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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Prometon.** Validation of Reviews of Rat and Rabbit Developmental Toxicity Studies.

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Marion Copley 12/9/92

I. CONCLUSIONS:

TB-I has reevaluated the rat and rabbit developmental toxicity studies on prometon (MRID Nos. 129983 and 921490-07, rat; 129984 and 921490-08, rabbit). This memorandum takes the place of supplemental DERs for these studies. Both studies are Core-minimum and acceptable for regulatory purposes as previously determined. For the most part the reviews accurately reflected the data but TB-I did not agree with assignment of the maternal toxicity NOEL (at 120 mg/kg/day) in the rat study. The rabbit study was determined to be marginally acceptable due to reduced number of litters at high dose. No significant developmental toxicity was observed in either species at doses that caused overt maternal toxicity.

Rat developmental toxicity study: Doses tested: 0, 36, 120 and 360 mg/kg/day by gavage in corn oil; Days 6 - 15 of gestation. Strain: Crl COBS® CD® (SD) BR

Maternal toxicity NOEL = 36 mg/kg/day
Maternal toxicity LEL = 120 mg/kg/day, based on increased incidence of excess salivation and chromorhinorrhea. At 360 mg/kg/day, chromodacryorrhea, decreased motor activity, increased lacrimation, increased respiration rate and decreased maternal body weight/body weight gain observed.

CC R. Taylor (PM25)

Recycled/Recyclable

Developmental toxicity NOEL ≥ 360 mg/kg/day
Developmental toxicity LEL not determined.

Rabbit developmental toxicity study: Doses tested: 0, 0.5, 3.5 and 24.5 mg/kg/day by gavage in corn oil; Days 6 - 18 of gestation. Strain: New Zealand White

Maternal toxicity NOEL = 3.5 mg/kg/day
Maternal toxicity LEL = 24.5 mg/kg/day, based on decreased body weight/body weight gain during treatment and slightly increased incidence of lacrimation.
Developmental toxicity LEL ≥ 24.5 mg/kg/day
Developmental toxicity NOEL not determined.

The studies are discussed below in greater detail. Data tables are included, where appropriate, to support the conclusions and supplement the original reviews.

II. ACTION REQUESTED:

TB-I was asked by the Health Effects Division RfD/Peer Review Committee to reevaluate the rat and rabbit developmental toxicity studies on prometon (memo from G. Ghali to R. Taylor, 11-25-92). The Committee determined that the data evaluation records (HED Doc. nos. 3700, original review, and 4781, reevaluation following company response) for these studies were inadequate and that the studies should be reexamined to validate the conclusions of the original reviews.

III. DISCUSSION:

A. RAT: TB-I agrees with the classification of this study as Core-minimum but not with the assignment of maternal toxicity NOEL (120 mg/kg/day) and LEL (360 mg/kg/day). The study is considered acceptable for regulatory purposes.

1. Maternal toxicity: In the original DER it was determined that clinical effects were seen at all dose levels, whereas in the reevaluation the maternal toxicity LEL was designated at 360 mg/kg/day. Clinical observations are presented below in Table 1:

TABLE 1: CLINICAL SYMPTOMS OBSERVED DURING DAYS 6 - 15 (TREATMENT PERIOD) OF GESTATION[1]

	Dose, mg/kg/day			
Observation	0	36	120	360
Excess salivation	0/0[2]	7/7	20/59	23/153
Chromorhinorrhea	0/0	3/4	21/55	23/112
Chromodacryorrhea	0/0	2/4	2/2	14/22
Decreased motor activity	0/0	0/0	0/0	15/32
Lacrimation	0/0	0/0	2/2	8/12
Increased respir. rate	0/0	0/0	0/0	9/17

1 Taken from study Table 1
2 # animals affected/# days symptom observed

2

A marked increase in incidence of excess salivation and chromorhinorrhea was seen at 120 and 360 mg/kg/day. Since incidences increased with dose and were seen in almost all dams in those dose groups, TB-I considers these effects treatment-related. Increased incidences of chromodacryorrhea, decreased motor activity, lacrimation and increased respiration rate at 360 mg/kg/day also appeared to be treatment-related. The slightly increased incidence of some symptoms over controls at 36 mg/kg/day (eg. salivation, chromorhinorrhea, chromodacryorrhea) was marginal and did not appear to be clearly treatment-related. The above symptoms are also typically seen in acute toxicity studies on prometon. Based on these clinical effects, TB-I considers 120 mg/kg/day the LEL and 36 mg/kg/day the NOEL for maternal toxicity.

