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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID# 080804-000100 Prometon Review of a 1-Year Dog Feeding Study

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CONCLUSIONS

Ciba-Geigy Corporation has submitted the information requested by Tox. Branch I (EPA document # 9328), to upgrade the classification of a chronic oral toxicity study of technical Prometon in the dog (MRID 400979-01) from Core Supplementary to Core Minimum, under Guideline 83-1. The NOEL is 5 mg/kg/d, and the LOEL is 20 mg/kg/d, based on depression of body weight in the females and increased emesis in dogs of both sexes. Clinical symptoms of toxicity at the 50 mg/kg/d dose included ptosis, mydriasis, lethargy and salivation.

BACKGROUND

Ciba-Geigy Corporation has submitted information in response to a memorandum dated February 28, 1992 (EPA document # 9328), pertaining to the acceptability of a chronic oral toxicity study of technical Prometon in the dog (MRID 400979-01). Tox. Branch I concluded that the study could not be classified as Core Minimum under Guideline 83-1, because the primary symptoms of toxicity,

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emesis and diarrhea, were observed in all groups, including controls, and thus a NOEL could not be established. Review of the study was limited because the initial report gave the incidence of diarrhea and emesis on a weekly, instead of daily, basis, and thus the relationship between dosing time and incidence of the symptoms could not be established. This raised the question of whether the dogs actually received the doses tested and retained sufficient quantities to cause some of the other symptoms observed in the mid- and high-dose animals (ptosis, mydriasis, lethargy, weight gain depression, decreased absolute body weight), some of which could be attributed to poor health and/or decreased food consumption.

Tox. Branch I determined that the study was upgradeable from Core Supplementary to Core Minimum, providing that the sponsor furnish additional information explaining the recurring emetic and diarrhetic episodes in all dose groups, evidence that the dogs received and retained the intended dose, and any other pertinent information (e.g., how the dosages used in the study were chosen, and why the test material was administered in capsular form, rather than directly in the food).

DISCUSSION

Health status of the dogs used in the study:

To substantiate the health status of the dogs used in the study, the sponsor has submitted the Standard Operating Procedure (Attachment 1 of the submission) for the physical examinations of dogs, which was used in this study. Data were submitted for the preliminary and 12 monthly examinations for each dog in the study (Attachments 2-4 of the submission). The results of these exams indicated the animals were healthy throughout the study; therefore, the incidences of emesis and diarrhea observed were likely not due to poor health.

Range-finding study:

The dosages used were based upon a 4-week range-finding study, which was completed by Bio/dynamics in November, 1976 (Study No. 76-1446, MRID No. 00054309, included in the submission as Attachment 11). In the range-finding study, 1 dog per sex was fed 0, 100, 300 or 3000 ppm Prometon for the first 2 weeks of the study, then 0, 1000, 2000 or 3000 ppm technical Prometon mixed into their feed for weeks 3 and 4. At 3000 ppm, the animals lost approximately 10% of their body weight during the 4-week period; the control dogs gained weight. The dogs in the high-dose group also exhibited a decrease (approximately 43% ♂ and 27% ♀) in food consumption, but no additional signs of toxicity were noted. When dogs originally fed 300 ppm were switched to 2000 ppm diets, the dogs exhibited weight loss (about 2% ♂, and 9% ♀).

Since in the range-finding study 3000 ppm caused weight loss and

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depressed appetite, 90 mg/kg/d which corresponds to 3600 ppm, was chosen for the high-dose in the present study because it was thought that level would elicit significant toxicity. A mid-level dose of 50 mg/kg/d (2000 ppm) was selected since it was not clear that the weight losses observed in the range-finding study were due to toxicity or decreased food consumption. A low-level (15 mg/kg/d) dose was chosen which was expected to produce no toxic effects. The test material was given orally in capsule form, since the laboratory was experienced with this form of dosing and capsular administration would circumvent palatability problems. Due to the dose-related increase in emesis (the dogs in the highest dose group exhibited severe emesis) during the first 5 days of the present study, the animals were taken off the test diet for 2 days, then the test groups lowered to 5, 20 and 50 mg/kg/d and fed those levels of Prometon for 365 days.

