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## Safety of a topically applied metaflumizone spot-on formulation for flea control in cats and kittens

K. Heaney<sup>a,\*</sup>, R.G. Lindahl<sup>b</sup>

<sup>a</sup> Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543, USA

<sup>b</sup> MPI Research, 54943 North Main Street, Mattawan, MI 49071, USA

### Abstract

Four laboratory studies were conducted in cats of various ages to evaluate the safety of a novel low-volume topical spot-on containing 20% metaflumizone (ProMeris<sup>®</sup> for Cats, Fort Dodge Animal Health, Overland Park, KS) when used in cats according to the recommended minimum dosage of 40 mg metaflumizone kg<sup>-1</sup> delivered via fixed volume doses of 0.8 ml for cats ≤4.0 kg and 1.6 ml for cats >4.0 kg. Study parameters included body weight, food consumption, clinical, physical and neurological examinations, and clinical pathology including complete hematology, coagulation, clinical chemistry and urinalysis. Exaggerated and repeated topical applications of metaflumizone at 1×, 3× and 5× the proposed recommended dose in adult cats and kittens 8 weeks of age had no effect on mortality, body weight, food consumption, clinical, physical or neurological examinations, or clinical pathology parameters. Transient salivation was sporadically noted following some, but not all treatment applications. It occurred and resolved within minutes of treatment application in all groups, including cats treated with placebo. Consequently, it was not considered a direct result of treatment with the active ingredient, metaflumizone. Cats orally administered 10% of the recommended topical dose exhibited considerable avoidance behaviors including spitting, head shaking, and salivation. Therefore, voluntary oral exposure is unlikely. No other adverse signs were observed. Repeated use of metaflumizone caused no adverse health effects when administered at 5× the recommended dose and is safe when used as directed, even on kittens as young as 8 weeks of age.

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**Keywords:** ProMeris<sup>®</sup>; Semicarbazone; Metaflumizone; Safety; Cat

### 1. Introduction

Metaflumizone is a novel semicarbazone insecticide that has not been used previously in veterinary medicine. Metaflumizone works by blocking sodium channels in the nervous system of insects and has no known cross-tolerance by insecticide-resistant strains (Klein and Oloumi, 2005). It has demonstrated excellent efficacy against fleas on cats (Holzmer et al., this volume). In studies of mammalian toxicity, metaflumizone was

characterized as having very low acute toxicity, with rat oral and dermal acute LD<sub>50</sub> > 5000 mg kg<sup>-1</sup>, and relatively low toxicological potential following sub-chronic and chronic oral exposure in rats, mice and dogs with reduced weight gain and/or decreased food consumption the primary observable adverse effects noted in dogs treated orally for 12 months with of 30 mg metaflumizone/kg/day (EPA, 2006).

Four studies were conducted to evaluate the safety of a spot-on formulation containing 20% w/v metaflumizone (ProMeris<sup>®</sup> for Cats, Fort Dodge Animal Health, Overland Park, KS) when used for control of fleas in cats 8 weeks of age and older. Two margin of safety studies (Study 1 and Study 2) of similar design, one in adult cats and one in 8-week-old kittens, were

\* Corresponding author. Tel.: +1 732 631 5822;  
fax: +1 732 631 5832.

E-mail address: [heaneyk@pt.fdah.com](mailto:heaneyk@pt.fdah.com) (K. Heaney).

conducted to evaluate the safety of a single topical application of 1×, 3×, or 5× the recommended dose compared with cats treated with placebo (formulation without insecticide) at the 5× volume. Study 3 was conducted to evaluate the effect of seven topical applications of 1×, 3×, or 5× the recommended dose of metaflumizone or placebo at 2-week intervals in 8-week old kittens. Study 4 was conducted to evaluate the safety and behavioral responses following oral administration of 10% the recommended dose, the amount that estimates potential oral exposure due to licking after topical application.

## 2. Materials and methods

Each study was conducted in accordance with the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (GLP) ENV/MC/CHEM(98)17 and/or in accordance with Good Laboratory Practice (GLP) Standards as set forth by EPA in 40 Code of Federal Regulations (CFR) Part 160 (FIFRA).