Maternal body weight/weight gain is shown below in Table 2:

TABLE 2: BODY WEIGHT/WEIGHT GAIN (GRAMS) DURING GESTATION[1]

	PROMETON, MG/KG/DAY (# PREGNANT DAMS/TOTAL # DAMS)			
INTERVAL	0 (23/25)	0.5 (24/25)	3.5 (24/25)	24.5 (22/25)
MATERNAL BODY WT.				
DAY 0	241.6	240.7	242.5	242.0
DAY 6	276.6	275.6	277.9	277.7
DAY 15	323.6	319.2	318.9	306.6**
DAY 20	393.0	392.2	386.9	374.5**
BODY WT. CHANGE				
DAY 0 - 6	35.0	34.9	34.4	35.7
DAY 6 - 15	47.0	43.6	41.0	28.9**
DAY 15 - 20	69.4	73.0	68.0	67.9
DAY 0 - 20	151.4	151.5	144.4	132.5**

1 Data taken from Table 3 of study
** $p < 0.01$

TB-I agrees with the original reviews that the statistically significant decreases in maternal body weight and body weight gain during treatment at 360 mg/kg/day were treatment-related.

2. Developmental toxicity - Cesarean and litter data is presented below in Table 3:

TABLE 3: CESAREAN/LITTER DATA[1]

Parameter	Dose, mg/kg/day 0	36	120	360
# Animals inseminated	25	25	25	25
# Animals pregnant (%)	23	24	24	22
# Litters	23	24	24	22
Maternal Wastage				
# Died	0	[illegible]	0	0
# Aborted	0	[illegible]	0	0
# Non-pregnant	2	[illegible]	1	3
Corpora lutea/dam	16.7	15.3	16.2	16.4
Implantations/dam	15.2	14.6	14.4	14.4
Live fetuses/dam	14.1	14.0	13.8	13.6
Dead fetuses/dam	0.0	0.0	0.0	0.0
Late resorptions/dam	1.04	0.58	0.54	0.77
Early resorptions/dam	0.0	0.0	0.04	0.0
% Dead or resorbed fetuses	7.23	3.73	4.28	5.75
Fetal body wt. (g)	3.56	3.75	3.62	3.58
Male:female ratio	48.0	46.3	51.8	59.9**

1 Data taken from Tables 5 and 7 of study
** $p < 0.05$

TB-I agrees with the original review that there was no apparent treatment-related developmental toxicity at any dose. A statistically significant increase in male:female pup ratio was seen at high dose. This increase was probably within historical control range (values not provided by study authors) and probably represented biological variation rather than treatment-related effects. There was no decrease in fetal weights of female pups at high dose. This effect was not observed in the rat 2-generation reproduction study on prometon (MRID no. 403615-01; HED Doc. no. 9679). There was no evidence of treatment-related developmental abnormalities upon examination of fetal viscera and skeletons (data not presented).

3. Study deficiencies: There were no significant data lacking for Guideline 83-3a that would affect the conclusions of this study. Historical control data for cesarean and developmental parameters were not included in this report. Maternal food consumption was not measured. Analyses of dosing solutions were performed subsequent to this study which determined that prometon is stable and homogeneous in vehicle but verification of concentration at time of study was not performed.

B. RABBIT: TB-I agrees with the choice of maternal and developmental NOELs and LELs and the classification of this study as Core-minimum as determined in the study reevaluation. The study is considered acceptable for regulatory purposes despite reduced litter size at high dose (discussed below).

1. Maternal Toxicity:

Clinical observations are shown below in Table 5:

TABLE 5: CLINICAL OBSERVATIONS[1]

Observation	Dose, mg/kg/day 0	0.5	3.5	24.5
Anorexia	14/75[2]	10/75	10/47	12/111
Lacrimation	2/17	2/6	2/10	4/70

1 Data taken from Table 1 of study
2 # animals affected/# days observed

TB-I considers increased lacrimation at high dose treatment-related. Increased lacrimation was also observed in rats at high dose (360 mg/kg/day) and occurs in acute oral toxicity studies using prometon. TB-I does not agree with the original review that anorexia at high dose was clearly related to treatment.

