

Elanco Response to EPA's Data Evaluation Records on L899 Insecticide

Cross-Reference numbers in the text are used to demark verbiage containing confidential information which has been moved to a confidential attachment

DP 379111 – Spinetoram Companion Animal Safety Study – Cats – (OPPTS 870.7200), MRID 47899910 (Adult Cats)

DP 372448 – Spinetoram Companion Animal Safety Study – Cats – (OPPTS 870.7200), MRID 47899912 (Kittens)

Intended Dose Clarification

At the time the Companion Animal Safety (CAS) studies were conducted, the final dose for the product had not been chosen by the Registrant. The 1X dose in the CAS studies was a 0.7 mL application, whereas the final dose based on product performance testing was determined to be 0.5 mL (note the applicator is filled to 0.57 mL to ensure a 0.5 mL dose is delivered to the cat as a small amount of residual stays in the applicator tube, due to the viscous nature of the formulated L899 Insecticide). Therefore, these studies represented approximate doses of 1.4X, 4.2X and 7X. Also note the initial label that was submitted stated the volume as 0.55 mL. The Registrant reconfirmed the calculation and recognized there was an error. The volume is 0.57 mL which still correlates to 0.019 fl oz. The correction has been made on the label that was resubmitted with this response.

Solvent Toxicity

Cross-Reference #1

The pure solvent results in toxicosis that is a well-defined and understood phenomenon such that predictable toxicity can be ascribed. Clinical signs documented in literature for cats include marked ataxia and convulsions, slight to severe hyperesthesia, muscle fasciculations of the head and ears, slight depression progressing to severe depression, inability to stand, and pupils being dilated and fixed. In addition, some animals respond violently to noise. Onset of clinical signs can occur within hours. Signs may progress to death within hours depending upon dosage and frequency of administration (Kimura et al).

Based upon the observations recorded for eight of the 8-week old kittens in the original 5X vehicle control group (Study 130-163), Elanco acknowledges that the clinical signs appear consistent with solvent toxicity. The eight animals which died or were euthanized from control article (vehicle only) complications received a dose of 2 mL of the solvent which equates to 2080 mg (5X vehicle control group in CAS study). Dermal LD50 (rabbit) of the solvent from the literature or various manufacturers' MSDS is given as 2000 mg/kg. The body weight data given in MPI Study 130-163 details the pooled mean body weight of the vehicle control group animals on Day 1 to be 0.81 kg, which would result in the mean application dose being 2567 mg/kg. The additional animals added to the vehicle control group and dosed at 1X neat solvent (0.4 mL) was 467 mg/kg (pooled mean weight – 0.89 kg). The toxicosis for the solvent is clearly dose-related (mg/kg). When L899 Insecticide was applied at the same 5X dose, with the same amount of the solvent theoretically available for toxicosis, no similarities in symptomology or observations were noted between the L899 treated kittens and the 5X vehicle control kittens. Elanco

believes this is due to the unique formulation properties and toxicological profile of L899 Insecticide that prevent "free" solvent from being absorbed into the body. Thus, the toxicity profile inherent to the pure solvent is dramatically altered due to apparent changes in pharmacodynamics that reduce or otherwise impact absorption of the solvent in the L899 Insecticide formulation.

In order to address the Agency's concerns of solvent accumulation, the Registrant has engaged academic scientists in pharmacology and veterinary toxicology with the international Pet Poison Helpline (PPH) to help examine the concept of accumulation of the solvent, and offer any comment or opinion as to how it might impact the safety of the proposed L899 Insecticide formulation. Given the fact that PPH has an academic affiliation with the University of Minnesota and access to resources both within their Center and the University, a more in-depth evaluation of the issue was possible. It is their view that although the feline metabolism of the solvent is somewhat altered as compared to other mammalian species, accumulation occurring subsequent to single acute applications with 30 day wash out periods was not pharmacologically nor toxicologically plausible. Furthermore, they examined their database which contains exposures in the hundreds of thousands of poison/chemical exposures for feline cases involving products that contain the solvent of discussion or the pure solvent for evidence of accumulation related toxicity. None could be found. Furthermore, the published data evaluation reports reporting the adverse incident data from a marketing product (Advantage) containing the solvent show no evidence of clinical toxicity consistent with solvent toxicity or accumulation related toxicity of the solvent. Finally, the previously mentioned impact of the pharmacodynamic characteristics of the as-formulated product (L899 Insecticide) on solvent absorption further supports an additional level of safety in this regard.

