CASWELL FILE

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

008419

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JUN 24 1991

MEMORANDUM

SUBJECT: Carbofuran - 21-Day Subacute Dermal Toxicity Study with Technical Carbofuran in Rabbits

Caswell No.: 160A
Record No.: 262,578
Project No.: 0-1054
MRID No.: 00155429

FROM: William Dykstra, Reviewer
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

William Dykstra 7/9/90

TO: Joanne Edwards, PM Team 74
Reregistration Branch
Special Review and Reregistration Division (H7508C)

THRU: Roger Gardner, Acting Section Head
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

06/14/91 (for RG)

Karl Baetcke 6/14/91

Requested Action

Review 21-day subacute dermal toxicity study in rabbits with technical carbofuran.

Conclusion and Recommendation

The 21-day repeated dose dermal toxicity study in rabbits with technical carbofuran is acceptable as Guideline data. The NOEL is 1000 mg/kg/day (HDT). There were no compound-related toxic, cholinergic, or systemic effects in the study at doses up to 1000 mg/kg/day (HDT).

Reviewed By: William Dykstra William Dykstra 7/19/90
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Roger Gardner, Acting Section Head
Section I, Toxicology Branch I - IRS (H7509C)
06/14/91
(for RG)

DATA EVALUATION REPORT 008419

Study Type: 82-2 - 21-Day Dermal, Rabbit TOX Chem. No.: 160A

Accession Number: N/A MRID No.: 00155429

Test Material: Carbofuran technical, 96.9% purity

Synonyms: FMC 10242

Study Number: FMC Study No. A85-1678

Sponsor: FMC Corporation

Testing Facility: FMC Toxicology Laboratory, Princeton, NJ

Title of Report: 21-Day Repeated Dose Dermal Toxicity Study in Rabbits With FMC 10242 Technical (Carbofuran).

Report Issued: October 31, 1985

Conclusions:

The NOEL is 1000 mg/kg/day (HDT). There were no compound-related effects in body weight, food consumption, toxic signs, hematology, clinical chemistry, plasma, RBC, brain cholinesterase (ChE) activity, gross pathology, organ weight, and histopathology of selected organs. There were minor skin changes in treated skin of all dose groups (including controls) in comparison to untreated skin.

Classification: Core-Guideline

Special Review Criteria (40 CFR 154.7): N/A

Review:

Twenty-one-day repeated dose dermal toxicity study in rabbits with FMC 10242 technical (carbofuran) (FMC Study No. A85-1678; October 31, 1985).

Quality Assurance Statement was signed by William D. Barta on October 28, 1985. Additionally, a scientific statement attesting to the validity of the study results was signed by supervisory personnel. A Statement of Compliance with the EPA Good Laboratory Practice Standards was signed by the Study Director.

Test Material - FMC 10242 (carbofuran) technical was received by the testing laboratory on February 28, 1985 Lot No. M607210; purity, 96.9%; brown solid; indefinite stability.

Animals - Male and female young adult New Zealand White (NZW) rabbits were received from Hazleton Research Products, Inc. (Denver, PA). Rabbits were observed twice daily during a 14-day acclimatization period for signs of toxicity or mortality. Food (Purina High Fiber Rabbit Chow #5326) and water were offered ad libitum. Animals in apparent good health were released from acclimation and assigned to the study. Study animals were individually housed.

Study Design:

Randomized* groups of six male and six female NZW rabbits with approximately 10 percent of body surface shaved, but not abraded, received the test material, which was moistened, on the intact skin for approximately 6 hours for each of the 21 consecutive days. The test material was held in place by a moistened gauze pad and occluded with hypoallergenic tape. Plastic sheeting was wrapped around the trunk of each animal and taped securely. Elizabethan collars were also worn by each rabbit during treatment.

Following the 6-hour exposure period, the wrappings, pads, and excess material were removed but the Elizabethan collars remained on the rabbits for the duration of the study (except when recording body weights).

The doses of technical carbofuran employed in the study were 0 (saline control), 10, 100, and 1000 mg/kg bwt/day.

---

*The animals were assigned to the study on a staggered basis (3/sex/dose) over 4 consecutive days.

Animals were observed twice daily for overt signs of toxicity and mortality. Local skin irritation was recorded daily prior to dosing. Body weights were recorded on days 0, 1, 8, 15, and at termination of day 21.