Maternal body weight/body weight gain are shown in Table 4 below:

TABLE 4: MATERNAL BODY WT./BODY WT. GAIN (KILOGRAMS)[1]

	PROMETON, MG/KG/DAY (# PREGNANT DOES/TOTAL DOES)			
INTERVAL	0 (16/18)	0.5 (13/16)	3.5 (13/16)	24.5 (11/16)
MATERNAL BODY WT.				
DAY 0	4.18	4.28	4.32	4.32
DAY 6	4.23	4.37	4.37	4.41
DAY 12	4.23	4.33	4.35	4.22**
DAY 18	4.26	4.31	4.37	4.11**
DAY 30[2]	4.23	4.43	4.46	4.53
BODY WT. CHANGE				
DAY 0 - 6	0.05	0.09	0.05	0.09
DAY 6 - 12	0.00	-0.04	-0.02	-0.19
DAY 12 - 18	0.03	-0.02	0.02	-0.11
DAY 18 - 30	-0.03	0.12	0.09	0.42
DAY 6 - 18	0.03	-0.06	0.00	-0.30**
DAY 0 - 30	0.05	0.15	0.14	0.21

1 Data taken from table 4 of study
2 Day 30 wts taken from 13, 9, 11 and 9 does, respectively (aborted or naturally delivering does excluded)
** $p < 0.01$

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Body weight and body weight gain was slightly but statistically significantly lower during treatment at high dose (24.5 mg/kg/day). The study authors' calculations of maternal body weight change were slightly but not significantly different in some cases than those in the above table. These mathematical differences did not affect the results of the study. TB-I agrees with the original reviews that this effect appeared to be treatment-related and represented the maternal LEL.

2. Developmental Toxicity: Cesarean section and litter data are shown below in Table 6:

TABLE 6: CESAREAN SECTION/LITTER DATA[1]

Parameter	Dose (mg/kg/day) 0	0.5	7.5	24.5
# Animals Inseminated	18	16	16	16
# Animals Pregnant (%)	16 (89)	13 (81)	13 (81)	11 (69)
# Litters	15	11	13	9
# Litters delivered before termination	2	2	2	0
Maternal Wastage				
# Died	0	1	0	0
# Aborted	1	1	0	2
# Non-pregnant	2	3	3	5
Corpora lutea/doe	10.15	10.33	10.18	10.33
Implantations/doe	7.15	7.11	7.82	8.67
Live fetuses/doe	6.23	6.89	6.55	8.00[2]
Dead fetuses/doe	0	0	0	0
Late resorptions/doe	0.85	0.22	1.18	1.67
# Early resorptions	1	0	1	0
% Dead or resorbed fetuses	9.84	2.70	20.22	21.80
Fetal body wt. (g)	48.46	53.06	51.32	53.84[2]
Male:female ratio	44.44	40.32	55.56	62.89**

1 Data taken from Tables 6 and 8 of study
2 Calculations do not include 1 litter with complete resorptions
** $p < 0.01$

TB-I agrees with the reevaluation of the study that the developmental NOEL was $\geq$ 24.5 mg/kg/day. The original review of this study indicated that the decreased pregnancy rate observed in high dose females may have been treatment-related; however, since impregnation occurred prior to treatment, TB-I does not

consider it a treatment-related effect.

A slight decrease in live fetuses at high dose and increases in % dead fetuses/resorptions at mid and high dose were observed. High dose values included a single doe with complete litter resorption (8 fetuses). TB-I agrees with the original reviews that these are not treatment-related effects. There was no dose-response, no effect on fetal body weight, increases were not statistically significant and the reduced number of litters at high dose may have affected interpretation of the results. The preliminary range-finding study was also included with the study report and no effect on fetal viability was observed at doses up to 30 mg/kg/day.

As in the rat study, a statistically significant increase in the male:female pup ratio was observed at high dose. Values were 44.4%, 40.32%, 55.56% and 68.89%. TB-I agrees with the original review that this probably represented biological variation rather than treatment-effect. There was not a marked decrease in fetal weights of females compared to males, no increases in late resorptions in those high dose litters with few or no females and the smaller number of litters at high dose may have skewed the results. There were no apparent treatment-related increases in fetal abnormalities or other fetal/reproductive effects observed upon examination of fetal viscera and skeletons in this study.

3. Study Deficiencies: Although the number of viable litters at high dose is reduced below Guideline recommendations (8 vs. 12), TB-I considers this study marginally acceptable since a maternal NOEL and LEL were determined and since there was no indication of treatment-related developmental toxicity in this study or in the preliminary range-finding study. Historical control data for cesarean and developmental parameters and maternal food consumption were not included; however, these are not required by the Guidelines for 83-3b and lack of this information is not anticipated to affect the conclusions of this study. Analyses of dosing solutions was not performed at time of study; subsequent analyses determined that prometon was stable and homogeneous in the corn oil vehicle.