

Appendix D

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Study Type: One-Year Feeding Study in Beagle Dogs

Accession Number: 250740-250744

MRID Number: Not specified

Sponsor: FMC Corporation, Princeton, NJ

Contracting Lab: ToxiGenics, Inc., Decatur, IL

Date: 6 June 1983

Test Material: Carbofuran, Technical

Protocol:

1. Test substance and purity: Carbofuran, Technical Grade, 96.1 percent purity, Code Number FMC 10242(2843), Lot Number M607210, assigned ToxiGenics test article code number 9/81-261, light brown, crystalline solid.

2. Species of animals: Purebred beagle dogs were obtained from the closed breeding colony of White Eagle Laboratories, Doylestown, PA. The dogs were six to eight months of age and weighed five to ten kilograms at the beginning of the study. Experimental and control groups contained six dogs of each sex. Prior to shipment, all dogs were inoculated against canine distemper, infectious canine hepatitis, and rabies.

3. Dosing Schedule: The animals were delivered, quarantined, and fed a pulverized basal diet, Purina Certified Canine Diet

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5007, on a 24-hour per day schedule for three weeks. Thereafter until study termination, the dogs were maintained on a 2-hour per day feeding interval. After three months of quarantine, the dogs received carbofuran in the diet at concentrations of 0, 10, 20 or 500 ppm.

The diets were prepared at weekly intervals and stored at ambient temperature until use. Carbofuran was mixed with the basal diet with a Hobart Model V-1401 mixer to the above designated concentrations. Samples of the diets were extracted and analyzed by gas chromatography during the one week storage period.

4. Parameters to be examined: Pre-test evaluations were for the following: ectoparasites, endoparasites, body weight, hematology, clinical chemistry, ophthalmologic analysis, urine analysis, plasma cholinesterase activity and erythrocyte cholinesterase activity. The test parameters examined during the one year chronic study of carbofuran included the following:

- mortality, morbidity and pharmacotoxic signs were observed daily.
- body weight and food consumption were recorded weekly and were used to calculate the grams of food consumed per kg body weight.
- ophthalmologic analysis was conducted at six month intervals
- routine clinical chemistry was carried out monthly.

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- plasma, and erythrocyte cholinesterase were analyzed monthly and brain cholinesterase at 12 months.
- hematology was evaluated monthly.
- urinalyses were conducted every two months.
- organ weight and organ-to-body weight ratios were determined at necropsy.
- microscopic examinations of 32 tissues plus all gross lesions were carried out.

5. Statistics used: In the study, statistical analyses were conducted for continuous and non-continuous variables. Quantitative continuous variables were analyzed using Analysis of Variance (ANOVA). Significant differences determined by ANOVA were further examined using Scheffe's (unequal population) or Tukey's (equal population) procedures. Non-continuous variables were analyzed by the Kruskal-Wallis Statistic Test. Significant differences determined by this test were further analyzed by the Kruskal-Wallis' Multiple Comparison Test.

Results

1. Preliminary Health Evaluation - Pretest evaluation of all animals for growth and clinical pathology parameters reflected normal strain variance and no unusual findings.
2. Diet Analysis - Analyses of sample test diets confirmed that diets were mixed homogeneously and that they were stable for 7 days.

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Over the one year chronic study period, among the monthly dietary analyses reported, only one diet exceeded the $\pm 20\%$ range of the target concentration (treatment month, 10; target concentration 10 ppm; assayed concentration, 12.3 ppm).

3. Mortality - One death occurred during the study. One male died following 201 days of exposure to the 500 ppm carbofuran test diet. A pronounced deterioration in the health of this animal was observed in the week before death. At necropsy, the body was emaciated and dehydrated. Microscopic pathology revealed atrophy, hypoplasia, and discoloration of numerous tissues and organs plus mild renal mineralization and adrenal cortical degeneration. These observations are consistent with metabolic disease. Death was considered to be directly related to dietary exposure to carbofuran. In order to protect against further reductions in body weight and to prevent additional deaths, the remaining animals in the 500 ppm groups were provided supplemental control diet intermittently through study termination. The frequency and consumption of control diet provided the 500 ppm animals were not reported.

