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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ID. No. 010308-RR. Sumilarv, Response to Developmental Study

Tox. Chem. No.: 129032
DP Barcode #: D204286
Record No. : S466319

FROM: Melba S. Morrow, D.V.M. MSM 12/9/94
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Health Effects Division (H7509C)

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THRU: Joycelyn E. Stewart, Ph.D. JES 12/14/94 KB 1/27/95
Head, Review Section II
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CONCLUSIONS: Based on information provided under MRID 432154-01 thru 432154-03, the original developmental study conducted in rabbits (MRID 413217-20) can be upgraded to core minimum.

When Sumilarv was administered by gavage to JW-NIBS rabbits at doses of 0, 100, 300 or 1000 mg/kg on gestation days 6 thru 18, the developmental NOEL was > 1000 mg/kg. The maternal NOEL was 100 mg/kg and the maternal LOEL was 300 mg/kg based on an increased incidence of soft stools, emaciation, lusterless fur, decreased activity, premature delivery and bradypnea. At 1000 mg/kg, the incidence of premature delivery had increased to such a degree that only four dams had viable litters at the time that Cesaerian sections were performed.

Embryotoxicity was also observed and the NOEL for this endpoint was 300 mg/kg. At 1000 mg/kg, embryotoxicity was observed as evidenced by abortions at days 15 and 18 of gestation in two of the dams.

A copy of the DER is attached for your reference.

In addition to addressing the deficiencies in the developmental study in rabbits, the registrants submitted a two week study conducted in rabbits that was used to determine the doses for the pivotal rabbit developmental study. In this study, the NOEL was 100 mg/kg and the LOEL was 300 mg/kg based on decreased body weight gain (40%) when compared to controls. A summary of this study is also included in the DER.

Reviewed by: Melba S. Morrow, D.V.M. MSM 12/9/94
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, Ph.D. JES 12/14/94
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity (addendum to original MRID 413217-20)

GUIDELINE #: 83-3b

TOX. CHEM. #: 129032

MRID #: 432154-01, -02 and -03

TEST MATERIAL: Sumilarv,
2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine

SYNONYMS: S-31183

STUDY NUMBERS: NNT-80-0033

SPONSOR: Sumitomo Chemical Company
Osaka, Japan

TITLE OF REPORTS: Response to EPA Review of Teratogenicity/Developmental Toxicity Study of Sumilarv (S31183) in Rabbits; Addendum to Final Report; and Two-Week Administration Study of S31183 in Rabbits

AUTHORS: Atsuko Hirohashi

REPORT ISSUED: 4/27/94 (addendum)

CONCLUSIONS: Based on the information provided in these three reports, the original report filed under MRID 413217-20 can be upgraded to core minimum. When doses of 0, 100, 300 or 1000 mg/kg of Sumilarv (S-31183) were administered by gavage on days 6 thru 18 of gestation to JW- NIBS rabbits the developmental NOEL was > 1000 mg/kg. The maternal NOEL was 100 mg/kg and the maternal LOEL was 300 based on soft stools, emaciation, lusterless fur, decreased activity, premature delivery and bradypnea. Embryotoxicity was observed and the NOEL for this endpoint was 300 mg/kg. The LOEL for embryotoxicity was 1000 mg/kg based on increased incidences of abortions on days 15 and 18 of gestation. At 1000 mg/kg the incidence of premature delivery had increased to a degree that only four of the original 13 pregnant dams had viable litters at the time Cesaerian sections were performed (Day 28).

CLASSIFICATION: Minimum

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DISCUSSION:

In the initial review of the data for this study, a supplementary classification was given. The study was deemed upgradeable pending receipt of summary data which provided gravid uterine weights, information on total resorptions, data separating early/late resorptions from stillbirths and summary data for litter incidence of malformations/variations.

The sponsor has provided the following comments in response to issues raised in our (Tox Branch I) original review.

1. The number of litters in the high dose group was too low(4).

The company has responded that the low number of dams with litters was due to the toxic effects of the compound. Eighteen animals were assigned to the high dose group, of which 13 were pregnant. Abortion or premature delivery occurred in 6/13, death was reported in 1/13 and 2/13 were sacrificed in a moribund condition. No fetal abnormalities were reported for the 26 fetuses from the 4 surviving litters.

2. There was no separation of early and late resorptions from stillbirths.

The response from the company was that at Sumitomo (laboratory conducting the studies), early and late resorptions are distinguished from each other by the tissue that is present. Early resorptions would involve implantation sites, implantation scars, placental remnants, embryonic/placental tissues and macerated tissue. Late resorptions would include fetal tissue and placenta, macerated fetuses and dead fetuses.

Stillbirths were only recorded in this particular lab when deliveries were normal and were not evaluated in the case of Cesaerian section. This response is acceptable. Based on the performing laboratory's definition of a stillbirth, none would be recorded for this study.

3. The original study in rabbits failed to report totally resorbed litters.

Based on the results there were no totally resorbed litters.

