9-27-93

Chronic Feeding/Oncogenicity Study 83-5

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DATA EVALUATION REPORT

STUDY TYPE: Rat Chronic Feeding and Oncogenicity- (83-5)

TOX. CHEM NO: 954

P.C.CODE.: 129032

MRID NO.: 421783-14

TEST MATERIAL: Methyl-2-(4-phenoxyphenoxy)ethoxy)pyridine

SYNONYMS: Nylar; S-31183; Sumilarv

STUDY NUMBER: HWA 343-214

SPONSOR: Sumitomo Chemical Company, Limited

TESTING FACILITY: Hazleton Washington, Inc.

TITLE OF REPORT: Sumilarv: Combined Chronic Toxicity and Oncogenicity Study in Rats with S-31183

AUTHOR(S): Merill R. Osheroff, Ph.D., D.A.B.T.

REPORT ISSUED: September 6, 1991

CONCLUSION:

Sumilarv was administered in the diet to Sprague-Dawley rats (Crl:CD BR) at 0, 120, 600, and 3000 ppm. On the basis of food consumption data (on a time weighted basis) dose levels were determined to be 5.42, 27.31, and 138 mg/kg/day in males and 7.04, 35.1, and 182.7 mg/kg/day for females. Food consumption and dose administration data were also determined for the satellite group and these data were consistent with those determined in the main study.

At this time, a NOEL for toxicological effects cannot be established. Additional assessment of this study will be required once the requested data are submitted. See section D (discussion of study data) and section E, (deficiencies). Note that trends in absolute and/or relative weights are apparent for both spleen (decreased at the interim sacrifice) and liver (increased at both the interim and final sacrifice). However, at terminal sacrifice, findings are not reported as statistically significant, but data are only based on ten animals per sex and no dose related liver

histopathological findings were observed. However, in the 90-day rat study (Study number 343-208), both statistically significant elevated liver weights and liver-to-body weight ratios as well as liver histopathology findings were noted at a dose level of 2000 ppm after only thirteen weeks of dosing.

Slight but statistically significant and dose related increases in alkaline phosphatase levels were noted in low dose males at weeks 52 and 78 but not at week 104. At 600 ppm, this finding was apparent at week 104, but no values were reported as statistically significant at this interval. The lack of statistical significance at this interval appears concomitantly with a large increase in standard deviations. It should be noted that elevated alkaline phosphatase levels were also observed at comparable dose levels in the one year dog study.

In addition, the investigators failed to present a dosing rationale based upon the 90-day or other range finding data. Based upon review of available data for this two year oncogenic study and the minimal level of toxicity observed in this rat study, and in consideration of the level of toxicity observed in the 90-day rat study at higher dose levels, it is unlikely that an MTD was selected for oncogenic assessment in this two year study.

Classification: Core-Supplementary Data

At this time, this study does not satisfy the guideline requirement for a chronic feeding and oncogenicity study (83-1/2) in rats. There are several significant reporting deficiencies relative to tabulation and presentation of data listed at the end of this review that need to be corrected by the registrant. As well, organ weight data are only provided for only ten animals per sex rather than for all animals of at least the high dose and controls and for target organs at lower dose levels. If this deficiency cannot be resolved, this study ~~will~~ may not be upgraded to fulfill the requirement for a chronic toxicity study.

Relative to oncogenic assessment, pathology data are not appropriately tabulated and the registrant will need to re-submit the data in an acceptable format combining appropriate data sets. In addition, no dosing rationale is presented but based upon the available 90-day rat study, an MTD was apparently not selected for testing in

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this two year study. Therefore, unless a stronger dose rationale can be presented by the registrant, it is unlikely that this study can be upgraded to fulfill the testing requirements for an oncogenic assessment in the rat.