4. Body weight - The mean body weights for all test and control groups at ten week intervals are summarized in Table 1. Body weight gains for male and female dogs in the 10 and 20 ppm groups were similar to their respective controls showing no adverse effect of

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TABLE 1

MEAN BODY WEIGHT FOR MALE AND FEMALE BEAGLE DOGS RECEIVING CARBOFURAN
FOR ONE-YEAR

Treatment Group	Mean Body Weight (kg)							
	Initial Week	Week 10	Week 20	Week 30	Week 40	Week 50	Final Week	Total Weight Change ^a
Male								
Control (0 ppm)	7.5 0.9 ^b	8.8 1.1	9.3 1.3	9.6 1.3	9.6 1.3	10.0 1.4	10.0 1.4	2.5 -
10 ppm	7.8 1.9	9.1 2.1	9.6 2.2	10.0 2.2	9.9 2.2	10.3 2.2	10.2 2.2	2.4 -
20 ppm	7.7 0.9	9.0 1.1	9.3 0.9	9.6 1.0	9.6 0.9	10.0 1.0	9.9 1.0	2.2 -
500 ppm	7.5 0.9	7.2 1.0	6.1** 1.0	7.0 ^c 0.9	6.5* 0.7	6.5* 1.0	5.6* 1.3	0.9 ^c
Female								
Control (0 ppm)	6.3 1.0	7.1 1.0	7.5 0.9	7.7 0.9	8.0 0.9	8.0 1.0	7.8 1.0	1.5 -
10 ppm	6.7 1.1	7.2 1.4	7.5 1.4	7.6 1.2	7.7 1.4	7.7 1.5	7.8 1.5	1.1 -
20 ppm	6.4 1.0	7.0 1.1	7.3 1.3	7.1 1.2	7.4 1.5	7.7 1.6	7.6 1.6	1.2 -
500 ppm	6.9 1.4	6.6 0.9	6.2 0.9	7.0 0.9	6.4 0.8	6.3 0.9	5.5 0.7	-0.4** -

^aDifference between mean initial weights and mean final weights at death.

^b + standard deviation

^cOne animal died in week 29, hence weights in the 30th to final weeks represent the mean of animals in this group.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

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carbofuran at these doses. Significantly lower body weights were reported for the 500 ppm males from week 20 to the study termination. At the end of the study, body weight losses for the 500 ppm animals of both sexes were significant. The LOEL for body weight effects in male and female dogs was 500 ppm and the NOEL for both sexes was 20 ppm.

5. Food and Test Article Consumption - Table 2 summarizes the mean food consumption and calculated carbofuran consumption for all groups. Food and test article consumption by 10 and 20 ppm groups of males and females were similar to their respective controls. The only significant intergroup differences were in the 500 ppm groups in which food consumptions were lower at 44 weeks. Test article consumptions were approximately two-fold higher in the 20 ppm groups and 30 to 60-fold higher in the 500 ppm groups compared with the 10 ppm groups.

6. Clinical Chemistry - The clinical parameters examined monthly throughout the study included the following: BUN, glucose, alkaline phosphatase, SGOT, SGPT, LDH, total cholesterol, total and direct bilirubin, total protein, albumin, calculated globulin, calculated albumin to globulin ratio, Na, K, Cl and Ca. Most of the statistically significant changes in clinical chemistry were found in the 500 ppm male group in month 12. These are summarized in Table

3. Statistically significant depressions in total protein, calcium,

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TABLE 2

MEAN DAILY FOOD CONSUMPTION AND CALCULATED MEAN DAILY CARBOFURAN CONSUMPTION
FOR MALE AND FEMALE DOGS IN ONE-YEAR ORAL TOXICITY STUDY