4. The study did not distinguish between premature delivery or abortion.

The sponsor has provided a table which gives the day of abortion or premature delivery for all affected groups. Based on the results reported in Table 1, it appears that in the high dose group, two of the animals that were sacrificed may have aborted on days 18 and 15 of gestation. One animal in the high dose

group died on day 18 of undetermined causes. The remaining animals (6) in this group appeared to have delivered prematurely between days 22 and 25 of gestation.

5. Gravid uterine weights were not reported.

The sponsor has provided estimates of gravid uterine weights based on the total fetal weight of each litter. Corrected body weight has been determined by subtracting the total fetal weight from the total maternal body weight gain. The following Table provides mean values for body weight, body weight gain total fetal weight and corrected body weight gain. All figures have been rounded to the nearest hundredth. No statistical significance was found in the weight gain differences between the controls and the highest dose tested.

Table I: Body Weight and Body Weight Gain

	Dose Group (mg/kg)			
	0	100	300	1000
# Animals	13	12	11	4
Mn body wt (kg)				
Day 0	3.00	2.93	3.05	2.91
day 28	3.28	3.23	3.41	3.15
Body Wt gain (kg)	0.28	0.30	0.36	0.23
Fetal Wt (kg)	0.26	0.27	0.30	0.24
Corrected body weight gain (kg)	0.02	0.03	0.06	- 0.01

6. Litter incidence data for malformations were not provided in a summary format.

Litter incidence of malformations/variations were provided. There were reported increases in litter incidence of bipartite sternebrae, shortened hyoid arch, curved hyoid arch and bifurcation of the vermiform appendix when high dose fetuses and litters are compared to controls. These increases in litter incidences are somewhat misleading and have no biological significance since they involved a maximum of 3 fetuses from 2 different litters (50% incidence based on the fact that there were only 4 litters in the highest dose group).

7. An additional study was submitted with the registrants response. The study is summarized below. (MRID 432154-03)

Title: Two Week Administration Study of S-31183 in Rabbits

Study #: 375

Date: March 3, 1988

12/20/94
12/20/94

Author: Atsuko Hirohashi

Laboratory: Sumitomo Chemical Co., Ltd.

Summary: S-31183 (Sumilarv), 97.2% purity was administered by oral gavage to nonpregnant JW NIBS rabbits at doses of 0, 100, 300 and 1000 mg/kg for two weeks. The treatment groups consisted of 4 animals per group. Animals were individually housed in wire-bottom cages and food and water were provided ad libitum. Animals were maintained on a 12 hour light/dark cycle.

Body weight, food consumption and general condition of the test animals were monitored at regular intervals during the two week period. Differences in body weight, weight gain, food consumption and food consumption per kilogram were analyzed using the T test for significance. ($p = 0.05$).

Animals were sacrificed by exsanguination on day 15. A gross examination of thoracic and abdominal organs was conducted.

No deaths were reported; however, one rabbit in the highest dose group had soft stools and emaciation. Body weight gain was significantly decreased in the 300 mg/kg and in the 1000 mg/kg group on day 3 of the study. In the 300 mg/kg group, the body weight gain recovered; however, in the 1000 mg/kg group, body weight gain continued to decline. Food consumption was also lower in the high dose group but not to a level of statistical significance. Differences reported for the highest dose group were primarily attributed to one animal in that group that appeared to be in a chronic state of malnutrition.

The NOEL for this study was 300 mg/kg and the LOEL was 1000 mg/kg based on body weight gain decrements from days 3 thru 15 of the study.

Gross pathological findings were present in only one animal in the high dose group and these were suggestive of chronic wasting. These findings included discoloration of the heart, nonviscous brown bile, hemorrhage in the gastric pylorus, absence of contents in the small intestines, viscous and muddy cecal contents, thinning of the cecal wall and intracecel gas retention. Based on these findings a maximum dose of 1000 mg/kg was selected for the developmental study. (See Table I for body weight/ weight gain).

TABLE I
Body Weight (kg)

	Dose (mg/kg) 0	100	300	1000
1	2.94	2.97	2.96	2.96
3	2.99	2.99	2.95	2.88
5	2.98	2.99	2.97	2.86
7	2.98	2.99	2.97	2.79
9	3.02	2.98	2.98	2.74
11	3.00	3.00	2.99	2.73
13	3.02	3.04	3.01	2.71
15	3.04	3.05	3.02	2.69
Bwt Gain				
1 - 3	0.05	0.02	-0.01	-0.08
3 - 11	0.01	0.01	0.04	-0.13
11- 15	0.04	0.05	0.03	-0.04
1 - 15	0.10	0.08	0.06	-0.27

Data derived from Table I of submission.

Statistical significance was not indicated in the Table; however, an accompanying graph demonstrated significance at day 3 in the group receiving 300 mg/kg ($p > 0.05$) and from day 3 thru day 15 in the group receiving 1000 mg/kg ($p > 0.01$).