### 2.1. Animals

All studies were performed with purpose-bred, domestic, shorthaired cats or kittens. Young adult cats (Studies 1 and 4) were approximately 6 months old and weighed from 1.8 to 5.0 kg at study initiation. Kittens used in the single-dose study (Study 2) were 8 weeks old and weighed 0.51–0.75 kg at the time of treatment. Kittens used in the repeated treatment study (Study 3) were 8 weeks old and weighed 0.63–1.01 kg at the time of first treatment. In Studies 1 and 2, 24 male and 24 female animals were ranked by weight within gender, blocked into groups of four and randomly assigned to four treatment groups of 12 animals. In the repeated treatment study (Study 3), 16 males and 16 females were ranked by weight within gender, blocked into groups of four and randomly assigned to four treatment groups of eight animals. In the oral exposure study (Study 4), eight male and eight female cats were ranked by weight within gender, blocked into groups of two and randomly assigned to two treatment groups of eight animals.

### 2.2. Housing and care

Adult cats and kittens were individually housed in cages according to animal welfare regulations (Guide for the Care and Use of Laboratory Animals, rev. 1985 National Institutes of Health; Animal Welfare Act,

USDA/APHIS). Solid cage walls and partitions prevented contact between animals. Cats and kittens were fed an age appropriate maintenance ration of a commercial dry canine feed with water available *ad libitum*. All animals were observed at least twice a day for morbidity, mortality, injury, and the availability of food and water.

### 2.3. Formulation and dosage

For all studies the commercial formulation containing 20% w/v metaflumizone was used. The target minimum dose of active ingredient was 40 mg kg<sup>-1</sup>. To achieve this target dose, the product was applied in fixed volumes of 0.8 ml or 1.6 ml for cats ≤4.0 kg and >4.0 kg, respectively. For Studies 1–3, three treatment groups received the test substance at 1×, 3× and 5× multiples of the recommended dose. Controls received a placebo spot-on formulation comprised of inert ingredients used to formulate the metaflumizone spot-on applied at the 5× volume. Volumes were rounded up to the nearest 0.1 ml. In Study 4, cats were dosed orally either 0.08 ml or 0.16 ml, which is 10% the recommended dose for cats ≤4.0 and >4.0 kg, respectively. Controls were dosed with 0.8 ml or 0.16 ml bacteriostatic sodium chloride.

### 2.4. Masking

For all studies, persons conducting and recording observations were not aware of treatment allocation.

### 2.5. Experimental design

#### 2.5.1. Studies 1 and 2 – single treatment in adult cats and kittens

In Studies 1 and 2, the four groups were treated with the metaflumizone formulation as a single topical application of 1×, 3×, or 5× the proposed recommended dose volume or placebo comprised of inert ingredients applied at the 5× volume. Treatments were applied topically along the dorsal midline between the scapulae. The cats were observed for 4 weeks following dose administration. Food consumption was measured daily and reported weekly. Body weights were measured prior to treatment and weekly during the course of the study. Detailed clinical examinations were conducted twice daily. These included, but were not limited to, changes in skin, fur, eyes, mucous membranes, respiratory system, circulatory system and heart rate, central nervous system, behavior pattern, observations for central nervous system signs

(seizures, depression, sedation, tremors, salivation), vomiting, and diarrhea. On the day of treatment, additional clinical examinations were performed prior to treatment and 15 min post-treatment and at 1, 2, and 3 h post-treatment. All cats received detailed physical and neurological examinations prior to dosing, at 4 h post-treatment and at 1, 7, and 21 days after treatment. Blood and urine for hematology, coagulation, clinical chemistry and urinalysis were collected once pretreatment, and at 1, 7 and 21 days after treatment.

