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

MAR 22 1995

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: ID. No. 010308-RR, Sumilarv, Subchronic Toxicity in Mice and Supplements to Rat and Mouse Oncogenicity studies.

Tox. Chem. No.: 129032
DP Barcode #: D204283
D208894
Record No. : S466680
S476051

FROM: Melba S. Morrow, D.V.M. MSM 2/14/95
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Joe Tavano/ Marion Johnson, Team 10
Registration Division (H7505C)

THRU: Joycelyn E. Stewart, Ph.D. 7/22/95 KB 2/24/95
Head, Section II
Toxicology Branch I
Health Effects Division (H7509C)

CONCLUSIONS: Toxicology Branch I has completed our reviews of the subchronic toxicity study in mice and of the supplements filed in support of the rat and mouse oncogenicity studies. We have the following comments regarding these three studies:

82-1(a) Subchronic Toxicity Study - Mice; MRID 432105-04

When technical Sumilarv (95.3%, Lot # PYG 87074) was administered to male and female CD-1 mice at dietary levels of 0, 200, 1000, 5000 or 10000 ppm (approximate mg/kg/day calculated equivalents: 0, 28.2, 149.4, 838.1, 2034.5 for males and 0, 37.9, 196.5, 963.9 and 2345.3 for females), there was an increase in mortality in both sexes at the highest dose tested. In animals of both sexes that received the two highest doses, kidney lesions were present. Macroscopically, there was dilation of the renal pelvises, fluid filled renal pelvises, unequal kidney sizes, cysts and paleness. Microscopically, there was nephrosis with renal tubular dilatation and dilatation and mineralization of the renal pelvises.

In addition to these effects, there was a decrease in body weight gain in males at the two highest dose levels (at 5000 ppm, 62% lower than controls), significant decreases in red blood cells, hemoglobin, hematocrit, MCV and MCH and increased liver to body weight ratios. Females at the 5000 ppm dose level had significant decreases in red blood cells, hemoglobin and hematocrit, significantly increased liver weights and significantly increased liver to body weight ratios ($p \leq 0.05$). At 10000 ppm there was only one surviving female; therefore, the numbers were not sufficient for statistical evaluation.

The NOEL and LOEL for systemic toxicity was 1000 ppm and 5000 ppm, respectively based on renal pathology, increases in liver weights, increases in liver:body weight ratios, decreases in red blood cell parameters and decreases in body weight gain in males.

The kidney pathology was not associated with any clinical findings. Urinalysis was unremarkable. With regard to serum chemistry, of the parameters that could be correlated with renal disease, only the BUN was elevated in both sexes at 5000 ppm. No similar elevations in BUN were reported in the three surviving males and in the one surviving female at 10000 ppm.

CLASSIFICATION: Minimum.

83-5 Chronic/Oncogenicity Study - Rat; MRIDs 432105-01, -02 and -03

Based on the information presented in the subject MRIDs, the chronic feeding/oncogenicity study in rats is acceptable and can be upgraded to core minimum. The sponsor has adequately responded to all of the deficiencies cited in the September 15, 1993 DER for this study. There was no evidence of increased tumor incidence in this study when S31183 (Sumilarv) was administered in the diet to Sprague Dawley rats at levels of 0, 120, 600 or 3000 ppm (mg/kg/day: 5.42, 27.31, and 138 in males and 7.04, 35.1 and 182.7 in females). The NOEL for systemic toxicity was 600 ppm and the LOEL was 3000 ppm based on a 16.9% depression in body weight gain in females when compared to controls for weeks 0 - 78.

This decrease in body weight gain in the first 78 weeks of the study is indicative of minimal toxicity and the MTD may have been slightly underestimated based on the fact that the effects observed in the 90 day study (increased cholesterol, and phospholipids, decreased mean red cell, hematocrit and hemoglobin counts and increased liver to body weight ratio) were not reproduced. Repeating the study at doses higher than 3000 ppm would provide little additional information on the chronic toxicity or on the carcinogenic potential of the test material.

CLASSIFICATION: Minimum

83-2 Mouse Oncogenicity; MRIDs 432105-01, 434132-01 and-02

Sumilarv, 95.3% (S-31183) was administered to male and female CD-1 mice at dietary levels of 0, 120, 600 and 3000 ppm (equivalent to 0, 16.8, 84.0 and 420 mg/kg in males and 0, 21.9, 109.5 and 547 mg/kg in females). Fifty animals/sex/dose level received the test material for 78 weeks; ten animals/sex/group were designated for interim sacrifice after 52 weeks on the study.

There was no increased tumor incidence in either sex that could be associated with the administration of the test material. The NOEL for systemic effects was 600 ppm and the LOEL of 3000 ppm was based on an increased incidence of renal lesions in both sexes. In males, there was an increase in chronic progressive nephropathy, characterized by enlarged kidneys with tubular cysts and renal calcification and mineralization. In females, there was an increase in the incidence of mineralization of the renal tubules.

