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RONMENTAL PROTECTION AGENCY
HINGTON, D.C. 20460

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SEP 13 '93

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: 069003. Tetramethrin Developmental Toxicity Study in Rabbits - Review of Historical Control Data and Range-Finding Study

PC Code 069003
Tox. Chem. No. 844
Project No. D194266
Submission No. S446427
MRID No. 428789-01, 428789-02

TO: Linda Deluise, PM Team # 51
Special Review and
Reregistration Division (H7508C)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley
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THRU: Roger L. Gardner, Section Head
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Health Effects Division (H7509C) Karl A. Hoffman for
9/3/93

Background and Request:

In order to fulfill reregistration requirements, Sumitomo Chemical Company, Inc. submitted a developmental toxicity study conducted with rabbits on tetramethrin (MRID No. 419950-05). The study was classified as Core Minimum and was considered to be acceptable for regulatory purposes. In response to the Data Evaluation Record (DER), the Registrant submitted historical control data for maternal body weight gain during gestation (MRID No. 428780-02) and the range-finding study conducted prior to the main study (MRID No. 428780-01). The Toxicology Branch (TB-I) has been requested to review the submitted data.

Toxicology Branch Response:

TB-I has reviewed the submitted data and has determined that the developmental toxicity study conducted with rabbits on tetramethrin is classified as Core Minimum and is acceptable for regulatory purposes. The maternal NOEL is greater than the highest dose tested (420 mg/kg/day calculated from analytical chemistry results). The developmental NOEL is also greater than

the highest dose tested. The study is acceptable because the range-finding study indicated that the LEL for maternal toxicity was approaching 500 mg/kg/day. In addition, a new study would not provide any additional information for risk assessment because an acceptable rat study is available in which the NOEL for maternal toxicity is 500 mg/kg/day and the LEL is 1000 mg/kg/day. It appears that the rat is either an equivalent or more sensitive species.

In addition to the above conclusion, in rereviewing the DER, the cover memorandum to the DER and the letter submitted to the Registrant, TB-I notes that there were some discrepancies between these items. Also, in some places, the study was referred to as a rat study when it was actually a rabbit study. On the front page of the DER, the cover memorandum and the letter sent to the Registrant, the study was classified as Core Minimum. However, on page 7 of the DER, the study was classified as Core Supplementary pending submission of historical control data on maternal body weight gain during gestation and results from the range-finding study. These discrepancies are superseded by this memorandum.

In the main study, New Zealand White rabbits were administered tetramethrin via gavage at 0, 30, 100, 300 or 500 mg/kg/day during gestational days 7 through 19. The DER stated that the maternal NOEL was 100 mg/kg/day and the LEL was 300 mg/kg/day based on a nonstatistically significant decrease in corrected body weight gain and decreases in body weight gain during the dosing and gestational periods. The NOEL for developmental toxicity was greater than the highest dose tested (420 mg/kg/day calculated from analytical chemistry results). Historical control data on body weight gain during gestation and the preliminary range-finding study were requested in order to support the conclusion that the decreased body weight gain is a true effect of the test compound as opposed to normal variation.

In re-examining the data from the main study, there were decreases in maternal body weight gain at the highest dose group (420 mg/kg/day) to the amount of 10% and 20% less than the control values. However, these decreases were not biologically significant because they were not statistically significant when compared to controls, they represented only a small fraction (1 - 5%) of the mean body weight values and there were no statistically significant decreases in body weights at any time when compared to controls.

In the preliminary range-finding study, groups of 5 inseminated female New Zealand white rabbits were treated by gavage with tetramethrin on days 7-19 of gestation at the following dose levels: 250, 500, 1000 or 1500 mg/kg/day. The control group was treated in a similar manner with the vehicle,

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0.5% carboxymethyl cellulose. One, 4 and 1 does died in the 500, 1000 and 1500 mg/kg/day dose groups, respectively. With these rabbits, the most common clinical sign was decreased feces. Statistically significant decreases in body weights and body weight gains were observed in does during dosing at 1000 and 1500 mg/kg/day. At 500 mg/kg/day, statistically significant decreases in body weights were not observed at any time, but significant decreases in body weight gain were observed for days 7-19, 16-19, 19-25, 25-29 and 7-25 of gestation. These data do not show much of an effect at 500 mg/kg/day; however, one doe had died and 2 aborted at this dose level (there were no indications of treatment-related deaths or abortions at this dose level in the main study). At 1000 mg/kg/day, 4 does aborted and at 1500 mg/kg/day, 5 does aborted. There appeared to be a dose-response in abortions. Gross pathological findings were observed in animals that either died or were killed at term in the 1000 and 1500 mg/kg/day groups. These included pale area(s) on the liver and/or dark areas on the mucosa of the stomach. These effects were not observed in the main study. The report stated that "among rabbits which died or aborted in the 500, 1000 and 1500 mg/kg/day groups there was an increased incidence of late resorptions, and among dead or aborted fetuses and aborted late resorptions abnormalities of domed skull, protusion of the brain, open eye(s) and eventration of the intestines were common. For the 250 mg/kg/day group, and for rabbits in the 500 mg/kg/day group- surviving to termination without abortion, the uterine and fetal parameters were unaffected." In the range finding study, the data are difficult to assess since there were so few animals and the data were not clear-cut. It appears that 500 mg/kg/day was selected because of the indications of a trend towards maternal effects at 500 mg/kg/day and above (particularly because 4/5 animals died at 1000 mg/kg/day).