### 2.5.2. Study 3 – repeated treatment

In Study 3, the four groups were treated with metaflumizone administered at 1 $\times$ , 3 $\times$ , or 5 $\times$  the proposed recommended dose or a placebo comprised of inert ingredients applied at 5 $\times$  volume. Seven treatments were applied at 14-day intervals and cats were observed for 97 days after the initial treatment. The treatments were applied topically along the dorsal midline between the scapulae on Days 1, 15, 29, 43, 57, 71 and 85. Body weights were recorded three times a week from acquisition through the first 2 weeks of the study, and weekly for the remaining weeks. Food consumption was measured daily and reported weekly. Detailed clinical examinations as described for Studies 1 and 2 were conducted at least once daily through study termination. Additional clinical examinations were performed on each treatment day, prior to treatment and at 5–15 min, 1, 2, 3, and 10 h post-treatment. All animals received detailed physical and neurological examinations, including heart rate and rectal body temperature, prior to each dosing, at 4 h post-dosing, the day after each dosing, and 7 days after each dosing. Blood and urine for hematology, coagulation, clinical chemistry and urinalysis were collected once pretreatment, the day after each treatment, and 7 days post-treatment for treatments 1, 3, 5, and 7; Days 1, 29, 57 and 85, respectively.

### 2.5.3. Study 4 – oral exposure

In Study 4, treatments were administered on the tongue, once on Day 1. Cats were observed for 7 days following dosing. Food consumption was measured daily through study termination. Body weights were recorded on Days –7, –1, and 8. Detailed clinical examinations were conducted as previously described at least once daily through study termination. On the day of treatment, animals were also examined prior to treatment, at 5–15 min and 30–45 min post-treatment, and at 1, 2, 3, and 10 h post-treatment. If an adverse reaction or behavior was observed, the clinical observations continued at hourly intervals until the

reaction or behavior resolved. Physical and neurological examinations, including heart rate and rectal body temperature, were conducted on Day 1, approximately 4 h post-treatment on Day 1, and on Days 2 and 8. Blood for hematology, coagulation and clinical chemistry were collected on Days 1, 2, and 8.

### 2.6. Clinical pathology

In all studies, the hematology parameters evaluated were leukocyte count (total and differential), erythrocyte count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated), reticulocytes (punctate, aggregate, total), platelet count, prothrombin time and activated partial thromboplastin time. The clinical chemistry parameters evaluated were alkaline phosphatase, total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dl), aspartate aminotransferase, alanine, aminotransferase, gamma glutamyl transferase, urea nitrogen, creatinine, total protein, albumin, globulin and A/G (albumin/globulin) ratio (calculated), glucose, total cholesterol, electrolytes (sodium, potassium, chloride), calcium, phosphorus and creatine phosphokinase.

In Studies 1, 2 and 3, the urinalysis parameters evaluated were volume, specific gravity, pH, color, appearance, protein, glucose, bilirubin, ketones, occult blood, urobilinogen and microscopy of sediment.

### 2.7. Statistical analyses

All calculations were performed using SAS version 8.01 or 8.2 (SAS Institute, Cary, NC). Repeated measures analyses were performed on body weight (Studies 1–3), food consumption (Studies 1–3), heart rate (Studies 3) and body temperature (Studies 3) using the PROC MIXED procedure in SAS. The model contained pretreatment values as corresponding covariates, and treatment, sex, treatment  $\times$  sex, time, sex  $\times$  time, treatment  $\times$  sex  $\times$  time, and treatment  $\times$  time as the fixed effects with time as the repeated fixed effect. The interactions were tested at the 5% level whereas treatment effects were tested at the 10% level. All quantitative hematology, coagulation and clinical chemistry (Studies 1–4), body weight (Study 4), food consumption (Study 4), heart rate (Study 4), and body temperature (Study 4) were analyzed using the PROC MIXED procedure with pretreatment measurements as corresponding covariates, and treatment, sex and treatment  $\times$  sex as fixed main effects and interaction. Interactions were tested at the 5% level of significance.

and treated groups' least square means (LSM) were compared to the control group LSM by the two-sided Student's *t*-test at the 10% level for that parameter.