There was a reported increase in mortality. However, this appeared to be related to the presence of systemic amyloidosis that has a historically high background incidence in CD-1 mice, and which may have been exacerbated by the administration of Sumilarv.

Based on the observed renal lesions, the doses used in this study were adequate to evoke a carcinogenic response.

CLASSIFICATION: Minimum.

Copies of the DERs are attached for your reference.

Reviewed by: Melba S. Morrow, D.V.M. MSM 1/25/95
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, Ph.D. JES 1/25/95
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Toxicity Study in mice

GUIDELINE #: 82-1a

TOX. CHEM. #: 129032

MRID #: 432105-04

TEST MATERIAL: S-31183

SYNONYMS: Sumilarv (95.3%, Lot # PYG 87074)

STUDY NUMBERS: 343-209

SPONSOR: Sumitomo

TESTING FACILITY: Hazleton Lab
Vienna, Va. 22182

TITLE OF REPORT: Sumilarv- Subchronic Toxicity Study in Mice

AUTHORS: R.H. Cox, PhD.

REPORT ISSUED: January 20, 1990

EXECUTIVE SUMMARY: When technical Sumilarv (95.3%, Lot # PYG 87074) was administered to male and female CD-1 mice at dietary levels of 0, 200, 1000, 5000 or 10000 ppm (approximate mg/kg/day calculated equivalents: 0, 28.2, 149.4, 838.1, 2034.5 for males and 0, 37.9, 196.5, 963.9 and 2345.3 for females), there was an increase in mortality in both sexes at the highest dose tested. In animals of both sexes that received the two highest doses, kidney lesions were present. Macroscopically, there was dilation of the renal pelvises, fluid filled renal pelvises, unequal kidney sizes, cysts and paleness. Microscopically, there was nephrosis with renal tubular dilatation and dilatation and mineralization of the renal pelvises.

In addition to these effects, there was a decrease in body weight gain in males at the two highest dose levels, significant decreases in red blood cells, hemoglobin, hematocrit, MCV and MCH and increased liver to body weight ratios. Females at the 5000 ppm dose level had significant decreases in red blood cells, hemoglobin and hematocrit, significantly increased liver weights and significantly increased liver to body weight ratios. At 10000 ppm there was only one surviving female; therefore, the

numbers were not sufficient for evaluation.

The NOEL and LOEL for systemic toxicity was 1000 ppm and 5000 ppm, respectively based on renal pathology, statistically significant increases in liver weights and in liver:body weight ratios, and statistically significant decreases in red blood cell parameters and in body weight gain in males.

The kidney pathology was not associated with any clinical findings. Urinalysis was unremarkable. With regard to serum chemistry, of the parameters that could be correlated with renal disease, only the BUN was elevated in both sexes at 5000 ppm. No similar elevations in BUN were reported in the three surviving males and in the one surviving female at 10000 ppm.

CLASSIFICATION: Minimum. This study fulfills the requirements for a rodent subchronic toxicity study as specified in Guideline 82-1a. Data from this study were used to determine the dose levels to be used in the mouse oncogenicity study (MRID 421783-10).

MATERIALS: S-31183 (Sumilarv), 95.3% a.i., Lot # PYG 87074, was the test material. The test animals were CD-1 mice, (obtained from Charles River Laboratories in Raleigh, N.C.) that were 7 weeks of age at the initiation of the study and weighed 27.6 to 32.1 grams (males) or 19.8 to 24.3 grams (females).

METHODS: After a three week acclimation period, animals were assigned to dosage groups that received the test compound for 13 weeks in the diet at levels of 0, 200, 1000, 5000 or 10000 ppm. Ten males and ten females were assigned to each dose group. Control animals received the basal diet. Food and water were available ad libitum.

Mortality and moribundity were measured twice daily and toxic effects of the compound were assessed once daily. Physical examinations, body weights, and food and water consumption were evaluated once a week. Ophthalmic examinations were conducted prior to the administration of the test material and at week 12.

Blood samples, from the orbital sinus or from the abdominal aorta, were collected for clinical pathology on week 13. Urine samples were collected at the end of 13 weeks from collection cages. The following parameters were evaluated (x):

x Hematocrit (HCT)
x Hemoglobin (HGB)
x Leukocyte count (WBC)
x Erythrocyte count (RBC)
x Platelet count
x Leukocyte differential
x Mean corpuscular hemoglobin
x Mean corpuscular hemoglobin concentration
x Mean corpuscular volume
Reticulocytes

Blood clotting measurements:
Thromboplastin time
Clotting time
Prothrombin time

Electrolytes:
x Calcium
Chlorine
Magnesium
Phosphorous
x Potassium
x Sodium

Enzymes:
Creatinine phophokinase
Alkaline phosphatase
Lactic dehydrogenase
x SGPT (ALT)
x SGOT (AST)
x Gamma glutamyl transferase
Glutamate dehydrogenase
Cholinesterase

Other Serum Chemistry Values:
x Albumin
x Phospholipids
x BUN
x Cholesterol
x Globulin
x Glucose
x Total Bilirubin
x Total protein
x Triglycerides
Serum protein electrophoresis

Urinalysis
x pH
x appearance
x glucose
x ketones
x protein
x blood
x bilirubin
x urobilinogen
x sediment

All surviving animals were anesthetized with sodium pentobarbital and exsanguinated. Necropsies were performed on all animals.