The historical control data were not in a form that could be used for comparison purposes. Thus, although the data are presented in this memorandum, they are not discussed.

The following tables summarize the mean body weight and body weight gain data from the main and range-finding studies and from the submitted historical control data for comparison purposes. The historical control data only consisted of one study. Other tables from the range-finding study are also included.

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Mean Body Weights (Kg) for Main Study

Gestation Day	0	30	100	300	500
0	3.176 ± 0.255	3.252 ± 0.198	3.279 ± 0.258	3.257 ± 0.221	3.140 ± 0.257
7	3.317 ± 0.267	3.395 ± 0.192	3.404 ± 0.235	3.372 ± 0.215	3.281 ± 0.293 (99%)
10	3.392 ± 0.277	3.448 ± 0.202	3.458 ± 0.253	3.420 ± 0.215	3.316 ± 0.302 (98%)
13	3.467 ± 0.294	3.523 ± 0.202	3.519 ± 0.268	3.467 ± 0.212	3.377 ± 0.306 (97%)
19	3.559 ± 0.293	3.625 ± 0.216	3.653 ± 0.267	3.562 ± 0.258	3.478 ± 0.324 (98%)
22	3.635 ± 0.289	3.670 ± 0.240	3.698 ± 0.254	3.637 ± 0.231	3.562 ± 0.328 (98%)
25	3.704 ± 0.294	3.733 ± 0.266	3.762 ± 0.252	3.710 ± 0.244	3.631 ± 0.341 (98%)
29	3.797 ± 0.290	3.831 ± 0.285	3.894 ± 0.255	3.807 ± 0.230	3.721 ± 0.360 (98%)

( ) = % of control value.

Mean Body Weight Gain (g ± S.D.)) for Main Study

Days Group	0-7	7-10	10-13	7-19	19-29	0-29	Corrected 7-29
0	140 ± 65	57 ± 37	75 ± 35	226 ± 49	238 ± 44	610 ± 75	40 ± 98
30	147 ± 55	53 ± 40	75 ± 44	230 ± 63	203 ± 99	579 ± 132	10 ± 92
100	126 ± 59	54 ± 59	61 ± 53	226 ± 94	241 ± 87	587 ± 106	50 ± 98
300	115 ± 59	48 ± 42	47 ± 69	181 ± 125	240 ± 85	551 ± 122	-40 ± 115
500	141 ± 67 (101%)	36 ± 42 (63%)	61 ± 53 (81%)	182 ± 102 (81%)	242 ± 99 (102%)	565 ± 144 (92.6%)	-10 ± 115

( ) = % of control value.

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Mean Body Weights (Kg) for Range-Finding Study

Group Day	0	250	500	1000	1500
0	3.577 ± 0.259	3.508 ± 0.215	3.616 ± 0.272	3.616 ± 0.249	3.530 ± 0.195
7	3.650 ± 0.246	3.498 ± 0.260	3.683 ± 0.274 (101%)	3.718 ± 0.266 (102%)	3.640 ± 0.111 (98%)
10	3.697 ± 0.266	3.614 ± 0.199	3.636 ± 0.219 (98%)	3.534 ± 0.245 (96%)	3.451 ± 0.287 (93%)
13	3.732 ± 0.238	3.647 ± 0.208	3.542 ± 0.258 (95%)	3.361 ± 0.228 (90%)	3.278 ± 0.347 (88%)
16	3.812 ± 0.259	3.736 ± 0.204	3.541 ± 0.285 (93%)	3.212 ± 0.249** (84%)	3.154 ± 0.318** (83%)
19	3.864 ± 0.255	3.699 ± 0.126	3.480 ± 0.322 (90%)	3.089 ± 0.247** (80%)	3.010 ± 0.280** (78%)
25	4.032 ± 0.285	3.925 ± 0.164	3.594 ± 0.470 (89%[b])	-[a]	-
29	4.089 ± 0.296	3.957 ± 0.187	3.900 ± 0.460 (95%[b])	-	-

[a]Animals were either all dead or aborted.
[b]Only two animals available.
** p < 0.01 (Dunnett's); ( ) = % of control value.