Treatment Group	Mean Daily Food Consumption (Grams + SD)		
	Week 1	Week 30	Week 44
<u>Male</u>			
Control	241 ± 21	224 ± 28	177 ± 16
10 ppm	256 ± 40 (2.6) ^a	227 ± 27 (2.3)	180 ± 33 (1.3)
20 ppm	209 ± 38 (4.2)	225 ± 34 (4.5)	189 ± 21 (3.6)
500 ppm	182 ± 54 (91.0)	217 ± 78 (108.5)	113 ± 26 ^{**} (56.5)
<u>Female</u>			
Control	278 ± 57	238 ± 28	186 ± 37
10 ppm	238 ± 18 (2.4)	184 ± 75 (1.8)	182 ± 44 (1.8)
20 ppm	249 ± 46 (5.0)	222 ± 60 (4.4)	219 ± 54 (4.4)
500 ppm	204 ± 49 (102.0)	212 ± 86 (106.0)	109 ± 28 [*] (54.5)

^aNumber in parenthesis is the calculated mean daily carbofuran consumption in milligrams.

^{*}Significantly different from control values ($p \leq 0.05$)

^{**}Significantly different from control values ($p \leq 0.01$).

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TABLE 3

SUMMARY OF STATISTICALLY SIGNIFICANT DIFFERENCES
IN CLINICAL CHEMISTRY AND HEMATOLOGY DATA
BETWEEN THE UNTREATED CONTROL AND 500 PPM
CARBOFURAN TREATED MALES AFTER ONE-YEAR
OF FEEDING

Clinical Parameter	Treatment Group	
	0 ppm Control	500 ppm
Total Protein (g/dl)	6.5 $\pm$ 0.4	5.3 $\pm$ 0.5*
Calcium (mg/dl)	10.7 $\pm$ 0.3	9.2 $\pm$ 0.7**
Sodium (meq/l)	155 $\pm$ 2	144 $\pm$ 8*
Hematocrit (%)	47.6 $\pm$ 2.3	37.8 $\pm$ 3.6**
Hemoglobin (g/dl)	16.9 $\pm$ 1.0	13.1 $\pm$ 1.3**
Total Erythrocyte	7.4 $\pm$ 0.5	5.9 $\pm$ 0.5 **

*Significantly different from control value ($p \leq 0.05$).**Significantly different from control value ($p \leq 0.01$).

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and sodium were determined in the high-dose males. Occasional depressions in total protein, calcium, sodium, cholesterol, bilirubin and reticulocytes were observed in the 500 ppm males in earlier treatment months, but were normal at terminal sacrifice (not tabulated).

Cholinesterase Activity - Plasma and erythrocyte cholinesterase activities are summarized for all test and control groups at day three, and one, six and twelve months in Table 4. Brain cholinesterase was determined only at twelve months. The NOELs for this enzyme activity are based on approximately 70% of control being a biologically significant effect margin. Depressions in plasma and erythrocyte cholinesterase activity were observed and were compound related. Significant reductions in plasma cholinesterase activity are reported in Table 4 for both male and female carbofuran-treated beagle dogs. In the 10 ppm males, the plasma enzyme activity was slightly reduced between day 3 and one month and was similar to the controls for months 6-12. Plasma cholinesterase activity was significantly depressed in 20 ppm and 500 ppm males from day 3 through 12 months. An apparent dose-response was observed in the plasma of male groups. The LOELs for plasma cholinesterase effects were 500 ppm for both sexes. The NOELs for both sexes are 20 ppm.