L899 Insecticide Study Review

Kitten CAS Study (Study 130-163)

In Study 130-163, with the exception of the initial vehicle control group (discussed above), EPA concluded that only one animal (#124; 5X spinetoram treated) had potentially treatment related observations. Commonly observed clinical signs were not deemed to be related to L899 Insecticide. Changes in hematology or clinical chemistry were not deemed to be biologically significant in spinetoram treated animals.

One 5X-spinetoram treated male (animal # 124) was observed and reported as ataxic on Day 2 of the study and could have been detailed in the final report. This observation of ataxia is not considered to be treatment related due to the isolated incidence of the observation, the lack of any other clinical abnormalities, and the absence of similar effects to those observed in the 5X-vehicle control kittens. The single observation of ataxia in animal # 124 is considered to be the likely result of an increased sensitivity by technical staff to this particular observation the morning of Day 2.

The unscheduled observation of ataxia was recorded by technician #8430 on June 4, 2009 (Day 2) at 7:02 AM. Animal # 124 was also observed as normal on June 4, 2009 (Day 2) at 7:23 AM by technician #8763. Animal # 124 was observed at least twice daily from Day 1 through Day 44 and was considered to be normal at every one of these observations except for this one instance on Day 2. Ataxia was not noted by veterinary staff for animal # 124 on Day 2. The spontaneous and complete resolution of effect within 22 minutes of the only reported observation adds credence to alternative explanation.

In addition to being observed in animal # 124, ataxia was also observed during the morning of Day 2 in 7 other animals (animal # 114, 115, 125, 130, 133, 135, and 146), all of which were in the 5X-vehicle control group. Animal # 124 is the only incidence where ataxia was the only clinical observation

recorded and is not recorded at subsequent observations. In every other instance that ataxia was recorded the morning of Day 2, additional observations were also noted that further describe the event (e.g. tremors, convulsions, prostration, decreased activity etc.).

As a standard, ataxia is not graded by severity within the glossary of the Provantis™ data collection software. The severity of ataxia was not recorded on this study by technical staff as part of the detailed clinical observations. Ataxia was described by veterinarians during consultation as severe in seven of eight 5X vehicle control animals that ultimately were euthanized in extremis. The remaining kitten which was not classified as severely ataxic was already classified as laterally recumbent at the 8:00 am consultation (the same observation time when the other 7 kittens were noted as severely ataxic). Animal # 124 was not mentioned at any time point by the veterinary staff as ataxic or severely ataxic.

The observation of ataxia in animal # 124 would probably not have been made under circumstances in which other animals were observed as normal. Given the fact that the technical staff performing detailed clinical examinations was blinded to the treatment of each animal and that the observation of animal #124 came after observing a number of other kittens with a series of other significant and numerous neurological clinical observations including ataxia, it is likely that the technician's sensitivity to ataxia was increased. The occurrence of some slight incoordination during an early morning observation would be a reasonable finding for a normal kitten of this young age of kitten. Observation times of ataxia on Day 2 are listed below:

animal	technician	time
125	8763	5:51
130	8763	6:03
133	8763	6:05
135	8763	6:07
115	8763	6:27
146	8763	6:31
114	8763	6:33
115	8430	6:57
124	8430	7:02
125	9160	7:06
146	8430	7:06
135	9160	7:09
146	8763	7:33
135	7525	9:10
125	8810	14:26
146	8810	15:03

In the absence of any other abnormality or similar finding observed in the 5X-vehicle control animals, animal # 124 is not considered to be related to treatment.

