UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

29/APR /2002

MEMORANDUM

Subject: EPA Reg. No: 2724-UOG Wellmark International / RF 2007 Collar
DP Barcode: D280714
Case No: 070821
PC Code: 047802, 105401

From: Masih Hashim, Toxicologist
Technical Review Branch
Registration Division (7505C)

Brant T. Bowles 4/29/2002 JCR

To: Suku Oonithan, PM 04
Insecticde-Rodenticide Branch
Registration Division (7505C)

Registrant: Wellmark International
1100 East Woodfield Road
Schaumburg, IL 60173

ACTION REQUESTED: The study on the new dog collar, RF 2007 Collar, with Propoxur 10% and Methoprene 2% is submitted for registration. Wellmark International is submitting a package with study MRID 45588701 conducted with exposure groups at 3x and 5x the proposed exposure dose. Rationale for using this product is given in the cover letter MRID 45588700 dated 8-1-2000.

COMMENTS AND RECOMMENDATIONS:

1. MRID 45588701 is a companion animal safety study in dogs. This study has been reviewed and classified by TRB as Acceptable. An adequate safety margin (>3x, with minimal effects at 5x) has been established.

2. Following is the executive summary for the proposed product:

EXECUTIVE SUMMARY: A companion animal safety study (MRID 45588701) was conducted to evaluate the safety margin of RF 2007 Collar (Propoxur 10%, Methoprene 2%) to be used for flea and tick control on dogs. Study consisted of three groups of dogs each with 6 males and 6 females (12 week old beagles, Source: Marshall Farms, North Rose, NY) in each group. Each dog in the two exposure groups wore 3 or 5 collars (3x & 5x proposed use rate), while the controls each wore 5 placebo collars. Termination of the study was determined when the plasma and red blood cell (RBC) cholinesterase ChE activity levels of the treated groups showed no significant differences for two consecutive analysis as compared with the controls. The animals were observed for viability and symptoms twice daily.

All animals survived to study termination. Two animals from Group 2 and one animal from Group 3 were found with their collars caught in their mouths and exhibited signs such as tremors, coughing, retching , excessive salivation, vomiting , diarrhea, dehydration, decreased activity, contracted pupils, cold to touch, ataxia, low posture, rough and soiled hair coat, blue mucous membranes of eyes and gums, and swollen abdomen . Three of these incidences occurred in Week 1 and one occurred again during Week 3 of the study. Salivation was noted in 5x animals in four incidences at the 1- or 2-hour observation on the day of collar application. These clinical signs appear to be consistent with ingestion of propoxur. There were no dose related differences in body weight or food consumption between the control and test groups.

Following application of the collar, plasma ChE values showed (statistically) significant decreases in male and female animals from Groups 3x and 5x. The treated males in both groups showed significant decreases at 8, 24 and 48 hours and 7, 14 and 21 days. Additionally 5x males showed significant differences at 28, 40 and 47 days. The females in the 3x and 5x Groups also showed differences at 8 and 24 hours and 7 days. Female animals from the 3x Group also showed a significant decrease at 48 hours. Mean RBC ChE for 5x males was significantly decreased at 48 hours. However, mean RBC ChE values for 5x males were often lower (by at least 18%) than control values, and this was occurring even near the end of the study (Day 54: 34.4 vs 48.8, a depression of about 30%). However, there was no indication of an effect in RBC ChE in 3x males from Day 21 to end of the study. The females showed no significant differences in mean RBC ChE values. Plasma ChE values were no longer significantly depressed by Day 14 in 3x and 5x females. The more frequent significant ChE depression in males may have been due in part to their biting the collars of other males during exercise periods.

Hematology, clinical chemistry (except for ChE) and urinalysis revealed no treatment related changes in 3x and 5x groups. There were no remarkable changes in any of the parameters measured.

3. The acute toxicology of the product will be satisfied by studies submitted for EPA Reg. No. 2724-254. The toxicity is mostly due to Propoxur. Precautionary labeling of for File Symbol 2724-UOG should be similar to #2724-254.