Special Review Criteria (40 CFR 154.7) None

A. MATERIALS:

1. Test compound: S-31183 technical, Description: as a solid, grayish-white crystalline and as a liquid, described as pale yellow with a light viscous texture, Lot/Batch #:PYG 87074 received in two shipments, Purity: 95.3 % ai., Stability of compound: reported to be on file with the sponsor; data not provided, CAS #: Not provided

2. Vehicle and/or positive control: Mixed by serial dilution with Purina Certified Rodent chow #5002, Lot/Batch # Not available

3. Test animals: Rat

   Species: Sprague-Dawley

   Strain: Crl:CD BR

   Age: 29 days of age when received, April 20, 1988 but approximately 6 weeks of age at initiation of dosing.

   Weight ranges at initiation: the males of the main study weighed from 186.4 to 240.5 g and the females weighed from 136.2 to 182.1 grams. In the satellite study, the males weighed from 181.1 to 243.3 grams and the females weighed from 137.8 to 180.3 grams.

   Source: Charles River Laboratories, Inc., Kingston, New York

B. STUDY DESIGN:

1. Animal assignment

   Animals were assigned to test groups as shown in Table 1

by first eliminating the animals with extreme body weights (± 20% of the mean weight of each sex) and then by "selecting the random assignment which produced homogeneity of both the variance and the means by Bartlett's test and one-way ANOVA."

TABLE 1: STUDY DESIGN

Test Group	Dose in diet (ppm)	Main Study 24 months		Satellite Study*	
		males	females	males	females
1 Control	0	50	50	30	30
2 Low (LDT)	120	50	50	30	30
3 Mid (MDT)	600	50	50	30	30
4 High (HDT)	3000	50	50	30	30

* During weeks 13, 26, 52, 78, and 104, ten animals per sex (in order of increasing animal number) were used for clinical chemistry and hematology determinations. The authors also noted that serum chemistry samples were not collected at the Week 13 interval. After 52 weeks of treatment, 10 animals/sex/ satellite group were weighed, anesthetized, exsanguinated and necropsied. At term, all surviving Satellite animals were euthanized and discarded without necropsy.

2. Diet preparation and analysis

Test diets were prepared by serial dilution using the following procedure:

The test material was placed in a 50-60° C water bath to achieve a liquid state. A stock premix was then prepared and serial dilutions of the premix were then used to prepare the test diets. Diets were prepared weekly and no adjustment was made for purity. The technical grade test material (S-31183), lot number PYG 87074, (95.3% pure) was received from the sponsor apparently in two shipments (The September 8, 198, shipment was used for study weeks 0-34 and the April 4, 1988 shipment was used for study weeks 35-105). A ten gram reserve sample "of each shipment" was taken prior to dosing and at week 36 and stored in a freezer. Other samples were taken at weeks 28, 54, 80 and at termination and shipped to the sponsor. A sample of basal diet was taken prior to administration and also stored in the freezer. Samples of test diet prepared at 50 and 10,000 ppm were analyzed on days 0, 7, and 14. Stability analyses for days 7 and 14 were performed for samples stored at room temperature and under

refrigeration.

Two sets of 50 gram samples were taken from the top, middle, and bottom of each dose level. One set of samples was kept frozen while the other was analyzed for homogeneity. Homogeneity was determined prior to initiation of dosing and at week 54.

At four week intervals, two sets of 50 gram samples were taken from each dose level for routine concentration analyses. One set was analyzed and the other was stored in a freezer. All analyses were performed using a high performance liquid chromatography.

Results -

Homogeneity Analysis: Homogeneity data indicated that mixtures with feed were quite homogeneous both pretreatment and at week 54.

Stability Analysis: Analyses data demonstrated that the test material was stable after 14 days both with and without refrigeration at 50 and 10,000 ppm.

Concentration Analysis: Analyses at 4 week intervals throughout the study demonstrated that diets were consistently within 10 % of target at all dose levels.

3. Animals received food and water ad libitum.

4. Statistics - Statistical analyses were performed as described on page 26 of the test report and as diagrammed in Figure 1, page 27 of the test report. (See attachment 7).