Individual food consumption was recorded daily. Immediately following the final 6-hour exposure period, each animal was bled and the following parameters were measured:

1. Cholinesterase Activity

X	
X	Erythrocyte
X	Plasma
X	Brain (two samples; the right half and a section of 1.0 g from left half)

2. Hematology

X		X	
X	Hematocrit (HCT)*		Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)

3. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*		Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin*
	Alkaline phosphate	X	Total protein*
	Cholinesterase		Triglycerides
	Creatinine phosphokinase*		
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		

Approximately 15 minutes after bleeding, the rabbits were weighed, anesthetized, and exsanguinated. The brains were immediately removed and kept chilled on ice.

Animals were examined grossly for internal and external gross lessions. The liver, kidneys, and testes (males) were weighed.

The following tissues were preserved in buffered formalin:

	Digestive System	X	Cardiovasc./Hemat.	X	Neurologic
	Tongue		Aorta*	X	Brain*
	Salivary glands*		Heart*	X	Periph. nerve*
	Esophagus*		Bone marrow*		(sciatic
	Stomach*		Lymph nodes*		Spinsl cord (3
	Duodenum*		Spleens*		levels)*
	Jejunum*		Thymus*		Pituitary*
	Ileum*		Urogenital		Eyes (optic n.)*
	Cecum*	X	Kidneys*		Glandular
	Colon*		Urinary bladder*		Adrenals*
-	Rectum*		Testes*		Lacrimal gland
X	Liver*		Epididymides		Mammary gland*
	Gallbladder*		Prostate		Parathyroids*
	Pancreas*		Seminal vesicle		Thyroids*
	Respiratory		Ovaries		Other
	Trachea*		Uterus*		Bone*
	Lung*				Skeletal muscle*
				X	Skin (treated and untreated)
				X	All gross lesions all masses

All of the above checked tissues were examined microscopically by a pathologist.

Statistics:

Normal data, as determined by examination of plots of the data (normal plots of the residuals or a graph of the parameter vs. group) were analyzed by an Analysis of Variance (ANOVA) test. If differences existed between groups (Bartlett's Test), treatment group means were compared to the control mean using Dunnett's Test. If Bartlett's test indicated unusual variability, then the F-test was performed for each test group compared individually to control and followed by the appropriate T-test with Bonferoni correction. If the data were normal and the variance increased with the mean, a log transformation of the data was conducted before the ANOVA was performed. Non-normal data were analyzed using the Kruskal-Wallis Non-Parametric ANOVA which, if positive, was followed by Dunn's Test. In all cases, the preselected level of significance was $p < 0.05$.

Data were analyzed using the Statistical Analysis System computer software system. Dunn's Test for Multiple Rank

Comparisons was run using the program MULTCOM written by FMC Statistical Services.

Results:

There were no compound-related mortalities. One control female rabbit died on day 10 with clinical signs indicative of enteritis.

There were no compound-related effects in male body weight change during the 3-week period. The weight change (defined as final body weight [week 3] minus initial body weight) was (mean $\pm$ S.D.) 0.00 $\pm$ 0.114, -0.02 $\pm$ 0.079, -0.04 $\pm$ 0.155, and -0.006 $\pm$ 0.106 kg for the control, low-, mid-, and high-dose groups, respectively.

Similarly for females, there were no compound-related effects in weight change. The values were 0.06 $\pm$ 0.151, 0.05 $\pm$ 0.145, 0.09 $\pm$ 0.137, and -0.12 $\pm$ 0.175 kg for the control, low-, mid-, and high-dose groups, respectively.

Food consumption (g/animal/week) did not show any compound-related effects in males during the 3-week period. The means for food consumed were comparable between control and treated male rabbits.

In females during the first week, there was an increase (statistically significant) in food consumption in the low- and mid-dose groups, but not the high-dose group. However, the mean value of the high-dose group was slightly increased above controls, but was not increased statistically significantly.

During weeks 2 and 3, food consumption was essentially comparable between control females and all treated females. There were no biologically distinct effects in the low- and mid-dose group as well as the high-dose group in comparison to control.

In light of these findings, the results observed in the first week are not considered compound-related.

There were no compound-related clinical toxic signs during the study. Additionally, no skin irritation related to treatment was observed in treated rabbits.

There were no compound-related trends or effects in mean hematology values in male and female treated groups of rabbits in comparison to controls.

Additionally, there were no compound-related effects in clinical chemistry values except that the mean value for males for the high-dose Ca# was statistically significantly increased over

controls (13/63 vs. 14/72** mg/dL; **p < 0.01). This high-dose increase represents only a 7.4 percent increase and is not considered toxicologically significant. Other clinical chemistry values were comparable between control and treated groups for male and female rabbits.