Reviewer: Masih Hashim, DVM., Ph.D.
Secondary Reviewer: Byron T. Backus, Ph.D.

MH 4-29-02
BTB 4-29-02

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety Dog (OPPTS 870.7200)

EPA I.D. NUMBERS: : DB Barcode: D280714; MRID: 45588701

TEST MATERIAL: RF 2007 Collar, {P.C. Codes 047802 (Propoxur); 105401 (Methoprene)}

STUDY NUMBER: {Ricerca} 013038-1

TESTING FACILITY: Ricerca, LLC
7528 Auburn Road
Painsville, OH 44077-1000

SPONSOR: Wellmark International, 1100 East Woodfield Road, Schaumburg IL 60173

TITLE OF REPORT: A Companion Safety Study Evaluation Study in Dogs with RF 2007 Collar

AUTHORS: J. Bassett & M. Watson

EXECUTIVE SUMMARY: A companion animal safety study (MRID 45588701) was conducted to evaluate the safety margin of RF 2007 Collar (Propoxur 10%, Methoprene 2%) to be used for flea and tick control on dogs. Study consisted of three groups of dogs each with 6 males and 6 females (12 week old beagles, Source: Marshall Farms, North Rose, NY) in each group. Each dog in the two exposure groups wore 3 or 5 collars (3x & 5x proposed use rate), while the controls each wore 5 placebo collars. Termination of the study was determined when the plasma and red blood cell (RBC) cholinesterase ChE activity levels of the treated groups showed no significant differences for two consecutive analysis as compared with the controls. The animals were observed for viability and symptoms twice daily.

All animals survived to study termination. Two animals from Group 2 and one animal from Group 3 were found with their collars caught in their mouths and exhibited signs such as tremors, coughing, retching , excessive salivation, vomiting , diarrhea, dehydration, decreased activity, contracted pupils, cold to touch, ataxia, low posture, rough and soiled hair coat, blue mucous membranes of eyes and gums, and swollen abdomen . Three of these incidences occurred in Week 1 and one occurred again during Week 3 of the study. Salivation was noted in 5x animals in four incidences at the 1- or 2-hour observation on the day of collar application. These clinical signs appear to be consistent with ingestion of propoxur. There were no dose related differences in body weight or food consumption between the control and test groups.

Following application of the collar, plasma ChE values showed (statistically) significant decreases in male and female animals from Groups 3x and 5x. The treated males in both groups showed significant decreases at 8, 24 and 48 hours and 7, 14 and 21 days. Additionally 5x males showed significant differences at 28, 40 and 47 days. The females in the 3x and 5x Groups also showed differences at 8 and 24 hours and 7 days. Female animals from the 3x Group also showed a significant decrease at 48 hours. Mean RBC ChE for 5x males was significantly decreased at 48 hours. However, mean RBC ChE values for 5x males were often lower (by at least 18%) than control values, and this was occurring even near the end of the study (Day 54: 34.4 vs 48.8, a depression of about 30%). However, there was no indication of an effect in RBC ChE in 3x males from Day 21 to end of the study. The females showed no significant differences in mean RBC ChE values. Plasma ChE values were no longer significantly depressed by Day 14 in 3x and 5x females. The more frequent significant ChE depression in males may have been due in part to their biting the collars of other males during exercise periods.

Hematology, clinical chemistry (except for ChE) and urinalysis revealed no treatment related changes in 3x and 5x groups. There were no remarkable changes in any of the parameters measured.

3. The acute toxicology of the product will be satisfied by studies submitted for EPA Reg. No. 2724-254. The toxicity is mostly due to Propoxur. Precautionary labeling of for File Symbol 2724-UOG should be similar to #2724-254.

This study (870.7200) is classified **Acceptable** as demonstrating an acceptable (>3) margin of safety in dogs associated with the proposed use. Effects seen at 5x were minimal.

COMPLIANCE: The study has Quality Assurance Statement (p.4), Data Confidentiality (p.2) and Good Laboratory Practice Compliance (p.3) statements are included.