5. A signed and dated quality assurance statement was present.

   A signed and dated GLP statement was present.

6. Dose Selection Rationale - None presented

C. METHODS AND RESULTS:

1. Observations:

   Animals were inspected for signs of toxicity and mortality two times per day. Detailed observations were performed once daily and a physical examination was performed once each week.

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Results - Toxicity - No dose related increases in clinical signs were observed in the dose groups versus the controls. There was an apparent increase in the incidence of chromodacryorrhea in the dose groups but the finding did not demonstrate a dose response.

Mortality - Cumulative survival data did not suggest a dose related decrease in survival (see Table 2)

Table 2

Main Study and Satellite Study Survival Rates at 102 Weeks (%)

	Males				Females			
Study (Dose in ppm)	Group 1 (0)	Group 2 (120)	Group 3 (600)	Group 4 3000	Group 1 (0)	Group 2 (120)	Group 3 (600)	Group 4 3000
Main	62	80	58	54	48	50	51	72
Satellite	55	55	60	60	45	45	55	45

2. Body weight

Animals were weighed prior to treatment, weekly for weeks 1-14, and then once every four weeks thereafter.

Results -(See Tables 3 and 4) There were some statistically significant reductions in body weights at various intervals in high dose males and females. However, further examination of body weight and body weight gain demonstrate no effect in males and a possible but equivocal effect in females. The findings of statistical significance were noted in group 4 males only at weeks 13, 26, and 50 and in group 4 females at weeks 13, 26, 50, and 78. On a percent basis, reductions in the high dose female body weights at term approached 7 percent (only a 32 grams difference in terminal body weights) as compared to concurrent controls. In males, the difference in mean terminal body weights in high dose animals versus controls was only 4 grams, which could hardly be considered a biologically relevant differenc

An assessment of body weight gain was performed althc

it appeared that the potential for an effect was small and only possible in high dose level females. The results of this assessment are reflected in the following table which was extracted from data presented in Table 5A of the test report (See attachment 1A). This assessment shows larger differences in females as compared to concurrent controls since this type of assessment tends to magnify small and sometimes insignificant body weight gain differences (when biological relevance is considered) when the data are examined on a <u>percent change</u> basis. The basis for determination of an MTD in this manner (on the basis of body weight gain alone without due consideration of how small the change actually is as compared to the body weight of the animals at various intervals during a study, and the biological relevance of such a small change in terms of overall body weight at term) appears inappropriate in this case. In addition, depending upon the time interval assessed, a few grams may not result in a large percentage change over one month period, but over another time frame where the controls tend to vary more or less, the same few grams of body weight may result in a much larger percent change in body weight gain. Therefore, care must be exercised in the application of such an assessment as it can easily be used to justify the existence of an MTD when none may exist.

During the first year of this study, females gained 18 to 28% less than controls. This range is supported by decreases of 18, 9, 9, and 23 gram reductions in body weight gain as measured based upon 0-4, 4-8, 8-13, and 13 to 50 week intervals respectively. However, from week 50 to 102, high dose females gained 257% more than female controls during the same time frame. In addition, all female dose groups gained more weight than controls during the second year of the study. As well, males in all dose groups often did better than control males on a body weight gain basis from week 13 of the study.

Note the following tables 3 and 4 derived from Table 5A of the test report. This table includes data from the Main Study. In addition, an assessment of the Satellite study demonstrated that during the second year of the study, mean terminal body weights in males were 633 grams versus 690 grams in controls or a difference of 9%. However, it is also noted that the terminal weights are based on only 9 to 12 animals per group. In addition, the satellite male control mean was 55 grams more than in controls of the main study, while the high dose mean weight was only two grams greater than that observed in the satellite study.

In females, mean terminal weights were 419 grams versus 480 grams in controls or a difference of 13 percent. See table 5B, Attachment 1B. These data appear more convincing than those from the main study suggesting that at least for the high dose females level, there might be an effect on mean body weight. However, the N in this case is only 9 and therefore this assessment could easily be invalid.