The following CHECKED (x) tissues were collected for histological examination. Samples were embedded in paraffin and stained with hematoxylin and eosin. Gross lesions in the liver, lungs and kidneys were histologically examined for all animals; however, complete microscopic examinations were conducted only on animals in the control and high dose group and on unscheduled deaths.

Weighed organs are designated by (xx).

Digestive system	Cardiovasc./Hemat.	Neurologic
Tongue	x Aorta	x Brain
x Salivary glands	x Heart	x Periph. nerves
x Esophagus	x Bone marrow	x Spinal cord
x Stomach	x Lymph nodes	
x Duodenum	x Spleen	
x Jejunum	x Thymus	Glandular
x Ileum		x Parathyroids
x Cecum		xx Adrenals
x Colon	Urogenital	x Thyroid
x Rectum	xx Kidneys	x Pituitary
	x Urinary bladder	x Mammary
xx Liver	xx Testes	
x Gall bladder	Epididymides	Other
x Pancreas	Prostate	x Bone
	Seminal vesicle	x Skin
Respiratory	x Ovaries	x Skel. muscle
x Trachea	x Uterus	x All gross lesions
x Lung	Vagina	x Eyes
Nose		
Pharynx		
Larynx		

Dietary samples were collected from test diets of 50 and 10000 ppm for analysis of stability on days 0, 7 and 14. Homogeneity was determined using 50 gram samples collected prior to dosing and at weeks 1, 2 and 3 from the top, middle and bottom of each dietary mixture for each dose group and the control. The concentration of the test material in the diet was determined at weeks 4, 8 and 12. These analyses were conducted by high performance liquid chromatography (HPLC).

QUALITY ASSURANCE: A statement of quality assurance and a statement of compliance with GLPs were provided in the submission. Statements were signed on January 23, 1990.

STATISTICAL ANALYSIS: The following parameters were analyzed using the NCI statistical package, with a level of significance of $p = 0.05$: survival, body weight, body weight gain and organ weight.

RESULTS:

Stability, Homogeneity and Concentration:

Stability and homogeneity were demonstrated during week 3 of the study. Mixing procedures had to be changed following a reported lack of homogeneity at weeks 1 and 2. The concentration of the test material in the diet was acceptable throughout the study. The percent of nominal concentration ranged from 91.5 to 109 from weeks 3 - 12.

Mortality:

There was no reported increase in mortality in females receiving the test material at dietary levels up to 5000 ppm and in males receiving dietary concentrations of Sumilarv up to 1000 ppm. At 5000 ppm in males, two animals died during the 13 week study period. At 10000 ppm, only three males and only one female survived the study. At this dose level, death occured in one of the ten original male animals and was due to an error in blood collection technique. This animal was not included in the data base.

Survival at Week 13

	Dietary level (ppm)				
	0	200	1000	5000	10000
Males	10/10	10/10	10/10	8/10	3/9#
Females	10/10	10/10	10/10	10/10	1/10

Clinical Signs:

Clinical signs of toxicity were observed primarily in the two highest dose groups for both sexes and included hunched posture, thin appearance, reduced motor activity and polypnea. Clinical signs reported for the two lower dose groups were similar to those in the control animals and occurred sporadically across all groups.

Body Weight Gain, Food Consumption:

Weight loss was reported for males in the high dose group. In this group there was a mean weight gain of -4.7 grams compared to +6.6 grams for the controls. At 5000 ppm, the body weight gain for males was 2.5 grams. Food consumption was similar for all male animals, indicating that there may have been a compound related effect on feed efficiency at the two highest dose levels.

In females at the highest dose tested, there was weight loss or no weight gain during the first 4 weeks of the study. During

no weight gain during the first 4 weeks of the study. During this four week period, mean weight loss was 3.5 grams for females receiving 10000 ppm compared to weight loss of 6.5 grams in males at the same dose level. At four weeks, when 8/10 female animals were alive in the high dose group, statistically significant differences were reported for body weight. (See Table I).

Food consumption was similar for all groups of females, indicating that in females, as was the case in males, food efficiency may have been adversely affected by the administration of Sumilarv.