1. MATERIALS

A. Test Material: RF 2007 Collar-Test

Description: Black collar
Lot/Batch No.: (RF 2007) 00083100 (p. 15)
Active Ingredients: Propoxur 10% and Methoprene 2%
Storage Conditions: Room temperature, store in original container, away from children.

B. Administration:

Collars were applied to and worn around neck. "Treated dogs had either 3 or 5 collars placed around their necks to achieve 3x and 5x the recommended use rated, respectively. Collars were applied in either 3 per layer (3x) or in a combination of 2 per layer and 3 per layer (5x).Layers of collars were held together with zip ties to prevent individual collars from coming off during treatment. Occasionally, when collars were found off of a dog, the incident was documented and the collars were reapplied to the animal. In one case, the collars from one animal were missing and that animal was excluded from the mean cholinesterase determinations. Seven other dogs from Groups 2 and 3 were missing one or two collars toward the end of the study (Day 42 to the end). These were documented in the study file."

C. Control

RF 2007 Collars- placebo
Lot/Batch No. ED 2002

D. Test animals

Species: Dog
Breed: Beagle
Age and weight at study initiation: 12 weeks old, mean weight; male 2.9-3.5 kg, female 2.7-2.9 kg
Source: Marshall Farms, North Rose, NY
Housing: Individual
Diet: Certified Canine Diet #5007, PII Feeds, Inc., St. Louis, MO, *ad libitum*
Water: tap water, *ad libitum*
Environmental conditions:
Temperature: 64-84°F (18-29°C) [stated in the report on p. 17]
Humidity: 30-70%
Photoperiod: 12 hr dark/light
Acclimation period: 14 days prior to test article application.
Immunization: From p. 17 of MRID 45241603: The supplier immunized all the animals against Distemper, hepatitis, leptospirosis, parvo and parainfluenza.

II. STUDY DESIGN

A. In life dates

Study initiation January 16, 2001, Experiment start date February 8, 2001, Termination April 10, 2001.

B. Animal assignment/Dosage and Administration

Each dog was identified by a unique ear tattoo and cage card and a unique laboratory number placed on study. "Male and female animals were randomly assigned to the control and treatment groups as described in Study Design. One male and one female were assigned to a replacement group. Randomization was conducted to control bias. In order for the assignment to be considered acceptable, the body-weight mean for each sex of a treated group differed from the other group mean by no more than 20%. Animals from the replacement group were used as necessary in the event of injury, death, etc. of the treatment group animals prior to initiation of test material administration. Unused animals in the replacement group were disposed of on the first day of test article application."

"The test article was used as supplied by the Sponsor. The collars were removed from the supplied packages on the day of application."

"Treated dogs had either 3 or 5 collars placed around their necks to achieve 3x and 5x the recommended use rated, respectively. Collars were applied in

either 3 per layer (3x) or in a combination of 2 per layer and 3 per layer (5x).

Layers of collars were held together with zip ties to prevent individual collars from coming off during treatment. Occasionally, when collars were found off of a dog, the incident was documented and the collars were reapplied to the animal. In one case, the collars from one animal were missing and that animal was excluded from the mean cholinesterase determinations. Seven other dogs from Groups 2 and 3 were missing one or two collars toward the end of the study (Day 42 to the end). These were documented in the study file."

TABLE 1. Experimental design

Group	*No. of animals*		*Dose Level*	*Number of collars*
	Male	*Female*		
1	*6*	*6*	*Placebo Collar (0X)*	*5*
2	*6*	*6*	*3X*	*3*
3	*6*	*6*	*5X*	*5*

Data taken from p. 14, MRID 45588701
[a]Collars were applied on day 0.

C. Dose selection rationale

The study was intended to demonstrate safety for the use of the test article at 3x and 5x the proposed dose.