In conclusion, data are inadequate to support the contention that a MTD was selected for testing in this study. Data from the 90-day rat study (#343-208) demonstrated that after 13 weeks rats fed 5,000 ppm showed only a 8.4% (males) and a 9% (females) decrease in mean body weights as compared to controls. At 10.000 ppm these decreases were only 12.2 % in males and 11.7 % in females. It therefore appears that dose levels in this two year carcinogenicity study should have been significantly higher.

Table 3
Body Weight in Grams (Body Weight Gain/Loss) MALES
Main Study

Dose level	Start	4 Weeks	8 Weeks	13 Weeks	50 Weeks	102 Weeks
0 ppm	216	399 (183)	499 (100)	570 (71)	687 (117)	635 (-57)
120 ppm	214	395 (181) -2%	484 (89) -11	556 (72) +1.4%	691 (135) +15.3	621 (-70) -23
600 ppm	214	396 (182) -.6%	490 (94) -6%	563 (73) +3%	691 (128) +9%	632 (-59) -3.5%
3000 ppm	216	382 (166) -9%	469 (87) -13%	538 * (69) -3%	655 * (117) 0%	631 (-23) + 60%

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Table 4
Body Weight in Grams (Body Weight Gain/Loss) Females
Main Study

Dose Level	Start	4 Weeks	8 Weeks	13 Weeks	50 Weeks	102 Weeks
0 ppm	162	245 (83)	288 (43)	320 (32)	446 (126)	465 (19)
120 ppm	160	239 (79) - 5%	278 (39) -9%	309 (31) -.5%	429 (120) -5%	496 (67) +353%
600 ppm	160	237 (77) -8%	274 (37) -14%	306 (32) 0%	425 (119) -6%	460 (35) +46%
3000 ppm	159	224 (65) -22%	258 (34) -21%	281 * (23) -28%	384 * (103) -18%	433 (49) +257%

3. Food consumption and compound intake

Food consumption for each animal was determined weekly for weeks 1-14 and then once every four weeks thereafter. Mean test material consumption values were also calculated by the investigators. Water consumption was determined twice weekly at 3 and 4 day intervals to yield a weekly composite for weeks 1-14 and once every four weeks thereafter.

Results - Food consumption was generally not affected in the main or satellite studies. There were some marginal reductions in consumption of high dose females, but these reached statistical significance only at weeks 13, 26, and

50 and on a percent basis, reductions did not appear to be biologically relevant.

Compound consumption (time-weighted average) - Mean compound consumption was reported for the main study groups 2, 3, and 4 to be 5.42, 27.31, and 138.00 mg/kg/day for males and 7.04. 35.10, and 182.70 mg/kg/day for females, respectively. In the satellite groups 2, 3, and 4, the levels were 5.41, 27.23, and 138.74 mg/kg/day for the males and 6.96, 34.39, and 177.94 for the females, respectively.

Water consumption - was significantly reduced in all female test groups only at week 13. At other times, no consistent effect was apparent.

4. Ophthalmoscopic examination

Eyes were examined by an indirect ophthalmoscopic examination using 1% Mydriacyl as a mydriatic prior to treatment, at fifty-two weeks for those scheduled for sacrifice, and at week 104 for all animals.

Results - Examination of data presented in tables 9A and 9B of the test report did not demonstrate any findings that were associated with treatment.