Animal # 147 was observed on June 10, 2009 (Day 8) at 8:32 AM with impaired function of the left hind limb. The veterinary staff was consulted and a radiograph of the limb was taken on June 10, 2009. The radiograph confirmed that the limb was not fractured. At the recommendation of the veterinarian, consultation with the Sponsor, and approval of the Study Director, this animal was treated orally with an antibiotic Clavamox® (62.5 mg) BID to treat a possible infection and once daily via subcutaneous injection with an anti-inflammatory Meloxicam (2 mg) to relieve pain through June 18, 2009 (Day 16).

The limb function was described by technical staff as normal beginning on June 12, 2009 and as slightly impaired by veterinary staff through June 14, 2009. While both the veterinary staff and the technical staff physically evaluated the animal's limb impairment, slight discrepancies can result due to differences in expertise and training between the veterinary and technician staff.

The animal was not removed from study on the basis that impairment of hind limb function was considered to be a minor ailment that did not impact the animal's survivability and was easily treatable with routine medication without compromising the value of the data that could be obtained from animal # 147. The treatments used are not considered to have masked or obscured any abnormalities on the basis that apart from soft feces (observed on Day 2 and resolved on Day 3, prior to treatment with the concomitant medications), there were no other clinical observations to obscure. In addition, the clinical pathology endpoints following dosing on Days 1 and 30 (before and after medication) were comparable with other animals in that treatment group. Clavamox and Meloxicam are routine therapies used in veterinary medicine and are likely to be typical of concomitant medications cats could receive after registration of L899 Insecticide. Therefore, the information gathered on the concomitant administration of these products, while minimal, was useful.

Elanco believes that animal # 124 was therefore incorrectly described as ataxic in the one event, and that animal # 147 was justified in remaining on study since it responded well to treatment for the suspect hind limb impairment. No serious clinical signs were observed in the L899 treated kittens at up to 7X.

Adult CAS (Study 130-162)

Elanco agrees with EPA's conclusion that "No treatment - related clinical signs of toxicity were observed in the animals exposed to 1X, 3X or 5X the spinetoram-containing formulation" as it relates to Study 130-162 conducted in adult cats. Salivation, slight hair discoloration and hair sparseness can be expected side effects with L899 Insecticide treatment. Changes in hematology or clinical chemistry values were not biologically relevant and were within normal reference ranges.

Elanco does not agree with EPA's assessment that the death of cat # 125 was associated with the treatment with vehicle control. EPA cited the primary reason for death to be hypocalcemia and decreased bicarbonate as measured in the day 31 blood sampling. These two blood values loosely correlated to values observed in the serum chemistries from the kittens in the 5X vehicle control in Study 130-163. What does not correlate, however, are other diagnostic tests (CBC, Coagulation, and Serum Chemistry), clinical observations, and necropsy. None of these pathological processes are consistent with exposure to the solvent. The observed changes in calcium and bicarbonate, in and of themselves, do not suggest a connection between the solvent administered to animal # 125 and those adverse events that occurred in Study 130-163 especially given the trauma concomitantly experienced by the animal shortly before death.

Specifically, the clinical signs of solvent toxicity as noted in Study 130-163 were not observed in animal #125. The animal was dosed once on Day 0 and again on Day 30, with no toxicity to dermal exposure present. No classical pathogenomonic signs of solvent toxicity were observed in animal # 125. Twice daily observations for animal # 125 on both dosing days and those thereafter revealed no clinical abnormalities that are suggestive of solvent toxicity. No abnormalities were detected for observations pre-dose, 15 minutes, 1 hour, 2 hours, 3 hours, and 4 hours post-dose on Days 0 and 30. There were no abnormal health observations for both the am and pm observations on days 31 and 32 (2 full days post application). Neurologic effects associated with the solvent were observed within 24 hours of

application in study 130-163. Furthermore, given the size of this cat and the dose of the solvent, it is unlikely this cat received a large enough dose of the solvent to illicit a solvent related adverse incident (867 mg/kg).