D. Experimental Design

The test article is intended for use on domestic dogs as a neck collar for flea and tick control. This study was designed to demonstrate safety of the test article by using the test article at three (3x) and five (5x) times the proposed use rate. The animals remained on the on study until the plasma and red blood cell activity levels of cholinesterase for the treated dogs showed no statistically significant differences when compared with the control animals. Animals wore the collars until such levels were achieved and followed for one additional determination. This was the termination point of the study. Dose levels were selected (as shown above) by the Sponsor. The collars were supplied by the sponsor in plastic bags and were stored at the room temperature.

E Pathological parameters

Blood samples were collected via jugular vein from all animals fasted for 16-24 hours. Hematology, clinical chemistry and urinalysis were performed on all animals once (approximately 24 hours) prior to test material administration and during the first and last week of test article application. Plasma and red blood cell cholinesterase activities were determined in blood samples from all animals twice prior to and after exposure to the test article application for (approximately)

8, 24, 48 hours, and days 7, 14, 21, 28, 35, 40, 43, 47, 50, 54 and 57.
Cholinesterase activity was determined using a modified Ellman method employing conditions in accordance with EPA advisory notices'.
The following (checked) parameters were evaluated for each dog for hematology and clinical chemistry.

a. Hematology

X	Hemoglobin (HGB)*	X	Leukocyte differential count*
X	Hematocrit (HCT)*	X	Mean corpuscular HGB (MCH)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Leukocyte count (WBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count	X	Reticulocyte count
X	Blood clotting measurements (Thromboplastin time) (Clotting time) (Prothrombin time)*		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHERS
X	Sodium	X	Total protein*
X	Potassium*	X	Albumin
X	Calcium*	X	Globulin*
X	Chloride*	X	Albumin
	Inorganic Phosphorus*	X	Globulin (calculated)
X	Potassium*		Albumin/globulin (A/G) ratio (calculated)
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total Cholesterol
X	Aspartate aminotransferase (AST)	X	Blood creatinine*
X	Alanine amino transferase (ALT)	X	Blood urea nitrogen*
X	Alkaline phosphatase	X	Creatinine
X	Creatine kinase		
X	Gamma-glutamyltransferase (GGT)		
X	Cholinesterase(ChE) both plasma & RBC		
X			

*Recommended in OPPTS 870.7200 Guidelines.
Cholinesterase activity was determined using a modified Ellman method.

F. Urinalysis

Urine was collected in individual cages and the following parameters were evaluated.

-		X	
X	Specific gravity	X	Glucose
X	Occult blood	X	Nitrate
X	Protein	X	Urobilinogen
X	pH	X	Color/appearance
X	Bilirubin	X	Microscope examination of sediment
X	Ketones		

Note: Urinalysis not recommended in OPPTS 870.7200

G. Statistics

From page 22 of MRID 45588701 "Statistical analyses were performed separately for males and females. The statistical analyses were performed on body weight, body weight gain and food consumption to compare the treatment group means to the control group mean and to look for evidence of a dose-related trend. These statistical methods were also used to analyze hematology, blood chemistry and urinalysis parameters."

"First, Bartlett's test was used to test the normality of the data and variance homogeneity. Bartlett's test was performed at the 1% level of significance. If Bartlett's test was significant, nonparametric procedures were used. Dunn's summed-rank test was used to compare the treatment groups to the control group. If Bartlett's test was not significant, parametric (normal-theory) procedures were used. Bonferroni's t-test was used to compare the treatment groups to the control group except that, in the parametric cases, the test for trend was performed only if the test for lack of fit was not significant at the 1% level. A test for lack of fit was not applicable in the nonparametric cases. Regression analysis was used to test for a linear trend over the doses. In both the nonparametric and parametric cases, for the means comparisons, significance was reported at the two-sided experiment-wise error rates of 1 and 5% (p 0.01, p 0.05). In the tests for trend, significance was reported only at the two-sided 1% level (p 0.01)."

H. Disposition of animals

At the end of the study period, surviving animals were returned to the facility stock. No postmortem examinations were conducted.