### 3. Results

#### 3.1. Study 1 – adult cat single treatment

The actual quantities of metaflumizone administered to cats in the 1×, 3× and 5× groups were 41–89, 126–213 and 222–390 mg kg<sup>-1</sup>, respectively. All cats survived to study conclusion. Treatment with a single application of metaflumizone at up to 5× the recommended dose caused no adverse effect on food consumption, body weight, daily detailed clinical examinations or on repeated physical and neurological examinations. Although there was a statistically significant decrease in body weight relative to controls on Day 7 (*P* < 0.1) in females treated with 5×, this decrease was less than 3%, and there were no significant differences in body weight change from baseline. All animals maintained or gained weight during the study (Table 1). Several clinical pathology parameters reached statistical significance (*P* < 0.1) at various

post-treatment intervals; however, the direction and minimal magnitude of these changes were not clinically or physiologically meaningful and values remained within expected normal limits. Several cats exhibited transient salivation at 15 min post-treatment. This observation was seen at a comparable frequency in all groups, including the placebo-treated controls.

#### 3.2. Study 2 – kitten single treatment

The actual quantities of metaflumizone administered to kittens in the 1×, 3×, and 5× groups were 185–281, 561–848, and 1000–1409 mg kg<sup>-1</sup>, respectively. All kittens survived to study conclusion. Despite these very large doses, treatment with a single application of metaflumizone at up to 5× the recommended dose volume had no adverse effect on body weight, food consumption, clinical findings, and physical and neurological observations. All animals gained weight during the study (Table 2). Several clinical pathology parameters reached statistical significance (*P* < 0.1) when compared with placebo controls. However, the differences noted for all groups and individuals were minimal in degree, were not persistent, not

Table 1  
Summary of body weight values in adult cats (male and females combined) treated once with single or exaggerated doses of metaflumizone or placebo

Study day	Treatment group	Body weight (kg)			
		Mean	S.D. <sup>a</sup>	Range	
-1	Placebo	3.22	0.48	2.40	4.10
	1×	3.13	0.70	1.80	4.40
	3×	3.24	0.52	2.60	4.50
	5×	3.23	0.47	2.40	4.10
	7	Placebo	3.33	0.49	2.50
7	1×	3.18	0.67	2.00	4.50
	3×	3.28	0.48	2.70	4.30
	5×	3.29	0.56	2.40	4.30
	14	Placebo 1	3.40	0.53	2.50
14	1×	3.31	0.71	2.20	4.70
	3×	3.42	0.56	2.70	4.60
	5×	3.43	0.63	2.60	4.60
	21	Placebo	3.54	0.61	2.60
21	1×	3.42	0.76	2.30	4.90
	3×	3.55	0.65	2.70	4.90
	5×	3.58	0.70	2.60	4.90
	28	Placebo	3.62	0.65	2.60
28	1×	3.53	0.82	2.30	5.10
	3×	3.63	0.68	2.80	5.10
	5×	3.65	0.78	2.60	5.10

Males and females combined, six males and six females per group.

<sup>a</sup> S.D., standard deviation.

Table 2  
Summary of body weight values in kittens treated once on Day 1 with single or exaggerated doses of metaflumizone or placebo

Study day	Treatment group	Body weight (kg)			
		Mean	S.D. <sup>a</sup>	Range	
-1	Placebo	0.68	0.07	0.58	0.82
	1×	0.69	0.09	0.57	0.87
	3×	0.69	0.10	0.57	0.86
	5×	0.68	0.07	0.57	0.80
	6	Placebo	0.80	0.07	0.70
6	1×	0.81	0.12	0.69	1.01
	3×	0.81	0.12	0.60	0.99
	5×	0.82	0.09	0.65	0.97
	13	Placebo	0.91	0.10	0.77
13	1×	0.91	0.12	0.78	1.11
	3×	0.93	0.12	0.70	1.13
	5×	0.95	0.09	0.77	1.12
	20	Placebo	1.06	0.13	0.86
20	1×	1.06	0.13	0.89	1.33
	3×	1.09	0.15	0.79	1.34
	5×	1.12	0.12	0.91	1.38
	27	Placebo	1.19	0.12	0.99
27	1×	1.20	0.13	1.03	1.44
	3×	1.22	0.15	0.88	1.43
	5×	1.24	0.10	1.07	1.42

Males and females combined, six males and six females per group.

<sup>a</sup> S.D., standard deviation.