5. Blood was collected for hematology and clinical analysis from surviving animals during weeks 13, 26, 52, 78, and 104 of treatment from ten animals/sex/satellite group (at 104 weeks some animals were used from the main study due to poor survival in the satellite group. Blood was collected from the vena cava for blood smears for evaluation of leukocyte differential counts and cell morphology gradings from animals sacrificed or in a moribund condition. Samples for hematology and serum chemistry were obtained via orbital sinus puncture under anesthesia. Serum chemistry samples were not collected at week 13. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements (Thromboplastin time) (Clotting time)		

| | (Prothrombin time)
* Required for subchronic and chronic studies

Results -Dose related decreased trends (not reported as statistically significant, N only = 10) in RBC (MI/UL), HGB (G/DL), and HCT (%) were noted in males. With the exception of Group 2 males at 104 weeks, males demonstrated this decreased trend at all dose levels at weeks 13, 52, 78, and 104. Decreased trends in HGB and HCT values were routinely noted in males at the mid (600 ppm) and high (3000) ppm dose levels over the entire course of the study (See attachment 1C). These findings were noted at statistically significant levels at 2000 ppm in males of the 90 day rat study and at 5000 ppm in females of this study.

Accompanying these findings, increased grades for echinocytes and acanthocytes were noted to occur in group 3 and 4 males and females at most intervals sampled. The report provides only individual data and average grading/incidence per group is not provided. (Note: This effect was identified by the study pathologist, Dr. Richard Alsaker, DVM, as occurring in Group 4 animals.) As this type of tabulation is quite time consuming, it was not performed by the Agency and will need to be provided by the registrant. Therefore, these findings and their biological significance, could not be completely assessed at this time. (See attachment 1, extracted from Appendix 9 C of the test report as an example of this finding at 26 weeks).

As defined by Dorland's, acanthocytes are distorted erythrocytes characterized by protoplasmic projections of varying sizes and shapes, irregularly spaced, which give the cell a "thorny"appearance; the finding has been associated with abetalipoproteinemia (also known as Bassen-Kornzweig Syndrome). The biological relevance of this increased incidence in rats is unclear at this time.

Echinosis (echinocytes) is an irregularity of an erythrocyte, giving it a spiny appearance; Crenation,

It therefore seems appropriate that these hematology data should receive a more complete assessment by the registrant with more meaningful tabulations provided to the Agency. This assessment will be necessary before the Agency can consider the position that this finding is not associated with

treatment with the test material.

No other hematology effects were apparent.

b. Clinical Chemistry

X	Electrolytes:
x	Calcium*
x	Chloride*
	Magnesium*
x	Phosphorous*
x	Potassium*
x	Sodium*
	Enzymes
x	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)
x	Creatinine phosphokinase*
	Lactic acid dehydrogenase (LAD)
x	Serum alanine aminotransferase (also SGPT)*
x	Serum aspartate aminotransferase (also SGOT)*
x	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase

X	Other:
x	Albumin*
x	Blood creatinine*
x	Blood urea nitrogen*
x	Cholesterol*
x	Globulins
x	Glucose*
x	Total bilirubin
x	Total serum Protein (TP)*
	Triglycerides
	Serum protein electrophores

* Required for subchronic and chronic studies

Results - Data in Table 11 of the test report indicated alkaline phosphatase was statistically but only marginally elevated in males of the mid (600 ppm) and high dose (3000 ppm) and at all dose levels at weeks 52 and 78. At 104 weeks, the mid and high dose levels were still elevated over control levels but without a dose response relationship and without statistical significance. Despite the fact that reported increases are marginal, they are still likely associated with the administration of the test material since they were noted as occuring in other studies (e.g.- the one year dog study) (See attachment 2, extracted from the test report). Females were apparently not affected.

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Total cholesterol was significantly elevated in males of the high dose level at weeks 26 and 52 and not statistically elevated at week 78. At week 104 the control mean level was elevated due to two animals with unusually high levels. The investigators reported that with exclusion of these two animals, no statistical differences with controls at 104 weeks were apparent. (See attachment 3 extracted from the test report)

Gamma glutamyltransferase levels were statistically elevated in females of all dose levels at 26 weeks, in the mid and high dose level females at 52 weeks and in high dose males at 104 weeks. At 78 weeks in males, the level was also apparently increased but not at significant levels. The biological significance of this finding is quesionable due to the low magnitude of the increase (See attachment 3A)

Other findings were considered incidental since there was no consistency or dose response apparent.