Additionally, blood gas analysis was not required per the protocol; therefore a definitive diagnosis of systemic acidemia cannot be made. Metabolic acidosis due to bicarbonate loss, as seen in diarrhea and low intestinal obstruction, causes the body to compensate by decreasing the pH and causing acidemia (not assessed). If the cat was acidemic, this would present as hyperkalemia, which was not present in animal # 125. Additionally, other differences in serum chemistries would likely be present such as sodium and chloride anion.

This animal was under extreme stress from a mechanical injury, and there is no usable or reproducible information as related to the application of the solvent.

Overall, in assessing data from both kitten and cat CAS studies, dosing of L899 Insecticide (containing mainly the solvent of concern and spinetoram) at up to 7X did not result in serious clinical signs being observed in any of the 72 animals (36 kittens and 36 cats).

Formulation of L899 Insecticide

Elanco developed L899 Insecticide to be a single-use product that would work on all sizes of cats and kittens, especially given the active ingredient, spinetoram, has a large safety margin and is a reduced-risk pesticide. Elanco specifically chose this solvent as the excipient/carrier from the EPA approved inerts list due to its universal solvency and the fact that the solvent had been used safely in a registered product for cats for over ten years (Advantage, from Advantage MSDS). Maximization of spinetoram content in the L899 Insecticide clearly shifts LD50 dermal values to correlate more with the TGAI than the solvent. The viscosity of L899 Insecticide is favorably increased due to the high levels of spinetoram soluble in the formulation.

For the formulated L899 Insecticide product, the limit dermal LD50 (rabbits) is greater than 5000 mg/kg, which indicates that the product is at least 2X less toxic than the solvent. The viscosity of the solvent measured at room temperature by the Registrant is 6 cps (5.8 centistokes), the viscosity of the formulated L899 Insecticide according to the data developed for OPPTS 830-7100 is 132.5 cps @25 degrees C (124.5 centistokes), indicating that the formulated L899 Insecticide is more than 20X more viscous than the solvent. As previously pointed out to the Agency, Potter et al. when evaluating the skin penetration of carcinogens in oils found, for example, that with mice as the viscosity increases from 32 centistokes to 5000 centistokes (156X) the skin penetration was reduced five-fold. The authors reported similar results with human skin. The significantly reduced bioavailability of the solvent when applied in a more viscous medium significantly reduces the risk from dermal exposures. Lastly, precedence has been set for the use of this solvent in other registered spot on products, such as Advantage.

The Index of Cleared Studies was used to identify the September 23, 1997 Review of Domestic Animal Safety Studies with Advantage Spot-On Formulation by Virginia Dobozy (MRID 44157301 and MRID 44157302) both studies on kittens. In the second study which was considered acceptable, 12 eight week old kittens were treated at the 5X dose (Advantage) and 12 eight week old kittens were treated with the vehicle control at 1X – no treatment related toxicity (control or test article) was observed. However in the first study on six week old kittens, 12 kittens were treated at the 5X level (Advantage) and 12 kittens were treated with the vehicle control at 1X. Within 72 hours, four kittens (2 male and 2 female) in the

Advantage group had either died or had to be euthanized. Three female six week old kittens were added to the study on a revised protocol and treated with the vehicle at 5X. All three died within 24 hours. One of the study authors concluded that the kittens were stressed after being transported a long distance, were not eating properly when the study was initiated and were not properly conditioned. The dermal LD50 for Advantage is >2000 mg/kg (Advantage MSDS), which is more similar to the solvent than to the active ingredient, imidacloprid (>5000 mg/kg - EXTOWNET), and the viscosity of Advantage is 29 centipoises (Advantage MSDS), also somewhat close to that of the solvent. Therefore, the results Elanco saw in the 1X vehicle control group in study 130-163 did not differ from the results seen with Advantage, a currently registered product. No serious adverse incidents were seen at the 1X solvent dose in 8-week old kittens. Both Advantage and L899 also showed no serious adverse incidents at any of the treatment doses, including the 5X group.