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TABLE 4

PLASMA, ERYTHROCYTE AND BRAIN CHOLINESTERASE ACTIVITY FOR MALE AND FEMALE DOGS IN ONE-YEAR ORAL TOXICITY STUDY WITH CARBOPURAN

Treatment Group	Plasma (IU/ml)						Erythrocyte (IU/ml)					Brain (IU/m			
	Day 3 Con.	One Month Con.	Six Months Con.	Twelve Months Con.	Z	Day 3 Con.	One Month Con.	Six Months Con.	Twelve Months Con.	Z	Day 3 Con.	One Month Con.	Six Months Con.	Twelve Months Con.	Brain (IU/m
Male Control	2.11 0.25 ^b	2.30 0.26	2.01 0.19	2.26 0.16	100	1.49 0.22	1.46 0.15	1.54 0.19	1.66 0.15	100	1.49 0.22	1.46 0.15	1.54 0.19	1.66 0.15	0.49 0.07
10 ppm	1.73* 0.33	1.87* 0.35	1.74 0.38	1.99 0.44	88	1.30 0.19	1.40 0.24	1.39 0.15	1.56 0.18	94	1.30 0.19	1.40 0.24	1.39 0.15	1.56 0.18	0.48 0.07
20 ppm	1.59** 0.14	1.58** 0.18	1.53** 0.09	1.58** 0.14	70**	1.42 0.12	1.54 0.17	1.50 0.15	1.71 0.17	103	1.42 0.12	1.54 0.17	1.50 0.15	1.71 0.17	0.55 0.08
500 ppm	0.36** 0.11	0.35** 0.06	0.27** 0.06	0.49** 0.25	22**	1.49 0.20	1.33 0.14	1.13** 0.17	1.35 0.22	81	1.49 0.20	1.33 0.14	1.13** 0.17	1.35 0.22	0.37 0.05
Female Control	1.96 0.42	2.15 0.40	1.90 0.36	2.20 0.31	100	1.43 0.08	1.45 0.09	1.49 0.03	1.65 0.20	100	1.43 0.08	1.45 0.09	1.49 0.03	1.65 0.20	0.32 0.04
10 ppm	1.65 0.32	1.79 0.43	1.79 0.38	1.87 0.44	85	1.54 0.08	1.63 0.18	1.48 0.14	1.68 0.08	102	1.54 0.08	1.63 0.18	1.48 0.14	1.68 0.08	0.37 0.07
20 ppm	1.56 0.29	1.76 0.31	1.63 0.25	1.83 0.34	83	1.54 0.14	1.51 0.08	1.38 0.17	1.58 0.11	96	1.54 0.14	1.51 0.08	1.38 0.17	1.58 0.11	0.36 0.05
500 ppm	0.33** 0.07	0.40** 0.08	0.30** 0.07	0.50** 0.16	23*	1.54 0.12	1.56 0.11	1.30 0.18	1.55 0.20	94	1.54 0.12	1.56 0.11	1.30 0.18	1.55 0.20	0.46* 0.11

Percent of untreated control.

of standard deviation.

777-1000 is reported.

the 44% increase is reported.

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The erythrocyte cholinesterase activity in Table 4 was significantly depressed only in the 500 ppm (LOEL) male group and in no female groups. The NOEL for erythrocyte cholinesterase was 20 ppm in males and 500 ppm in females.

The brain cholinesterase activity at 12 months was 76% of the untreated control in the 500 ppm male group, but was 144% of the untreated control in the 500 ppm female group. The biological impact of these findings is probably not significant. However, recall that in order to sustain life, the high-dose animals were provided control diet intermittently as a supplement to the 500 ppm diet. In females, the increase perhaps reflects an overcompensation in readjustment to the control diet following removal of the test diet with the cholinesterase inhibitor.

7. Hematology - The hematocrit, hemoglobin and erythrocyte values were determined monthly in all animals. These values were significantly depressed ($p \leq 0.01$) in the 500 ppm male group, beginning with month 5 and continuing to the end of the study (Table 3). Less significant reductions ($p \leq 0.05$) were observed in 500 ppm females in months six and eight. The hematology values were normal all other months.