Clinical Pathology

At the two highest dose levels in both sexes, there was an effect on red cell parameters as evidenced by decreased red cell counts, hemoglobin and hematocrit. MCV and MCHC were also significantly decreased in males at 5000 ppm and 10000 ppm (only one female available at the highest dose). With the exception of the red cell count at 5000 ppm in males, all other red cell parameters were significantly decreased, $p < 0.05$ (See Table II). The effects appear to have been related to the dose of S 31183 that was administered.

Cholesterol was significantly increased in females at 1000 and 5000 ppm, but not at 10000 ppm. At 5000 ppm, there was a non-significant increase in AST and ALT in both sexes, but not at 10000 ppm. BUN was elevated in both sexes at 5000 ppm and phospholipids were increased at the same dose in females only. Both of these findings were associated with the administration of the test material. The elevation in BUN could be correlated with the renal pathology; however the significance of the increase in phospholipids is unclear.

There were no notable findings in the urinalysis of either sex.

Gross and Microscopic Pathology:

There was an trend for increasing liver weights in females and an increased liver:body weight ratio in both sexes, with statistical signficance ($p < 0.05$) being reported at 5000 ppm for females and at 10000 ppm for males.

Grossly, the kidney appeared to be the primary organ affected by the test material. Lesions in both sexes at the two highest dose groups included dilated renal pelvises, cysts, paleness, fluid filled pelvises, unequal kidney sizes and kidney enlargement. Gross liver lesions (dark livers) were observed in males from the two high dose groups.

Microscopically, lesions in the kidneys were the most consistent observation at the two highest dose levels in both sexes. Nephrosis with dilatation of the renal tubules and mineralization

and dilatation of the renal pelvis were observed with the greatest frequency in these two groups. Chronic progressive nephrosis was diagnosed throughout control and treated groups of sexes and did not appear to be related to the administration of the test material. In unscheduled deaths, dilated renal pelvis was the most frequent pathological finding in both sexes (See Table III for histopathology, liver weights and liver to body weight ratios).

There were no other histopathologic lesions which could be attributed to the administration of Sumilarv.

DISCUSSION:

This study is core minimum and satisfies the requirements for a subchronic rodent toxicity study. The NOEL in this study is 1000 ppm and the LOEL is 5000 ppm based on the observed effects on clinical, gross and microscopic pathology.

The information obtained in this study was used to set dose levels for the definitive 18 month mouse oral carcinogenicity study. Based on the information presented here, it is the opinion of Toxicology Branch I that the 18 month feeding study was conducted at appropriate dose levels.

TABLE I
Mean Body Weight (g)

Males	Dose (ppm)				
Week	0	200	1000	5000	10000
0	29.3	29.9	29.4	29.1	29.8
1	30.9	32.3	31.5	28.9	27.6
2	31.9	32.9	32.3	28.2	25.3
3	33.2	34.0	33.1	29.2	24.3
4	33.5	35.1	33.7	28.8*	23.3*
5	34.0	35.7	34.4	30.1	24.4
7	34.7	36.4	34.9	30.4	23.4
9	36.1	37.5	35.9	31.0	25.1
11	35.5	37.9	36.4	31.8	25.6
13	35.9	37.7	36.3	31.6*	24.9*
Gain					
1 -13	6.6	7.8	6.9	2.5	-4.1
Females					
Week					
0	22.0	22.4	21.9	22.5	22.2
1	23.2	23.6	23.5	23.2	21.2
2	23.8	23.6	23.5	23.6	19.4
3	24.6	24.2	24.8	24.4	19.4
4	25.2	25.2	25.4	24.9	18.7*
5	25.5	25.6	25.8	25.8	19.5
7	26.9	26.5	26.9	26.1	20.9
9	27.7	27.9	27.6	27.1	28.3a
11	27.9	28.1	28.5	27.6	28.9a
13	28.0	28.2	28.2	27.2	29.1a
Gain					
1 - 13	6.0	5.8	6.3	4.7	6.9

* $p \leq 0.05$
a = value for one animal.

Table II
Clinical Pathology

Males	Dose (ppm)				
Parameters	0	200	1000	5000	10000
Red cells (million/UL)	10.78	10.65	10.96	10.30	8.23*
Hemoglobin (g/DL)	17.4	17.3	17.00	14.8*	11.9*
Hematocrit (%)	51.0	50.5	50.2	44.5*	35.7*
MCV	47.4	47.5	45.8	43.3*	42.9*
MCH	16.2	16.2	15.5*	14.4*	14.4*
Females					
Parameters					
Red cell	10.87	10.62	10.51	9.77*	10.16a
Hemoglobin	17.50	17.30	17.30	15.30*	16.20a
Hematocrit	51.70	50.70	50.50	45.40*	48.00a

* $p < 0.05$
a = only one surviving animal in this group.