Food Consumption and Body Weight Gain:

Prometon had statistically significant ($p \leq 0.05$) effects on body weight gain at the 20 mg/kg/d level in females, and at the 50 mg/kg/d level in both sexes. Females in the 20 mg/kg/d group exhibited an absolute weight gain that was 42% lower than controls at the end of 6 months, and 55% less at 1 year. High-dose males had an absolute weight gain 42% less than controls at 6 months, and 49% less than controls at 1 year. Females in this group exhibited approximately 58% less weight gain than controls at 6 months, and 63% less at 1 year (from Text Table 4 and Attachment 14 of the submission).

The test compound also appeared to affect average food consumption at all levels of the test substance in females, and at the 50 mg/kg/d level in males; however, when the grams of food consumed per kg body weight were calculated, the female dogs on Prometon consumed 100% or greater than the control females dogs. The males consumed approximately 10% less than control males (see Text Table 5 and Attachment 15 of the submission). These differences were not statistically significant. Thus, it appears that the differences observed in body weights were related to toxicity rather than reduced food consumption. (See summary of body weight gains and food consumption in Table I, below).

Comparison of emesis and diarrhea in the control animals with historical chronic oral toxicity control data:

Historical control data were submitted for 12, 1-year chronic oral toxicity studies in dogs conducted at the sponsor's Safety Evaluation Facility (SEF), including the present Prometon study. Although out of the 12 studies only the Prometon study dogs received capsules, the administration of which could conceivably cause emesis and diarrhea, the occurrence of these symptoms in the control dogs of the Prometon study was within the normal range observed in the control dogs in the other 11 studies.

The incidence of diarrhea in all groups, including control, were highly variable. The total number of days diarrhea was observed was 52, 215, 70, and 132/365 study days in the control, 5, 20 and 50 mg/kg/d males, and 41, 22, 66, and 270/365 study days in the control, 5, 20, and 50 mg/kg/d females. These numbers are skewed by the fact that control and high-dose groups had more dogs (8/sex) than the low and mid-dose groups (5/sex). In addition, there was one low-dose male that had 162/215 observed episodes of diarrhea in that group, and 1 female in the high-dose group that had 186/270 observed diarrhetic episodes. The median number of days diarrhea was observed during the study was 7.5, 17, 9, and 14.5 in the 0, 5, 20, and 50 mg/kg/d males, and 1.5, 3, 16, and 4.5 in the 0, 5, 20, and 50 mg/kg/d female dogs. Thus, it appears that diarrhea was not dose-related.

Capsule studies indicate that the physical administration of capsules to dogs causes emesis comparable to control and low-dose groups:

The sponsor also stated that "capsule studies" were performed at the SEF which indicated that control animals receiving capsules can be expected to experience emesis on 3-17% of the study days (no data were provided). In the present study, the control dogs experienced episodes of emesis less than 1% of the total study days, an average of 0.75/365 and 2.62/365 observation days per male and female dog, respectively. The dogs in the low-dose group (5 mg/kg/d) also had emetic episodes less than 1% of the total study days, an average of 2.8/365 and 1.8/365 observation days per male and female dog. Thus, it appears that the vomiting exhibited by the control and low-dose animals were within the normal or expected range for healthy dogs. The mid-level group (20 mg/kg/d) appeared to exhibit slight but dose-related emetic episodes. The males in that group experienced emesis on 15.6/365 days, or 4.3% of the total study days/dog, and females had emesis on 8.4/365 study days (2.3%). Emesis in the high-dose group (50 mg/kg/d) increased to 50.5/365 days/male dog (13.8%) and 31.8/365 days/female dog (8.7%). (See Table II, below.)