6. Urinalysis

Urine was collected from fasted animals at weeks 13, 26, 52, 78, and 104 of treatment from 10 animals sex/satellite group. Several animals from the main study were used at 104 weeks due to low survival for the satellite study. The CHECKED (X) parameters were examined.

X		X	
x	Appearance*	x	Glucose*
x	Volume*	x	Ketones*
x	Specific gravity*	x	Bilirubin*
x	pH	x	Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*	x	Urobilinogen

* Required for chronic studies

Results -Data presented in Appendix 11, page 2067 demonstrate increased protein levels in group 4 females at 26 weeks. The investigators also note a slight decrease in pH in Group 3 and 4 females. This change is considered marginal at best. Other changes were not apparent from individual data presented in Appendix 11. Mean values for urinalysis were not noted in the submitted report.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Following 52 weeks of treatment, 10 animals/sex/satellite group were sacrificed and necropsied. At termination, all surviving animals from the main study were sacrificed and necropsied, but surviving satellite animals were discarded without necropsy. The (XX) organs, in addition, were weighed.

Histopathological examination was performed on all animals in the control and the high dose groups that were scheduled sacrifices and all unscheduled deaths from the main study only. Gross lesions and all grossly visible tumors were examined from all animals on study as well as animals from the satellite groups sacrificed at week 53. In addition, lung, liver and kidney tissues were examined microscopically from all low and mid dose animals of the main and satellite groups sacrificed at week 53.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	xx	Heart*	x	Periph. nerve*(sciatic)
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen	x	Eyes (optic n.)*
x	Jejunum*	x	Thymus*	Glandular	
x	Ileum*	Urogenital		xx	Adrenal gland*
x	Cecum*	xx	Kidneys*+		Lacrimal gland
x	Colon*	x	Urinary blad.*	x	Mammary gland*
x	Rectum*	xx	Testes*+	x	Parathyroids*++
xx	Liver *+	x	Epididymides	xx	Thyroids*++
	Gall bladder*	x	Prostate	Other	
x	Pancreas*	x	Seminal vesic	x	Bone(sternum)*
Respiratory		xx	Ovaries*+	x	Skeletal muscle*
x	Trachea*	x	Uterus*	x	Skin*
x	Lung*	x	clitoral gland	x	All gross lesions and masses*
	Nose	x	Harderian gla.		
	Pharynx	x	preputial gland		
	Larynx				

* Required for subchronic and chronic studies.
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

Results

a. Gross pathology -

Examination of gross pathology data presented in Table 12 A (Unscheduled deaths, main study), Table 12 B (Unscheduled deaths, satellite study), Table 12 C (Interim sacrifice, satellite study), and Table 12 D (Terminal Sacrifice, main study) no dose or compound related gross pathological effects were noted. Unfortunately, the investigators included no tables which combined data from these associated data sets.

b. Organ Weights -

Organ weight and terminal body weight data were presented in the report in Tables 13 A (Interim sacrifice, satellite study) and Table 13 B (Terminal Sacrifice, main study). Organ weights for only ten animals per sex were provided at terminal sacrifice. Therefore, a definitive assessment of organ weight data based upon such a small and limited sample (only 10 animals per sex) was not considered appropriate at this time. The registrant should be requested to supply additional data.

At the interim sacrifice mean absolute and relative spleen weights were slightly reduced in a dose related manner in both males and females. At terminal sacrifice (N only = 10) decreases in spleen weights were not apparent in the treated groups as compared with controls. (See attachment 4 extracted from the test report)

Increased absolute liver weights were apparent at the high dose level in both males and females at the interim sacrifice. This was also apparent on a relative basis in both sexes but reached statistical significance in high dose females only. (See attachment 5)

At the terminal sacrifice, mean absolute liver effects appear to be increased in mid and high dose males and in high dose females. On a relative basis, non statistically significant increases are apparent in both mid and high dose males and females. Since N is only 10, it would be difficult to demonstrate statistical significance for this finding at these dose levels or to determine whether the effect extends to the low dose level. However, this effect is considered real due to the clear dose response relationship observed and since the liver is noted to be a major target organ in both the 90-day rat study and in the one year dog study.