Table III
Histopathology

Males	Dose (ppm)				
Organ/Lesion	0	200	1000	5000	10000
Kidneys					
nephrosis	0/10	0/10	0/10	7/8	3/3
dil. renal pelvis	1/10	0/10	1/10	4/8	2/3
renal tubular mineralization	0/10	0/10	0/10	3/8	2/3
renal tubular dilatation	3/10	1/10	1/10	7/8	2/3
chronic progressive nephrosis	5/10	6/10	5/10	1/8	0/3
Females					
Kidneys					
nephrosis	0/10	0/10	0/10	8/10	0/1
renal tubular mineralization	0/10	0/10	0/10	6/10	0/1
renal tubular dilatation	1/10	2/10	0/10	7/10	1/1
chronic progressive nephrosis	3/10	4/10	3/10	0/10	1/1

Denominators at 5000 and 10000 ppm include surviving animals.

TABLE IV

Liver Weights (g)

Males	1.30	1.34	1.37	1.36	1.30
Females	1.06	1.07	1.11	1.24*	1.70*

Liver: Body Weight (%)

Males	4.148	3.994	4.366	5.075*	5.867*
Females	4.320	4.490	4.630	5.436*	7.100

* $p \leq 0.05$

Reviewed by: Melba S. Morrow, D.V.M. MSM 2/14/95
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, Ph.D. JES 2/21/95
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT SUPPLEMENT

STUDY TYPE: Rat Carcinogenicity

GUIDELINE #: 83-5

TOX. CHEM. #: 954 (129032)

MRID #: 432105-01, 02 and 03
(Original MRID # 421783-14)

TEST MATERIAL: S31183

SYNONYMS: Sumilarv

STUDY NUMBERS: 343-214

SPONSOR: Sumitomo Chemical Co.
Osaka, Japan

TESTING FACILITY: Hazleton
Vienna, Va.

TITLE OF REPORT: Response to EPA Review of Chronic Toxicity and Oncogenicity in Rats [and Mice]

AUTHORS: (response prepared by Wilkinson, Driver, Whitmyre and Dragula)

REPORT ISSUED: April 7, 1994

EXECUTIVE SUMMARY: Based on the information presented in the subject MRIDs, the chronic feeding/oncogenicity study in rats is acceptable and can be upgraded to core minimum. The sponsor has adequately responded to all of the deficiencies cited in the September 15, 1993 DER for this study. There was no evidence of increased tumor incidence in this study when S31183 (Sumilarv) was administered in the diet to Sprague Dawley rats at levels of 0, 120, 600 or 3000 ppm (mg/kg/day: 5.42, 27.31, and 138 in males and 7.04, 35.1 and 182.7 in females). The NOEL for systemic toxicity was 600 ppm and the LOEL was 3000 ppm based on a 16.9% depression in body weight gain in females when compared to controls for weeks 0 - 78.

This decrease in body weight gain in the first 78 weeks of the study is indicative of minimal toxicity and the MTD may have been slightly underestimated based on the fact that the effects (increased cholesterol and phospholipids, decreased mean red

cell, hematocrit and hemoglobin counts and increased liver to body weight ratio) observed in the 90 day study were not reproduced. Repeating the study at doses higher than 3000 ppm is not expected to provide additional information on the chronic toxicity or on the carcinogenic potential of the test material.

CLASSIFICATION: Minimum

DISCUSSION: The following comments have been provided by the registrant in response to the deficienies cited in the September 15, 1993 DER.

1. Rationale for dose selection.

The registrant has stated that the dose selection for the chronic/oncogenicity study was based on the results of a 90 day subchronic dietary study in rats. In this study, dietary doses of 0, 400, 2000, 5000 and 10,000 ppm were administered. At 2000 ppm, toxicity was demonstrated in males by an statistically significant increase in cholesterol and phospholipid levels and decreases in mean red blood cell count, hemoglobin and hematocrit levels. At 5000 ppm there was a statistically significant decrease in body weight (9.0%) and in body weight gain (19.7%) in females. Males also showed statistically significant decreases in these two values when compared to controls, although the percentage differences were not as high as those reported for females.

Based on the results of the 90 day study, a high dose of 3000 ppm was selected for the two year chronic/oncogenicity study. The rationale for dose selection is acceptable and is supported by reported decreases in body weight gain in high dose females during the first year of the study (20% decrease). (Body weight tables attached).

2. Adequacy of the number of animals (10/sex /group) for which organ weights were reported.

The registrant refers to the EPA/FIFRA Subdivision and Acceptance Criteria for 83-5 with regard to the number of animals that should have had their organs weighed in this type of study. Subdivision F Guidelines require that only 10 animals per sex per group be weighed. The acceptance criteria does not state that organ weights should be obtained for all animals on the study. The registrant also provides thoughts on the impact that more liver weights would have on the power of the test. Specifically, the registrant states that for the identification of a biologically relevant effect, a sample size of 10 animals should be sufficient. Finally, it is not possible to weigh additional livers retroactively.