I. Compliance

The study has Quality Assurance Statement (p.4), Data Confidentiality (p.2) and Good Laboratory Practice Compliance (p.3) statements are included.

III. RESULTS

A. Exposure levels

No information is provided in MRID 45588701 as to the weight of a representative collar. In addition, there is no information on the proposed label about the net weight of the collar.

B. Mortality

No dogs died on the study.

C. Clinical signs

From the study report summary physical observation data: Tables 1 and 2 Individual physical observation data: Tables A-1 and A-2)Two Group 3x dogs and one Group 5x dog were found with their collars caught in their mouths and exhibited several of the following clinical observations: tremors, cold to touch, vomit, contracted pupils, excessive coughing, retching, salivation, diarrhea, dehydration, decreased activity, ataxia, low posture, rough and soiled hair coat, mucous membranes of eyes and gums blue, soft feces and abdomen swollen. There were 3 incidences occurring in Week 1 and one incidence for one animal again during Week 3 of the study. These signs were treatment related, i.e.,suggestive of propoxur ingestion. Four incidences of salivation occurred in 5x Group dogs at the 1- or 2-hour observation on the day of collar application.

There were red ears and soft feces/diarrhea were noted in all groups throughout the study. These findings are common for the laboratory beagle and are considered not related to treatment with the RF 2007 collar. No other treatment-related clinical signs were noted throughout the course of the study.

TABLE 2. Selected clinical observations in dogs wearing propoxur-methoprene collars

Treatment group	Sex	Week	Observation
(0x) Control	M	3	soft feces (one animal)
3x treatment	M	1, 3	Tremors, cold to touch, vomit, contracted pupils, coughing, retching, ataxia, excessive salivation, swollen abdomen, dehydration, low posture, blue mucous membranes (2 animals)
5X - Treatment	F	1, 3	Tremors, cold to touch, excessive salivation, swollen abdomen, vomit, contracted pupils, coughing, retching, ataxia, dehydration, low posture, blue mucous membranes (one animal)

Data taken from p. 22, 81-84 MRID 45588701

D. Body weight and weight gain

The body weights of dogs at initiation were within 20% requirement. The 3x males showed higher mean body weights that were statistically significant difference ($p \leq 0.05$) for all except pretest 1, which was $p \leq 0.01$) the pretest weights, Day 0 and Weeks 1, 4, 5, 6, 7, 8 and 9. The higher body weights for 3x males continued through most of the study and are considered not related to application of the collars. No other significant differences in body weights were noted for either male or female dogs during the study.

E. Food consumption

The Food consumption was statistically significantly different from controls for the male dogs in Group 3x ($p \leq 0.05$ for Week 3 and $p \leq 0.01$) for Weeks 4-9, and for 5x males ($p, \leq 0.05$ Week 8). There was no relationship with the increase in food consumption to weight gain. This is no treatment related effect.

F. Hematology

Hematology data generated during the pre-dose period were all considered normal for beagle dogs of the age employed. Platelet counts were statistically significantly increased compared to controls ($p \leq 0.05$) for 5x females at Week 1 and at termination. Prothrombin time was prolonged in treated males, 3x females, and shortened in 5x females (all $p \leq 0.01$) at termination. Total white cell count in 5x females was significantly increased at Week 1 ($p \leq 0.05$). All the individual values in treated dogs were (generally) within the range seen in control dogs and the inter-group differences were not related to treatment with RF 2007 collar.

No other statistical differences in hematology data were noted.

G. Clinical chemistry

The total protein and globulin values for 5x males were decreased ($p \leq 0.05$) at termination, and the inorganic phosphorus values for3x males were increased ($p \leq 0.05$). These differences were biologically insignificant and unrelated to exposure to the collar. There were no other significant changes for clinical chemistry.