Cross-reference #2

While still rare, the two routes of misuse could come from two members of a household both dosing a cat (owners' miscommunication) and, purposely treating an animal with more product due to a severe flea infestation. The latter risk should be mitigated by proper guidance from a veterinarian in a veterinarian/owner/patient relationship. These instances, while very rare, should not result in adverse incidents since the use would be within the defined margin of safety for L899 Insecticide (up to 7X). Overall, Elanco believes the potential for misapplication is extremely low and less than current spot-on products.

Elanco acknowledges and can understand why EPA would have initial concerns about the solvent at excessive doses in kittens and might suggest reformulation as a mitigation step. We strongly believe, however, the Agency should not consider this solvent negatively as a solvent/carrier for feline and canine spot-on products *carte blanche*. In our specific situation, we have definitively demonstrated that the physical properties and acute dermal toxicology of the L899 Insecticide vastly differ from the solvent, indicating toxicity seen from the solvent alone at exaggerated doses are not indicative of any potential safety concerns of the L899 Insecticide. We also have evaluated information available in Data Evaluation Records (DER) for Enhanced Spot-on Reporting, focusing our attention on the leading products sold in the US feline market – Frontline (EPA Reg. No. 65331-2), Frontline Plus (EPA Reg. No. 65331-4) for Cats and Advantage for Cats (EPA Reg. No 11556-116 and 118). These products according to Brakke reports comprise well over 85% of total feline sales in the flea-only category (Brakke Consulting, Inc., Dallas, Texas. Brakke Report, 2008). When evaluating the effects from Frontline and Frontline Plus, the DERs show 1414 reported incidents via dermal exposure (combining the total from Table 2 in each report), with 1161 (82.1%) being minor. Twenty-two (22) cases were considered major, with 37 dermal exposures associated with death (2.6 %). Advantage data shows 534 dermal exposure incidents, with 499 (93.4%) being reported as minor. Two (2) incidents (0.4%) were listed as major, with 7 incidents (1.3%) associated with death. Further exploration of Advantage (which contains the solvent of concern) shows the seven deaths were distributed across age, weight and sex – with no apparent trends. As discussed earlier, any toxicosis with the solvent would show a marked propensity for adverse effects with young kittens and very small cats due to the mg/kg considerations of dermal exposure. The reported data with Advantage shows no reason for particular concern with products containing this solvent, especially when considering the millions of applications administered yearly of the product. Since L899 Insecticide has even higher viscosity values and better dermal LD50 values, we do not believe a reformulation is warranted. We believe with this additional information and data already reviewed that EPA can reach the same level of comfort as we have with L899 Insecticide as proposed.

Post Registration Product Stewardship

Elanco fully recognizes registration of L899 Insecticide will be a conditional registration with enhanced FIFRA 6a2 incident reporting. Elanco is fully prepared to comply with this requirement and also understands our commitment to product stewardship does not end with the registration. Elanco will be conducting additional studies to support registrations outside of the United States which can add to the safety profile of L899 Insecticide. Elanco can provide this information to EPA post registration as the information is available.

Other items of clarity, related to reviewer comments on DP372448 related to appropriate size of kittens, clarity around the dosing procedure and study design issues

Kitten Weight

The protocol specified (Section 3.6) that the animals would weigh approximately 550 to 800 grams at arrival as measured within 3 days of arrival. This weight is based upon previous experience of what could be expected from this supplier for healthy 6 week old kittens. A majority of the kittens fell in this range and day -14 and also were deemed to be a healthy via a physical exam on day -6. Since L899 Insecticide is intended for all sizes of cats and kittens greater than 8 weeks of age, there was no absolute weight range specified for this study as long as the kittens were healthy.