HED is able to make a decision on the data that is provided. A table has been included to show the effects of the compound on

liver weights. Based on the data provided for liver weights, statistically significant increases were reported for high dose females at the interim sacrifice, only. Similar findings were not present at the terminal sacrifice. (See DER by L. Chitlik, dated 9/13/93).

3.and 4. Tabulated data (combined) for both the satellite and main study for specific endpoints and for gross and histopathology data are needed.

Combined endpoints for main and satellite studies are provided. Combined data sets for gross and histopathology are also included in the resubmission. These data do not indicate that there were any compound related gross or microscopic lesions reported in the study. Additionally, there were no compound related effects observed on urinalysis or on the presence of rare erythrocytes (See # 5).

5. The significance of the hematopoetic effects that were reported in the study, specifically, the increased levels of acanthocytes and echinocytes should be addressed.

The registrant stated that low levels of rare erythrocytes do not appear to have biological significance nor are they expected to interfere with the oxygen carrying capacity of the blood. The lack of a dose response or statistical significance suggests that the differences between the controls and the treated groups are due to chance.

Acanthocytes and echinocytes are present in all dose groups according to data submitted by the registrant. This data places a numerical value on symbols that were used in the original report to denote the presence of these rare erythrocytes. A significant increase in the presence of acanthocytes only, was reported in males at week 78. This appears to be a sporadic occurrence because, by week 104, there was no difference between the value reported for high dose males and that reported for controls. No statistically significant increases were reported for echinocytes in either sex at any of the dose levels. It is the opinion of this reviewer that these findings lack biological significance and are not indicative of a toxic response. (See attachment).

COMMENTS:

The study is upgraded to core- minimum. There is no need to repeat the chronic/oncogenicity study at higher doses because the dose selection is supported by findings in both the 90 day subchronic study and in the chronic (1 year) portion of this study.

In the 90 day study decreases in red cell count, hematocrit and

hemoglobin levels were reported for males receiving dietary levels of 2000 ppm and higher. There was also an increase in cholesterol and phospholipids in males receiving 2000 ppm and higher. In the first 78 weeks of the chronic/carcinogenicity study weight gain was depressed in females receiving 3000 ppm by 16.9% when compared to controls, indicating that minimal toxicity may have been present.

According to a document authored by Senior Scientist, Dr. Reto Engler (Discussion and Thoughts on the MTD, undated), a case can be made for not repeating the study. Although the MTD was incorrectly predicted in that the toxic effects that were reported at 90 days did not materialize, it appears as though the MTD was slightly underestimated and repeating the study at higher doses would not provide additional information on either the chronic toxicity or on the carcinogenic potential of the compound. Furthermore, a NOEL for chronic toxicity could be established at 600 ppm due to the observed effect (decrease) on body weight gain reported at 3000 ppm in females during the first year and a half on the study.

TABLE I
Mean Body Weight (g)

Dose (ppm)	0	120	600	3000
Males				
Week				
0	216.8	214.5	215.3	214.1
1	275.4	273.0	273.6	268.2*
4	400.4	394.0	400.2	380.9*
8	501.7	486.9	495.4	468.0*
12	562.1	546.6	556.4	529.3*
18	612.2	600.6	606.5	578.0*
26	637.5	626.3	630.2	599.9*
34	665.3	660.5	667.1	636.5*
42	684.4	682.2	686.7	655.6*
50	692.0	693.5	692.9	666.2*
62	711.5	699.7	698.3	662.9*
70	696.3	693.5	691.5	656.4*
78	692.8	691.1	686.3	654.4*
90	690.5	676.4	665.9	650.3
102	649.5	615.9	628.5	632.0

* $p \leq 0.05$

Table I (Cont.)

	Mean Body Weight (g)			
Dose (ppm)	**0**	**120**	**600**	**3000**
Females				
Week				
0	160.8	159.2	160.1	159.4
1	185.9	183.1	182.9	178.3*
4	244.1	238.5	239.6	228.9*
8	285.6	275.8*	278.0	262.5*
12	312.1	304.7	307.5	285.5*
18	335.8	327.2	332.0	303.2*
26	362.1	353.2	364.8	326.8*
34	388.1	379.2	387.6	347.6*
42	412.8	401.5	412.3	368.0*
50	438.0	426.7	434.0	390.2*
62	471.7	450.1	466.7	412.0*
70	464.8	452.2	467.2	424.3*
78	474.9	464.7	481.0	425.6*
90	495.4	480.3	463.6	418.8*
102	468.9	487.0	471.5	430.5

* $p \leq 0.05$
Data taken from Table RI in Volume 39.