Cholinesterase (ChE)

Red blood cell ChE was noticebly decreased in 5x males at 24 hours (0.75 control value), 48 hours (0.81 control value), Day 14 (0.75x control value), Day 28 (0.77x control value) and Day 57 (0.83x control value). By contrast males in the 3x Group showed approx. 10% RBC (ChE) inhibition. One male (# 300571) was excluded from data for losing collar. This animal had consistently showed high RBC ChE activity in readings from baseline to Day 21. One male (#300572) in the 5X group showed an approximate 65% drop in plasma ChE value at 8 hours in relation to baseline. The females had no differences in the RBC ChE values. Statistically significant decreases in plasma ChE values were noted for male and female dogs after Day 7 for 3x and 5x treatments. Treated males showed significant decreases ($p \leq 0.01$) at 8 hours, 24 hours, 48 hours (3x Group only), and on Days 7 (5x Group only), 14 and 21. Decreases ($p \leq 0.05$) were noted for 3x Group on Day 7, and for 5x Group at 48 hours, and on Days 28, 40 and 47. There were no significant differences in ChE activity in males on Days 35, 43, 50, 54 and 57. Plasma ChE values in females were significantly decreased ($p<0.05$) at 8, 24 and 48 hours and Day 7 for 3x Group and at 8 and 24 hours, and Day 7 for the 5x females. There were no significant differences in ChE values by Day 14 for females and by

TABLE 3. Selected changes in cholinesterase activities in dogs wearing propoxur-methoprene collars[a]

Parameter /sample time	Males (values in U/L)			Females (values in U/L)		
	Controls	3X	5X	Controls	3X	5X
RBC ChE Baseline combined	59.3	63.0	59.8	58.7	65.2	68.2
RBC ChE at 8 hours	82.5	75.0	70.5	75.7	78.3	81.0
RBC ChE at 24 hours	70.0	66.2	52.5	64.2	68.7	67.0
RBC ChE at 48 hours	70.3	63.2	56.8*	58.0	66.7	70.2
RBC ChE at day 7	41.3	37.7	36.0	39.7	43.5	48.2
RBC ChE at day 14	54.2	49.5	40.7	41.7	48.2	48.7
RBC ChE at day 21	59.7	60.2	54.5	56.2	63.3	67.2
RBC ChE at day 28	53.3	49.2	41.0	47.2	49.5	52.5
RBC ChE at day 35	56.0	55.2	46.2	57.0	64.0	64.8
RBC ChE at day 40	54.2	53.3	38.2	48.2	54.2	56.0
RBC ChE at day 43	56.3	55.7	45.6	48.0	55.5	57.2
RBC Che at day 47	56.5	57.3	45.6	49.2	55.0	59.2
RBC Che at day 50	51.5	48.7	41.2	42.5	49.2	52.8
RBC Che at day 54	48.8	45.8	34.4	35.2	47.0	46.7
RBC Che at day 57	51.8	54.3	42.8	42.8	50.3	54.5
Plasma ChE Baseline combined	2103.1	1973.4	1962.6	1985.0	1904.1	1946.3
Plasma ChE at 8 hours	1918.8	1341.2**	1342.7**	1758.8	1271.0*	1272.3*
Plasma ChE at 24 hours	1887.5	1434.8**	1280.0**	1751.2	1229.0*	1276.5*
Plasma ChE at 48 hours	1825.0	1294.8**	1397.2*	1725.5	1311.5*	1369.3
Plasma ChE at day 7	1765.8	1362.7*	1213.0**	1597.7	1231.2*	1217.3*
Plasma ChE at day 14	1789.5	1401.7**	1317.5**	1494.7	1292.0	1227.2
Plasma ChE at day 21	1730.0	1342.0**	1347.8**	1517.5	1300.7	1292.7
Plasma ChE at day 28	1716.0	1421.7	1394.8*	1610.8	1334.3	1364.1
Plasma ChE at day 35	1775.2	1515.7	1497.0	1595.7	1414.2	1446.8
Plasma ChE at day 40	1811.5	1532.2	1445.4*	1622.3	1416.5	1475.7
Plasma ChE at day 43	1830.5	1624.7	1538.6	1667.3	1489.7	1523.5
Plasma ChE at day 47	1814.7	1574.2	1469.0*	1601.2	1477.8	1477.2
Plasma ChE at day 50	1823.0	1602.5	1555.4	1677.0	1509.8	1544.2
Plasma ChE at day 54	1854.5	1605.0	1587.4	1652.7	1530.8	1576.3
Plasma ChE at day 57	1850.8	1591.3	1582.8	1672.3	1526.0	1553.2