Table 3

Summary of neutrophil values in kittens treated once on Day 1 with single or exaggerated doses of metaflumizone or placebo

Study day	Treatment group	Neutrophils ( $10^3 \mu\text{l}^{-1}$ )			
		Mean	S.D. <sup>a</sup>	Range	
Pretreatment	Placebo	6.74	2.83	3.34	13.50
	1×	8.12	3.63	2.49	13.08
	3×	5.59	1.73	2.67	8.57
	5×	5.15	1.83	1.70	7.76
Day 2 (24 h after treatment)	Placebo	6.82	2.89	3.25	12.91
	1×	8.26	2.65	5.24	14.16
	3×	7.31	3.62	2.30	13.49
	5×	7.04	3.72	2.35	12.99
Day 8	Placebo	8.64	3.83	4.29	16.54
	1×	10.92	2.76	5.63	15.86
	3×	9.91	3.40	2.51	13.16
	5×	7.13	2.68	3.70	12.96
Day 22	Placebo	11.15	6.40	5.34	28.73
	1×	9.78	4.91	3.20	22.82
	3×	9.08	4.09	2.91	18.75
	5×	6.34	2.08	3.08	9.35

Males and females combined, six males and six females per group.

<sup>a</sup> S.D., standard deviation.

dose-dependent, and values were not physiologically or clinically meaningful. Specifically, on Day 8, leukocytes were statistically increased in kittens treated with 1× and 3×, but not with 5×. These increases were mild and due to variably increased neutrophils or lymphocytes (but not to a statistically significant degree), which did not exhibit a dose-dependent pattern. Neutrophils and lymphocyte values for each individual remained within normal limits (Tables 3 and 4). Alkaline phosphatase tended to increase over time in all groups, including placebo controls, but only reached statistical significance on Day 22 for kittens treated with 5× (Table 5). Again, values generally remained within normal limits and the increase was associated with the rapid growth rate of the kittens. Values for all other clinical pathology parameters remained within expected normal ranges for all individuals.

Transient salivation was noted at 1-h post-treatment in kittens treated with placebo and kittens treated with 3× and 5× volumes of metaflumizone spot-on. Salivation was not observed in kittens treated with 1×.

### 3.3. Study 3 – repeated treatment

The actual quantities of metaflumizone applied on initial treatment in the 1×, 3×, and 5× treatment groups were 181–229, 484–684, and 836–1151 mg kg<sup>-1</sup>, respectively. Subsequent administrations were adjusted

Table 4

Summary of lymphocyte values in kittens treated once on Day 1 with single or exaggerated doses of metaflumizone or placebo

Study day	Treatment group	Lymphocytes ( $10^3 \mu\text{l}^{-1}$ )			
		Mean	S.D. <sup>a</sup>	Range	
Pretreatment	Placebo	6.80	2.50	2.29	11.60
	1×	6.53	3.30	2.18	14.31
	3×	7.28	3.71	2.20	15.30
	5×	4.85	2.20	1.40	8.70
Day 2 (24 h after treatment)	Placebo	6.74	1.64	4.31	9.20
	1×	6.23	2.70	1.38	10.80
	3×	7.13	2.62	3.28	12.63
	5×	5.99	1.89	2.80	8.70
Day 8	Placebo	6.71	2.37	2.90	10.40
	1×	7.36	2.08	3.67	10.69
	3×	8.94	2.95	4.00	13.80
	5×	6.94	1.90	4.48	11.80
Day 22	Placebo	7.39	3.12	2.93	14.71
	1×	9.23	2.92	5.00	14.20
	3×	9.41	3.26	4.26	14.40
	5×	7.19	2.17	3.87	10.90

Males and females combined, six males and six females per group.

<sup>a</sup> S.D., standard deviation.

for growth so that so that all kittens continued to receive similar doses.

All cats survived to study conclusion. Exaggerated and repeated treatment with metaflumizone administered

Table 5

Summary of alkaline phosphatase values in kittens treated once on Day 1 with single or exaggerated doses of metaflumizone or placebo

Study day	Treatment group	Alkaline phosphatase (units l <sup>-1</sup> )			
		Mean	S.D. <sup>a</sup>	Range	
Pretreatment	Placebo	69.5	23.6	40	114
	1×	68.2	19.5	40	108
	3×	70.8	14.9	46	90
	5×	71.4	18.9	33	94
Day 2 (24 h after treatment)	Placebo	76.6	14.9	54	109
	1×	79.9	22.7	49	119
	3×	75.4	22.1	39	121
	5×	83.9	21.0	50	121
Day 8	Placebo	81.3	22.9	48	121
	1×	91.3	31.6	52	161
	3×	79.9	16.7	47	103
	5×	101.8	34.5	56	167
Day 22	Placebo	85.0	28.2	32	127
	1×	89.2	22.8	56	129
	3×	97.1	22.3	36	126
	5×	115.9	33.0	73	187

Males and females combined, six males and six females per group.