Pyriproxyfen

RIN 4445-96 P.C. 129032

Page 21 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Melba S. Morrow, D.V.M. 2/10/95
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, Ph.D. 2/21/95
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Supplement to Mouse Oncogenicity Study

GUIDELINE #: 83-2

TOX. CHEM. #: 954 (129032)

MRID #: 432105-01 (vol. 38), 434132-01 and 02 (vols. 45 and 46)
(Original MRID # 421783-10)

TEST MATERIAL: S31183

SYNONYMS: Sumilarv

STUDY NUMBERS: HLA 343-215

SPONSOR: Sumitomo Chemical Co.
Osaka, Japan

TESTING FACILITY: Hazleton
Vienna, Virginia

TITLE OF REPORT: Response to EPA Review of Chronic Toxicity and/or Oncogenicity Studies of Sumilarv (S31183) in Rats and Mice

AUTHORS: Response to EPA deficiencies prepared by Wilkinson, Driver, Whitmyre and Dragula

REPORT ISSUED: April 7, 1994; Amendment to Final Report dated October 3, 1994 and Supplement dated October 11, 1994

EXECUTIVE SUMMARY:
Sumilarv, 95.3% (S-31183) was administered to male and female CD-1 mice at dietary levels of 0, 120, 600 and 3000 ppm (equivalent to 0, 16.8, 84.0 and 420 mg/kg in males and 0, 21.9, 109.5 and 547 mg/kg in females). Fifty animals/sex/dose level received the test material for 78 weeks; ten animals/sex/group were designated for interim sacrifice after 52 weeks on the study.

There was no increase in tumor incidence in either sex that could be associated with the administration of the test material. The NOEL for systemic effects was 600 ppm and the LOEL of 3000 ppm was based on an increased incidence of renal lesions in both sexes. In males, there was an increase in chronic progressive nephropathy, characterized by enlarged kidneys with tubular cysts and renal calcification and mineralization. In females, there was an increase in the incidence of mineralization of the renal tubules.

There was a reported increase in mortality. However, this appeared to be related to the presence of systemic amyloidosis that has a historically high background incidence in CD1 mice, but which may have been exacerbated by the administration of Sumilarv.

Based on the observed renal lesions, the doses used in this study were adequate to evoke a carcinogenic response.

CLASSIFICATION: Minimum. This study satisfies the minimal requirements for a mouse oncogenicity study as set forth in Subdivision F section 83-2.

DISCUSSION:

The following responses have been provided to address specific deficiencies identified by EPA in the original mouse oncogenicity study (MRID 421783-10).

1. Rationale for dose selection.

The rationale for the selection of dietary dose levels of 120, 600 or 3000 ppm was based on the results of a Subchronic toxicity study in mice. In this study, 10 mice/sex/dose level received dietary concentrations of 200, 1000, 5000 or 10000 ppm for 90 days. Survival was affected at 10000 ppm,with only 3/9 males and 1/10 females surviving. At 5000 ppm, 8/10 male mice survived. Kidney lesions were present in groups of animals receiving 5000 and 10000 ppm; microscopic examination revealed tubular nephrosis with dilatation of the renal pelvis. (See DER for Subchronic Toxicity in Mice, M.S. Morrow, signature dated 1/25/95). It was concluded that 5000 ppm would exceed the MTD under conditions of chronic administration and 3000 ppm was selected as the highest dietary level for the 78 week mouse oncogenicity study.

Toxicology Branch I agrees with the rationale for dose selection. In the 90 day mouse study the following conclusions were made with regard to effect levels and acceptability of the study:

"When technical Sumilarv was administered to male and female CD-1 mice at dietary levels of 0, 200, 1000, 5000 or 10000 ppm .... there was an increase in mortality in both sexes at the highest dose tested. In animals of both sexes that received the two highest doses, kidney lesions were present. Macroscopically, there was dilation of the renal pelvises, fluid filled renal pelvises, unequal kidney sizes, cysts and paleness. Microscopically, there was nephrosis with renal tubular dilatation and dilatation and mineralization of the renal pelvises....

".... The NOEL and LOEL for systemic toxicity was 1000 ppm and 5000 ppm, respectively, based on renal pathology, increases in liver weights, increases in liver:body weight ratios, decreases

in red blood cell parameters and decreases in body weight gain in males.

"... This study fulfills the requirements for a rodent subchronic toxicity study as specified in Guideline 82-1(a)."

2. Identification of the MTD and the No Effect Level for Sumilarv.

The registrant contends that one of the key observations in the study was the depression in survival rate in mid and high dose males and in high dose females. Statistics are provided to support the conclusion that the observed mortality was treatment-related. The primary cause of early death in the control and treated animals was systemic amyloidosis and the registrant believes that the dietary administration of Sumilarv accelerated the development of amyloidosis and increased the incidence and severity of this condition.

The registrant has also provided information on the incidence of renal lesions and has documented the effects of Sumilarv on the kidneys of high dose male and female mice. Based on information that has been provided in these submissions, the registrant indicates that an MTD has been achieved and that a NOEL has been established.

