of claim 3, wherein said mivorilaner is administered to said feline in an amount selected from the group consisting of between about 0.06 mg/kg and about 5 mg/kg of body weight of said feline and between about 0.1 mg/kg and about 2.25 mg/kg of body weight of said feline.
6. The method of claim 3, wherein said administration provides a concentration of mivorilaner of more than about 60 ng/mL and less than about 18,000 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.
7. The method of claim 1, wherein said isoxazoline is fluralaner, or a salt thereof.
8. The method of claim 7, wherein said fluralaner is provided in a feed in an amount selected from the group consisting of between about 0.00003 to about 0.045 percent by weight of the feed and between about 0.00006 to about 0.03 percent by weight of the feed.

9. The method of claim 7, wherein said fluralaner is administered to said feline in an amount selected from the group consisting of between about 0.012 mg/kg and about 0.1 mg/kg of body weight of said feline, and an amount of between about 0.019 mg/kg and about 0.45 mg/kg of body weight of said feline.
10. The method of claim 7, wherein said administration provides a concentration of fluralaner of more than about 6 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.
11. The method of claim 1, wherein said isoxazoline is sarolaner, or a salt thereof.
12. The method of claim 11, wherein said sarolaner is provided in a feed in an amount selected from the group consisting of between about 0.000003 to about 0.045 percent by weight of the feed, and between about 0.000006 to about 0.03 percent by weight of the feed.
13. The method of claim 11, wherein said sarolaner is administered to said feline in an amount selected from the group consisting of between about 0.0015 mg/kg and about 0.12 mg/kg of body weight of said feline, and between about 0.0024 mg/kg and about 0.054 mg/kg of body weight of said feline.
14. The method of claim 11, wherein said administration provides a concentration of sarolaner of more than about 1.5 ng/mL and less than about 1200 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.
15. The method of claim 1, wherein said isoxazoline is afoxolaner, or a salt thereof.

16. The method of claim 15, wherein said afoxolaner is provided in a feed in an amount selected from the group consisting of between about 0.0000075 to about 0.045 percent by weight of the feed, and between about 0.000015 to about 0.03 percent by weight of the feed.
17. The method of claim 15, wherein said afoxolaner is administered to said feline in an amount selected from the group consisting of between about 0.003 mg/kg and about 0.25 mg/kg of body weight of said feline and between about 0.0045 mg/kg and about 0.113 mg/kg of body weight of said feline.
18. The method of claim 15, wherein said administration provides a concentration of afoxolaner of more than about 3 ng/mL and less than about 1800 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.
19. The method of claim 1, wherein said isoxazoline is lotilaner, or a salt thereof.
20. The method of claim 19, wherein said lotilaner is provided in a feed in an amount selected from the group consisting of between about 0.00006 to about 0.045 percent by weight of the feed and between about 0.00012 to about 0.03 percent by weight of the feed.
21. The method of claim 19, wherein said lotilaner is administered to said feline in an amount selected from the group consisting of between about 0.026 mg/kg and about 2 mg/kg of body weight of said feline and between about 0.04 mg/kg and about 0.9 mg/kg of body weight of said feline.
22. The method of claim 19, wherein said administration provides a concentration of lotilaner of more than about 12 ng/mL and less than about 4500 ng/mL in said feline's blood for a period of time selected from the group consisting of at least 30 days and at least 365 days.

23. The method of claim 1, wherein said isoxazoline is administered as a component of a dry cat food.
24. The method of claim 1, wherein said isoxazoline is administered as a component of a wet cat food.
25. The method of claim 1, wherein said frequency is selected from the group consisting of at least 3 times per week, substantially daily and daily.
26. The method of claim 1, wherein said effective time comprises administering the isoxazoline for a period of time selected from the group consisting of at least one week and at least two weeks.
27. The method of claim 1, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood within a period of time selected from the group consisting of one week of the first administration of said isoxazoline and two days of the first administration of said isoxazoline.
28. The method of claim 1, wherein said administration provides a therapeutically effective level of isoxazoline in said feline's blood for a period of time selected from the group consisting of at least 30 days, at least 60 days, at least 90 days, at least 180 days and at least 365 days.
29. The method of claim 1, wherein said isoxazoline is administered for a frequency selected from the group consisting of at least 15 out of 30 days, and at least 20 out of 30 days.
30. The method of claim 1, wherein said isoxazoline is a component of a feed that comprises one or more other active substances.

31. The method of claim 1, further comprising discontinuing the administration of isoxazoline for a period of time selected from the group consisting of at least 3 days and at least 7 days, wherein the feline's blood concentration of isoxazoline is maintained at a therapeutically effective level.

32. The method of claim 31, further comprising resuming the administration of isoxazoline after the discontinuing of the administration of isoxazoline and thereby maintaining the feline's blood concentration of isoxazoline at the therapeutically effective level.