8. Urinalysis - Urine tests on individual animals every other month were for appearance, specific gravity, pH, protein, glucose, ketones, occult blood, bilirubin, urobilinogen and microscopic

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elements. Occasional statistically significant depressions and elevations in urine pH were observed between control and test groups. All urinalyses were within the normal range and were not biologically abnormal responses to carbofuran treatment.

9. Organ Weights - A summary of the absolute brain and heart weights and organ-to-body weight ratios for these organs is presented in Table 5. The absolute weights of brain and heart were significantly depressed for the 500 ppm male group. These changes were considered to be treatment-related. Brain-to-body weight and heart-to-body weight ratios, however, were not significantly changed. The gross and microscopic pathology of these organs did not explain the depressed weights in males. The LOEL for depressed heart weight in males is 500 ppm.

10. Macroscopic Pathology - Gross examination at necropsy revealed lack of body fat in two of five males and alopecia in one of five males and one of six female in the 500 ppm group. These conditions support abnormal clinical observations induced by high-dose carbofuran treatment. Discoloration in the lungs was observed in control, 20, and 500 ppm groups and was apparently due to sodium pentobarbital anesthetization followed by exsanguination as the method of sacrifice. Cervical lymph node discoloration was observed in all treatment and control groups of both sexes in

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TABLE 5

ABSOLUTE BRAIN AND HEART WEIGHTS AND ORGAN TO BODY WEIGHT RATIOS IN CONTROL AND CARBOFURAN TREATED BEAGLE DOGS

Treatment Group	Body Weight (Kg)	Brain Weight (g)	Brain Weight Body Weight (%)	Heart Weight (g)	Heart Weight Body weight (%)
<u>Male</u>					
Control	9.95	83.37	0.84	83.12	0.84
	1.30 ^a	6.17	0.19	10.94	0.05
10 ppm	10.15	75.94	0.75	88.87	0.88
	2.24*	5.75	0.19	12.62	0.10
20 ppm	9.93	77.40	0.78	82.75	0.83
	0.98	5.55	0.07	13.68	0.07
500 ppm	6.64*	71.10*	1.07	51.75*	0.78
	1.30	5.04	0.23	11.41	0.11
<u>Female</u>					
Control	7.83	76.19	0.97	67.90	0.87
	1.02	7.60	0.16	8.42	0.12
10 ppm	7.75	74.80	0.97	67.32	0.87
	1.50	3.49	0.17	13.07	0.17
20 ppm	7.60	71.84	0.95	68.56	0.88
	1.62	3.70	0.18	11.61	0.18
500 ppm	6.47	74.84	1.16	53.05	0.82
	0.73	4.57	0.14	8.25	0.14

^aMean + standard deviation.

*Significantly different from control value ($p \leq 0.05$).

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TABLE 6

SUMMARY OF IMPORTANT HISTOPATHOLOGIC FINDINGS IN CONTROL AND CARBOFURAN-TREATED DOGS IN A ONE-YEAR ORAL TOXICITY STUDY

Organ or Tissue	Control Male No. (%)	Control Female No. (%)	10 ppm Male No. (%)	10 ppm Female No. (%)	20 ppm Male No. (%)	20 ppm Female No. (%)	500 ppm Male No. (%)	500 ppm Female No. (%)
Liver								
Cytoplasmic atypia centrifolular	0/6 ^a (0)	2/6 (33)	5/6 (83)	4/6 (67)	2/6 (33)	5/6 (83)	1/5 (20)	5/6 (83)
Lung								
Inflammation	0/6 (0)	0/6 (0)	1/6 (17)	2/6 (33)	0/6 (0)	1/6 (17)	5/5 (100)	2/6 (33)
Testes								
Seminiferous tubule degeneration, Giant cell formation aspermia	0/6 (0)		1/6 (17)		1/6 (17)		4/5 (100)	
Uterus								
Glandular or endometrial hyperplasia hydrometria		0/6 (0)		3/6 (50)		2/6 (33)		1/6 (17)
Kidney								
Glomerular degeneration, Cortical mineralization lipofuscinosis	3/6 (50)	6/6 (100)	4/6 (67)	5/6 (83)	3/5 (50)	5/6 (83)	3/5 (50)	4/6 (67)
Cervical Lymph Node								
Hemosiderin depositions, Hyperemia, lymphadenitis	1/6 (17)	2/6 (33)	3/6 (50)	2/6 (33)	2/5 (33)	1/6 (17)	2/5 (33)	1/6 (17)

^aNumber of animals with lesion per total number of animals examined.