<sup>a</sup> S.D., standard deviation.

topically at 1×, 3× and 5× the proposed recommended dose had no adverse effect on body weight, food consumption, physical/neurological examinations, clinical findings, heart rates, body temperature and clinical pathology parameters. All animals consistently gained weight for the duration of the entire study. Transient salivation was noted in several animals, following some, but not all, dosings and was observed most commonly 5–15 min post-treatment, in all groups except the 1×-treated group. Although several hematology and clinical chemistry parameters did reach statistical significance ( $P < 0.1$ ) when compared to controls, differences for each parameter were minimal in degree, not dose-dependent and none of the values were physiologically or clinically meaningful. Individual values were well within the realm of normal physiologic variation and comparable to pretreatment values.

#### 3.4. Study 4 – oral exposure

All cats survived to study conclusion. Metaflumizone spot-on for cats administered orally to cats at 10% the proposed recommended dose volume resulted in no effect on mortality, body weight, food consumption, heart rate, body temperature, physical or neurological examinations, or clinical pathology parameters. At dosing, avoidance behaviors including spitting, head shaking, and salivation were noted in all metaflumizone spot-on treated cats. Salivation persisted through the 5–15-min post-treatment observation interval. While considered an effect of treatment with metaflumizone spot-on, this observation was considered minor in nature and not deleterious to the overall health of the cats. Several hematology and clinical chemistry parameters reached statistical significance ( $P < 0.1$ ); however, all individual values were within expected ranges, were similar to pretreatment values, and none were physiologically or clinically meaningful.

#### 4. Discussion

Metaflumizone applied topically to cats and kittens 8 weeks of age and older at recommended volumes of 0.8 ml for cats  $\leq 4.0$  kg and 1.6 ml for cats  $> 4.0$  kg, designed to deliver a minimum of 40 mg kg<sup>-1</sup>, resulted in no adverse effect on mortality, body weight, food consumption, heart rate, body temperature, clinical, physical or neurological examinations, or clinical pathology parameters, even in kittens treated with doses 20–28 times the 40 mg kg<sup>-1</sup> minimum dose. Similarly, no adverse effects were noted even when kittens and cats were treated with seven applications of

five times the recommended dose, administered at 14-day intervals. In all the topical administration studies, transient salivation was observed sporadically in some cats and kittens, especially those treated with exaggerated dosages. However, salivation was noted with less frequency in animals treated with the 1× dose. In most instances, salivation initiated and resolved within minutes of treatment application. Since salivation was also noted in animals treated with placebo, it was likely unrelated to the active ingredient, metaflumizone.

Oral administration of 10% the recommended topical dose volume of the metaflumizone formulation, designed to mimic accidental exposure due to licking after application, resulted in considerable avoidance behaviors and transient salivation, but no other deleterious effects. Based upon the avoidance behaviors observed during forced oral administration, voluntary oral exposure is unlikely.

Although weight loss has been reported as the primary observable adverse effect noted in dogs treated orally with 30 mg metaflumizone kg<sup>-1</sup> daily for 12 months (EPA, 2006), the cats and kittens in the four studies described herein showed no such sign of reduced weight gain when dosed topically with this metaflumizone spot-on formulation, even when dosed repeatedly with five times the recommended dose at 2-week intervals.

The results of these studies show that metaflumizone is safe for repeated use in cats and kittens as young as 8 weeks of age.

#### 5. Conclusion

Metaflumizone repeatedly applied at doses up to and even greater than 5× the target dose caused no deleterious effects in cats and kittens. At recommended doses, it is safe for use in the control of fleas on cats 8 weeks of age and older.

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