Data taken from Tables 11& 12, pp. 38-41, MRID 45588701

[a]Mean values * $p \leq 0.05$ relative to control value ** $p \leq 0.01$ relative to control value

I. Urinalysis

The urinary pH recorded at termination for 3x males was significantly lower than the control value ($p = 0.05$). The difference was slight and there was no evidence of a dose-related trend. There were no other statistically significant differences noted for urinalysis."

Statistically significant differences between groups occurred in females during week 1, involving elevated levels of inorganic phosphorus (controls: 8.1 mg/dL; 1X: 9.0 mg/dL [statistically significant at $p \leq 0.05$]; 3X: 9.0 mg/dL [statistically significant at $p \leq 0.05$]; 5X: 8.8 mg/dL).Cholinesterase activities (particularly RBC, but also, to a lesser extent, plasma) were depressed (sometimes significantly) in a dose-related fashion in males and females of all collar-wearing groups at 8 hours, 24 hours, and 48 hours, as indicated in Table 3.

J. Necropsy Findings

"All the dogs on study survived the experimental period and were returned to the test facility stock. No animals were killed for necropsy.

IV DISCUSSION

All animals survived to study termination. Two animals from 3x Group and one animal from 5x Group were found with their collars caught in their mouths and exhibited signs (Table 2) consistent with propoxur ingestion. Following application of the collar, plasma ChE values showed (statistically) significant decreases in male and female animals from Groups 3x and 5x. The treated males in both groups showed significant decreases at 8, 24 and 48 hours and 7, 14 and 21 days. Additionally 5x males showed significant differences at 28, 40 and 47 days. The females in the 3x and 5x Groups showed differences at 8 and 24 hours and 7 days. Female animals from the 3x Group showed a decrease at 48 hours. Mean RBC ChE for 5x males was significantly decreased at 48 hours. However, mean RBC ChE values for 5x males were often lower (by at least 18%) than control values, and this was occurring even near the end of the study (Day 54: 34.4 vs 48.8, a depression of about 30%). However, there was no indication of an effect in RBC ChE in 3x males from Day 21 to end of the study. The females showed no significant differences in mean RBC ChE values. Plasma ChE values were no longer significantly depressed by Day 14 in 3x and 5x females.

The more frequent plasma ChE depression in males may have been in part due to oral exposure as a result of biting other dogs'collars during periods while the dogs were in group exercise. All the clinical symptoms and subsequent ChE variations due to collar bite may have been avoided by close supervision during exercise/socializing of the dogs.

There were no dose-related differences in any of the groups for the parameters measured including food consumption, body weight gains, hematology, clinical chemistry (other than ChE values) and urinalysis. Any variations have similar incidence in each group, sporadic or an adjustment to the RF 2007 collar wear.

The study in MRID 45588701 with RF 2007 Collar in dogs is **Acceptable** in accordance with the Sub-Division F guidelines. An adequate safety margin (>3x) and with minimal effects at 5x has been established.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D280714
2. **PC CODE:** 047802, 105401
3. **CURRENT DATE:** April 29, 2002
4. **TEST MATERIAL:** RF 2002 Collar, containing Propoxur and Methoprene

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion Animal Safety/Dogs/ Ricerca/2724-UOG/April 29, 2002	45588701	No mortality in the dogs by wearing RF 2007 collar at 3x and 5x the proposed use. There were no dose related effects in parameters including food consumption, body weight gains, hematology, clinical chemistry (except ChE values) and urinalysis. The study demonstrated (>3x) margin of safety in dogs associated with the proposed use. Toxic effects seen at 5x were minimal.	-	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self-Validated**