Mean Body Weight Gains During Gestation (kg) for Range-Finding Study

Days	0	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	1500 mg/kg/day
0 - 7	0.074 0.083 5[a]	-0.009 -0.198 5	0.067 (91%) 0.077 5	0.102 (138%) 0.060 5	0.110 (149%) 0.104 5
7 - 10	0.047 0.038 5	0.116 0.130 5	-0.048 0.134 5	-0.184* 0.051 5	-0.189* 0.216 5
10 - 13	0.034 0.041 5	0.033 0.041 5	-0.094 0.141 5	-0.173** 0.041 5	-0.173** 0.067 5
7 - 13	0.081 0.049 5	0.148 0.128 5	-0.142 0.238 5	-0.357** 0.092 5	-0.362** 0.274 5
13 - 16	0.081 0.040 5	0.089 0.084 5	-0.001 0.076 5	-0.149** 0.051 5	-0.124** 0.083 5
16 - 19	0.052 0.015 5	-0.036 0.088 5	-0.061* 0.081 5	-0.123** 0.035 5	-0.143** 0.055 5
19 - 25	0.168 0.046 5	0.226 0.059 5	-0.142** 0.083 2	-[b]	-

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Mean Body Weight Gains During Gestation (kg) for Range-Finding Study

Days	0	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	1500 mg/kg/day
25 - 29	0.057 0.093 5	0.032 0.053 5	0.306** 0.010 2	-	-
7 - 19	0.214 0.039 5	0.201 0.198 5	-0.204* 0.386 5	-0.629** 0.070 5	-0.629** 0.193 5
7 - 29	0.439 0.055 5	0.459 0.212 5	0.345 0.133 2	-	-
7 - 29 corrected	-0.054 0.0513 5	0.069 0.1488 5	-0.0151 0.1711 2	-	-

[a]Mean
S.D.
n
[b]The "-" means that all animals had either died or aborted.
* $p < 0.05$; ** $p < 0.01$ (Dunnett's)
( ) = % of control value.

Historical Control Data Rabbit NZW Body Weight Gain

Interval (Days)		Vehicle Control (10 mg/kg/day (IV)
0 to 6	Mean (S.D.)	0.116 (0.082)
	N	15
6 to 9	Mean (S.D.)	0.039 (0.060)
	N	15
9 to 12	Mean (S.D.)	0.052 (0.055)
	N	15
12 to 15	Mean (S.D.)	0.081 (0.053)
	N	15
15 to 18	Mean (S.D.)	0.039 (0.051)
	N	15
18 to 24	Mean (S.D.)	0.142 (0.056)
	N	15
24 to 29	Mean (S.D.)	0.097 (0.068)
	N	15

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The following tables were selected from the range-finding study.

Selected Group Incidence of Clinical Findings

Observations	0	250	500	1000	1500
No. of Animals Examined	5	5	5	5	5
Red fluid/discharge in tray	0	0	2	4	5
Aborted material in tray	0	0	2	4	5
Small amount/no feces in tray	0	0	3	5	4
Large amt. food left in hopper	0	0	1	3	2
Mucoid material in tray/feces	0	0	0	1	2

Group Maternal Performance

	0	250	500	1000	1500
# Does inseminated	5	5	5	5	5
# Does pregnant	5	5	5	5	5
# Does with live fetuses	5	5	2	0	0
# Does aborting	0	0	2	4	5
# Does that died on study	0	0	1	4	1
Mortality rate (%)	0.0	0.0	20.0	80.0	20.0
Pregnancy rate (%)	100.0	100.0	100.0	100.0	100.0

Incidence of Gross Pathological Findings

Sex	♀	♀	♀	♀	♀
Group	1	2	3	4	5
# Animals in group	5	5	5	5	5
# Animals examined	5	5	5	5	5
Liver					
Area depressed	0	0	1*	0	0
Area pale	0	0	0	1	2
Discoloration	0	0	0	0	1
Firm	0	0	0	0	1
Lymph node					
Discoloration	0	0	1*	0	0
Ovary					
Cyst	0	1	0	0	1
Stomach					
Area dark	0	0	0	2*	1

* Incidence for animals found dead.

Cesarean Section Observations

Dose (mg/kg/day)	Control	250	500
Corpora Lutea/Dam	10.6	7.8	9.5
Implantations/Dam	9.0	6.0	8.0
Live Fetuses/Dam	8.4	6.0	8.0
Resorptions/Dam	0.6	0.0	0.0
Early	0.4	0.0	0.0
Middle	0.2	0.0	0.0
Late	0.0	0.0	0.0
Dead Fetuses/Dam	0.0	0.0	0.0
Mean Fetal Weight (gm)	42.4	48.3	44.3
Preimplantation Loss(%)	14.6	22.9	15.4
Postimplantation Loss(%)	6.9	0.0	0.0
Sex Ratio (% Male)	42.9	53.0	61.9
Gravid uterus wt. (g)	493.4	389.6	496.0

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