The registrant should be required to submit organ weights for at

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least all listed organs for control and high dose animals at term. If any statistically significant findings are observed, the target organs must be weighed at the lower dose levels. (See attachment 6)

c. Microscopic pathology -

1) Non-neoplastic and Neoplastic

Examination of histopathology data presented in Table 15A (Unscheduled deaths, main study, Table 15B (Interim Sacrifice, satellite study) and Table 15C (Terminal Sacrifice, Main Study) did not reveal any dose related non-neoplastic or neoplastic findings at any dose levels tested. The study investigators did not make any attempt to combine data from terminal and unscheduled sacrifice animals.

As noted by the study pathologist, Dr. Samuel V. Machotka, there was a higher incidence of chronic progressive nephropathy in Group 4 females as compared to controls (13/29 vs 12/16), but this finding is not considered compound related but due to old age. In addition liver necrosis was observed in Group 4 males (Table 15A) of the unscheduled deaths as compared to controls (0/22 versus 8/23). However, as this finding was not observed at termination, it is considered unrelated to treatment.

D. DISCUSSION:

At this time the assessment presented in this DER should be considered only tentative. Both the presentation and analyses of data presented in the submitted study are considered inadequate at this time. More meaningful tabulation of the available data by the study investigators will assist the Agency in the review process. Note the list of reporting deficiencies listed below.

In addition, to the reporting deficiencies, it appears that a significant protocol deficiency exists relative to providing only organ weights for ten animals per sex at terminal sacrifice. Hopefully this is only a reporting error and the data can be made available to the Agency. This is considered a significant deficiency and may result in classification of the study as supplementary data.

Some issues/questions relative the effects of Sumilarv on the hematopoietic system persist. This study as well as the 90-day rat and one year dog study all indicate that this system is affected. In addition, the increased incidences of acanthocytes and echinocytes in this study and their biological significance relative to other sumilarv RBC toxicity remain unclear. Some basic clarification on these findings by the registrant may

resolve these questions. See deficiency 5 listed below.

In addition, it appears that dose levels utilized in this study may be inadequate for oncogenic assessment. No dosing rationale was presented by the investigators and the available 90-day rat study supports the contention that animals could easily have tolerated higher dose levels.

E. STUDY DEFICIENCIES

1. No dosing rationale was presented in this study. Examination of data presented in the 90-day rat study appears to support higher dose levels (MTD) for carcinogenic assessment than those utilized in this 2-year carcinogenicity study. Therefore, in the absence of an acceptable dosing rationale, the dose levels used in this study are considered inadequate for carcinogenic assessment.

2. At term, organ weights must be provided for at least all high dose and control animals. If significant effects are observed, weights from all animals for the affected organs must also be submitted. In this study, only weights from 10 animals per sex were provided and the additional data should be required from the registrant.

3. Tabulated data obtained by combining data from both the satellite and main study were typically not provided in the test report. Since denominators varied dramatically in different dose groups, and percentage data were not typically provided, analysis of study data were generally made unnecessarily complex. The registrant needs to supply combined data (from main and satellite studies) for all appropriate end points were data are available.

4. The gross and histopathology data presentation in the test report did not include a combination of appropriate data sets (e.g. - Moribund and terminal sacrifice data). This assessment must be provided by the testing facility.

5. Further assessment of the biological significance potential effects on the hematopoietic system, (e.g.- the increased levels of acanthocytes and echinocytes) should be provided.

Pyriproxyfen

RIN 4445-96 P.C. 129032

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