Dosing

In both the adult cat and kitten study, the hair was parted at a site of application. The site of application was between the shoulder blades and extended cranially and caudally as needed to prevent run off. The application site was not shaved. No run-off was recorded for any of the dose administrations. This application method was consistent with the application method described in the submitted labeling.

Study Design

While Study 130-163 deviated from the OPPTS 870.7200 guideline by using a non-concurrent vehicle control and by treating the vehicle control group at a 1X excipient level compared to a 5X excipient level, this approach was agreed upon by the EPA in informal correspondence via email with Dr. Byron Backus on June 26, 2009. Additionally, there is precedence in the DERs for other registered spot on products for EPA to consider and accept the use a vehicle control other than 5X as summarized below:

Product	Active Ingredient	MRID #	Vehicle Control Used
Vectra	Dinotefuran and pyriproxyfen	47199107, 47207101	5X
Frontline	Fipronil	434449-04, 143121112	5X
Frontline Plus	Fipronil and s-methoprene	44942009	Not dosed
Advantage	Imidacloprid	43679502	5X
		44157302	1X
		44157301	1X and 5X
Promeris	Metaflumizone	46437615, 46437616	5X
Zodiac	s-methoprene	No studies	NA
Zodiac	Etofenprox, S-methoprene	46513409	5X
Sergeant's	Etofenprox, Pyriproxyfen	46161309	Approx 2X
Ultraguard	s-methoprene	None	NA

With regard to the 3X and 5X treatments, it was not possible to increase spinetoram content (already 39.6% w/w in the L899 Insecticide formula), due to the solubility of spinetoram with the excipients in the formulation. Therefore, 3X and 5X the application volume needed to be utilized to achieve the 3X and 5X dose. This position was confirmed by Dr. Byron Backus in an email on 07 April 2009.

Conclusions

The overall vision of L899 Insecticide has been designed with the safety of the cat and the needs of the owner at the forefront. A single applicator, with one size for all cats, will allow owners to administer L899 Insecticide with confidence that their cat will be administered the correct amount of product when used according to label directions. This dose will result in highly effective control against flea infestations. Solvent related toxicity observed in 8-week old kittens administered 5X vehicle control is not indicative of toxicity that could be expected with L899 Insecticide since the physical properties of the L899 Insecticide differ greatly from that of the solvent. Dermal LD50 values of L899 Insecticide are greater than 2X less toxic than solvent alone. In addition, L899 Insecticide is 20X more viscous than the solvent alone, limiting L899's ability to be absorbed and systemically available.

L899 Insecticide, when tested at 1.4X, 4.2X and 7X the proposed commercial dose, has not exhibited any serious clinical signs or toxicity in cats or in 8-week old kittens. Minor side effects such as those seen with all spot-on products include salivation, hair sparseness, and an occasional transient discoloration of the application site and have been the majority of the few reported effects. These effects are described as possible side effects on the draft L899 Insecticide label provided with the original submission. Adverse incident data from other commercial products with this solvent show that an overwhelming majority of events are minor side effects and not serious events associated with the solvent.

While we believe the risks of this product are negligible, we believe L899 Insecticide offers unique advantages to current spot-on products

Cross-reference #3

In conclusion, the Registrant believes we have sufficiently demonstrated L899 Insecticide has a wide margin of safety when administered to cats and kittens 8 weeks of age and older. Additionally, we believe we have answered all the questions posed by the EPA in DP 379111 and DP 372448 and believe that the classification of the kitten CAS study (130-163) should be upgraded to "acceptable" by EPA in support of a conditional registration for L899 Insecticide.

References:

Kimura ET, Darby TD, Krause RA, et al . Cross-reference #4

Potter, D. Booth, E D. Brandt, H C. Loose, R W. Priston, R A. Wright, A S. Watson, W P. Studies on the dermal and systemic bioavailability of polycyclic aromatic compounds in high viscosity oil products. Arch Toxicol, 73(3):129-40, 1999 Apr-May.

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