Dose Received and Retained :

The sponsors have submitted data on the daily incidence of emesis and diarrhea for each dog in the study (Attachment 6 of the submission), and for each hour of observation for every dog in the high dose group (50 mg/kg/d; Attachment 8 of the submission). To reduce the likelihood of losing the entire dose of the test material due to emesis, the high-dose group received 50 mg/kg Prometon divided into 3 separate capsules, taken 1 hour apart; the mid-dose group received 20 mg/kg Prometon divided equally into 2 capsules; the low-dose group took 5 mg/kg in 1 capsule; and the controls were given 3 empty capsules. Observations during weekdays occurred in the morning, prior to dosing; at mid-day, after low-dose group had taken its capsule and the controls, mid- and high-

dose groups had taken their second capsule; and late afternoon 3-4 hours after the last capsule was taken by the control and high-dose groups. The dogs were observed twice on weekends and holidays, morning and late afternoon. If there was any doubt if a dose was lost due to emesis (i.e., if emesis was noted at the last observation of the day, and thus not known exactly when it occurred), then it was recorded as "dose lost". However, the dogs often were reported to have eaten the vomit and the dose (capsule), and thus partial dosages were considered when calculating "dose retained".

The number of daily episodes emesis/dog in the control animals ranged from 0-2 (♂) and 0-8 (♀); 1-7 (♂) and 0-4 (♀) in the low-dose group; 8-28 (♂) and 1-16 (♀) in the mid-dose group; and 16-110 (♂) and 10-77 (♀) in the high-dose group. The dose retention was calculated based on the numbers of capsules retained out of the total number of capsules given during the study. This information was not provided for control animals, but the low-dose group retained 99.7% (♂) and 99.9% (♀); mid-dose dogs retained 97.9 and 99.2 (♂/♀, respectively); and the highest-dose group retained 96.7% and 98.4% (♂/♀, respectively) of their total dosage (see Table I below). Therefore, all of the dogs in the study retained greater than 95% of the intended dose of the test compound. Evidence that the compound was retained is indicated in the clinical symptoms of lethargy (8/8 ♂, 7/8 ♀), mydriasis (8/8 ♂, 8/8 ♀), ptosis (4/8 ♂, 7/8 ♀), and salivation (3/8 ♂, 5/8 ♀) found in the high dose animals (from Attachment 4 of the submission). The occurrence of these other effects suggests that levels of the test compound were high enough for absorption and systemic distribution of the compound to occur.

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TABLE I

Dose (mg/kg):	Males 0	Males 5	Males 20	Males 50	Females 0	Females 5	Females 20	Females 50
Absolute Body Weight Gain (kg)[1]								
6 mos.	3.1	3.7	3.4	1.8*	3.1	2.5	1.8*	1.3*
1 year	3.7	4.4	3.7	1.9*	4.0	3.0	1.8*	1.5*
Percent Weight Gain[1]								
6 mos.	36	39	40	21*	40	31	24*	16*
1 year	43	50	44	21*	52	37	23*	20*
Average Body Weight (kg)[2]	10.6	11.3	10.4	9.9	10.2	9.8	8.7	8.5
Average Food Consumption (g)[2]	376	379	372	311	341	327	330	319
Average Food consumed per kg body weight[2]	35.5	33.5	35.9	31.8	33.6	33.5	37.9	37.8
% of Control[2]	--	94	101	90	--	100	113	112

[1] extracted from Text Table 4 of the submission

[2] extracted from Text Table 5 of the submission

* $p \leq 0.05$

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TABLE II

Group	#Dogs/Group	Mean # Daily Emetic Episodes Observed/Dog[1]	% Total Study Days in which Emetic Episodes were Observed	Range of # Daily Emetic Episodes/ Dog	Mean # Doses (capsules) Retained/Doses Given	% Doses Retained
Controls[2]						
♂	8	0.75	0.21	0-2	*	*
♀	8	2.62	0.72	0-8	*	*
5 mg/kg/d[3]						
♂	5	2.8	0.77	1-7	363.4/365	99.7
♀	5	1.8	0.49	0-4	364.6/365	99.9
20 mg/kg/d[3]						
♂	5	15.6	4.3	8-28	714.4/730	97.9
♀	5	8.4	2.3	1-16	724.4/730	99.2
50 mg/kg/d[3]						
♂	8	50.5	13.8	16-110	1059/1095	96.7
♀	8	31.8	8.7	10-77	1078/1095	98.4

[1] This includes days when emesis occurred before dosing, lost only part of the total dose, and when dogs reingested the dose by eating the vomit

[2] Data extracted or calculated from Attachment 5 of the submission

[3] Data extracted or calculated from Attachment 10 of the submission

* Data not provided in the submission