Tox Branch I has reassessed the information provided by the sponsor. It is apparent that the observed nephrotoxicity is related to the administration of the test material and that based on this, a NOEL of 600 ppm can be established. At 3000 ppm there was an increase in the incidence of chronic progressive nephropathy in males and an increase in the incidence and in the severity of chronic progressive nephropathy and mineralization of the tubules in females. (See Table I). These renal lesions were similar to those reported in the 90 day study in CD-1 mice at doses of 5000 and 10000 ppm. (Chronic progressive nephropathy is characterized by renal enlargement, tubular cysts, renal calcification and mineralization). Based on the renal pathology in both sexes, it appears that the study was conducted at adequate dose levels.

Amyloidosis, on the other hand, is not believed to be associated with the administration of the test material. The presence of Sumilarv could have exacerbated the systemic deposition of the amyloid and resulted in early deaths. This would be considered a secondary effect of the the test material and would not be considered in establishing a NOEL for the test material. As stated in an earlier review of this study and according to documentation provided by the registrant on the historical control incidence of amyloidosis in various organ systems, the background incidence can be as high as 100%.

Tables have been provided to address the severity of amyloidosis as it relates to the administration of the test material. If the total number of animals with severe and moderately severe renal amyloidosis are combined, there is no difference in severity between control and treated animals (except for the observations in females receiving 3000 ppm, in which all deaths were attributed to systemic amyloidosis). (See Table II). While amyloidosis is present in all groups at both the interim and terminal sacrifice, there is no significant, dose related increase in incidence at these intervals. Additionally, if the animals dying of systemic amyloidosis are disregarded, there is no difference in mortality in any of the dosed groups when compared to controls. (Refer to Table 4 of original DER prepared by S. Gross, dated 6/16/93).

When all of the findings of the mouse oncogenicity study have been weighed, the following conclusions can be made with regard to the acceptability of the study:

The study is acceptable and does not need to be repeated in another strain of mice. The NOEL for systemic toxicity was 600 ppm based on the observation of renal lesions at 3000 ppm. Based on the observed renal lesions, the study was conducted at doses high enough to determine the carcinogenicity of the test material. The compound was not associated with an increase in the incidence of neoplastic (or preneoplastic) lesions and with the exception of the number of animals surviving in the high dose male group, survivability in all other groups was adequate to assess the carcinogenicity of the test material.

The study satisfies minimum requirements for a mouse carcinogenicity study as per Subdivision F Guidelines, section 83-2.

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Table I
Incidence of Renal Lesions

	Dose (ppm)			
Males	0	120	600	3000
Interim sacr.				
Chr. progressive nephropathy (%)	4/9 (44)	2/10 (20)	1/9 (22)	4/9 (66)
Unscheduled deaths				
renal tubular mineralization	3/20 (15)	3/28 (11)	3/36 (8)	14/42 (33)*
Terminal sacrifice				
Chr. progressive nephropathy	10/28 (40)	10/22 (45)	4/14 (43)	8/9 (89)*
Females				
Interim sacr.				
Chr. progressive nephropathy	3/10 (30)	3/10 (30)	3/10 (30)	9/10 (90)**
Unscheduled deaths				
renal tubular mineralization	1/20 (5)	3/23 (14)	3/29 (10)	29/32 (90)**
Terminal sacrifice				
Chr. progressive nephropathy	7/30 (23)	10/27 (37)	6/22 (27)	10/18 (56)**
renal tubular mineralization	2/30 (7)	1/27 (4)	1/22 (5)	16/18 (89)**

* $p < 0.05$
** $p < 0.01$

Table constructed from information provided in Table 10 of volume 38 and Tables 6, 7 and 8 of volume 45 of the study report.

Table II
Amyloidosis: Incidence and Severity in Unscheduled Deaths

Unscheduled Death Rate

	Dose (ppm)			
	0	120	600	3000
Males	23/60	28/60	36/60	42/60
Females	20/60	23/60	29/60	32/60
# Males with Generalized Amyloid. (%)	19/23 (82)	22/28 (78)	28/36 (77)	35/42 (83)
# Females with Generalized Amyloid. (%)	14/20 (70)	18/23 (78)	18/29 (62)	32/32 (100)

Severity Assessment (% animals affected)

Males				
No findings	17	14	11	10
Minimal	0	0	0	0
Slight	0	7	3	5
Moderate	4	7	6	12
Mod Severe	74	64	61	40
Severe	4	7	19	33
[Mod Severe + Severe]	78	71	89	73
Females				
No findings	19	23	29	32
Minimal	16	9	21	0
Slight	0	4	10	0
Moderate	5	4	3	0
Mod Severe	11	48	21	13
Severe	58	30	45	84
[Mod Severe + Severe]	69	78	66	97

Table taken from Table 9 of Volume 38 of the study report.