Mean ChE values for males and females are presented in the two tables below:

MALES

Determination (Units)	Group I 0 mg/kg N	Mean	S.D.	Group II 10.0 mg/kg N	Mean	S.D.	Group III 100 mg/kg N	Mean	S.D.	Group IV 1000 mg/kg N	Mean	S.D.
RBC (u/mL)	6	1.93	0.568	6	1.93	0.175	6	1.78	0.479	6	1.72	0.337
Percent Control					99			91			88	
Plasma (u/mL)	6	0.88	0.075	6	1.03	0.207	6	0.85	0.217	6	0.72	0.214
Percent Control					117			97			82	
Brain Half (u/g)	6	15.13	1.388	6	15.13	1.569	6	12.00	4.600	6	11.25	3.489
Percent Control					100			79			74	
Brain Slice (u/g)	6	15.35	3.653	6	15.33	2.608	6	16.82	3.527	6	14.93	0.997
Percent Control					100			110			97	

FEMALES

Determination (Units)	Group I 0 mg/kg N	Mean	S.D.	Group II 10.0 mg/kg N	Mean	S.D.	Group III 100 mg/kg N	Mean	S.D.	Group IV 1000 mg/kg N	Mean	S.D.
RBC (u/mL)	5	1.78	0.268	6	1.57	0.418	6	1.60	0.228	6	1.62	0.293
Percent Control					88			90			91	
Plasma (u/mL)	5	0.86	0.114	6	0.90	0.253	6	0.92	0.172	6	0.77	0.163
Percent Control					105			107			90	
Brain Half (u/g)	5	12.74	3.124	6	14.07	2.431	6	12.58	4.442	6	13.25	2.558
Percent Control					110			99			104	
Brain Slice (u/g)	5	14.84	3.873	6	15.60	3.103	6	13.72	5.814	6	15.92	1.461
Percent Control					105			92			107	

As can be seen in the table of values for female ChE, there are no significant toxicological differences between control and treated rabbits for RBC, plasma, brain half, and brain slice.

In contrast, in males, brain half values at 100 and 1000 mg/kg/day are 79 and 74 percent of control. Evaluation of individual data for brain half values for all groups shows the following.

Brain half (u/g)

Control	Low	Mid	High
15.2	16.2	16.5	10.2
13.8	15.6	15.9	4.9
15.8	16.3	5.1	14.2
17.5	12.9	12.5	10.4
13.9	16.4	14.2	14.0
14.8	13.4	7.8	13.1

The brain half values of 5.1 u/g for the mid-dose and 4.9 u/g for the high-dose are quite low. If these two values are omitted, the mean brain half cholinsterase activities of the mid- and high-dose are 88 and 83 percent, respectively, of control. The mean cholinsterase activities for brain slices for the mid- and high-dose are 110 and 97 percent of control, respectively.

The decrease in brain half cholinesterase data for the mid- and high-dose is not considered a compound-related effect due to (a) the complete absence of clinical signs in the rabbits, (b) the absence of any effect on brain slice cholinsterase activity, (c) the lack of effect on plasma and RBC ChE activity, and (d) the lack of statistical significance in the mid- and high-dose groups in comparison to controls.

There were no compound-related effects in mean organ wights (brain, kidney, liver, testes) in treated male and female rabbits in comparison to controls. Also, there were no compound-related effects in mean organ/body weight ratio (percent) in treated male and female rabbits in comparison to control. Additionally, there were no compound-related effects in mean organ/brain weight ratios (percent) in treated male and female rabbits in comparison to control.

Although females in the mid-dose group had slightly lower mean kidney weights, kidney/body weight ratios and kidney/brain weight ratios compared to controls, these findings were not dose-related, and therefore they were not considered compound-related.

Microscopic evaluation of tissues by Diane Gunson B.V.Sc., M.R.C.V.S., Ph.D., Diplomate, American College of Veterinary Pathologists did not reveal any compound-related effects, when comparing the controls with the high-dose with respect to the brain, spinal cord, liver, and kidney. Untreated skin (0.9% saline) and treated skin (10, 100, or 1000 mg/kg/day) was examined from all rabbits of both sexes in control and all treated groups. There were no compound-related significant effects in treated skin.

Minor changes which were apparent in treated skin were increased thickness at the low-dose, but not the mid- or high-dose. Therefore, the effect was not dose-related. Additionally, increased lymphocyte infiltration in the high-dose group was observed. However, some control treated rabbits in addition to the high-dose treated rabbits also manifested these slight changes.

The toxicological significance of these slight changes in treated skin is questionable.

These minor skin changes were observed to a slightly greater degree in the treated skin compared with untreated skin.

Conclusion:

The NOEL for the 21-day repeated dosage study with carbofuran technical in rabbits is considered to be the high-dose of 1000 mg/kg/day.

Classification: Core-Guideline