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incidences between 17 and 50%. This discoloration was not treatment-related.

11. Microscopic Pathology - Important microscopic findings are summarized in Table 6. Hepatocellular cytoplasmic atypia (unspecified) with a centrilobular pattern of distribution was observed in two of twelve control animals and was increased to nine of twelve 10 ppm animals, seven of twelve 20 ppm animals and six of eleven 500 ppm animals. The increased incidences (33 to 83% in females and 0 to 83% in males) were treatment-related. Lung inflammation was not observed in controls, but was present in three of twelve 10 ppm animals, one of twelve 20 ppm animals and seven of eleven 500 ppm animals. These inflammatory changes in the lung were treatment-related. In males, degeneration and giant cell formation in seminiferous tubules and aspermia were not observed in control animals. These conditions were noted in one of six dogs in the 10 and 20 ppm treated groups and in four of five dogs in the 500 ppm group. In females, the incidence of uterine hyperplasia and hydrometria was 0/6 in controls and 3/6, 2/6 and 1/6 in 10, 20, and 500 ppm groups, respectively. No dose-response treatment effect was observed. Other histopathologic findings in kidney and cervical lymph node listed in Table 6 occurred in control and treated groups with similar frequency and do not appear to be treatment-related in the small number of animals tested in this study.

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Conclusions

A one year chronic study was conducted in which six beagle dogs per sex received 0, 10, 20 and 500 ppm carbofuran in the diet.

1. Only one death occurred during the study. One male died after 201 days of exposure to 500 ppm carbofuran in the diet. Death was treatment-related.

2. Carbofuran treatment induced significant body weight losses in 500 ppm males and females compared with their respective controls (LOEL=500 ppm).

3. The food and carbofuran consumption in the 500 ppm groups were less than in the controls. Reduced food consumption was related to the weight losses in the 500 ppm groups.

4. Depressions in total protein, calcium, sodium, cholesterol, bilirubin and reticulocytes were observed in 500 ppm males.

5. The plasma cholinesterase LOEL was 500 ppm in males and 500 ppm in females. The erythrocyte cholinesterase NOEL was 20 ppm in males and 500 ppm in females.

6. With 500 ppm carbofuran treatment, the hematocrit, hemoglobin and erythrocyte values were significantly depressed.

The electrolytes, calcium and sodium, were depressed.

7. The urinalyses were within the normal range for all test groups.

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8. The LOEL was 500 ppm for depressed heart weights in males and females.

9. In the 500 ppm groups, lack of body fat in males and alopecia in males and females were treatment-related.

10. Hepatocellular cytoplasmic atypia with a centrilobular pattern of distribution and inflammatory changes in lungs were observed at increased levels in 10 to 500 ppm groups over control groups and were treatment-related. Testicular degeneration and aspermia were induced in 10, 20 and 500 ppm males. The incidences in the 10 and 20 ppm groups of 1/6 and 1/6, respectively, were not significantly different from the control incidence of 0/6. The incidence in the 500 ppm group was 4/5 and was significantly increased ($p \leq 0.05$) over the control. The testicular effects were treatment-related in this 500 ppm group. For testicular degeneration and aspermia the NOEL = 20 ppm and the LOEL = 500 ppm. Uterine hyperplasia and hydrometria may be treatment-induced in females.

CORE CLASSIFICATION: Core Minimum

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