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

FEB 24 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Sumilarv 010308-RR. 21 day subchronic dermal study in rats. MRID No. 43004101. S453518. ID# 1021-RAEG. D196985. Tox. No. -New

TO: Richard Mountfort/Joe Tavano (PM 10)
Registration Division (H7505C)

FROM: Stanley B. Gross, PhD, DABT, CIH
Toxicologist/Hygienist
Toxicology Branch I
Health Effects Division (H7509C)

1/13/94

THRU: Joycelyn E. Stewart, PhD, Head
Section II, Toxicology Branch I
Health Effects Division (H7509C)

7/10/94

THRU: Karl P. Baetcke, PhD
Chief, Toxicology Branch I
Health Effects Division (H7509C)

KB 2/22/94

Registrant: Sumitomo Chemical Co., Osaka, Japan.

Action Requested: Review data on new chemical:

Submitted Study: Sumilarv -- 21 day dermal toxicity study in rats with S-31183.
AUTHOR(S): Micheal R. Moore, PhD, DABT
TESTING FACILITY: Hazleton Laboratories Washington, Vienna, VA.
REPORT ISSUED: HWA 343-244, Jan. 11, 1993.

SUMMARY:

Sprague-Dawley rats (5/sex/group) were treated dermally with sumilarv suspended in corn oil, applied 6 hours per day for 21 days. Sumilarv was applied at dose levels of 0 (corn oil only) and 100, 300 and 1000 mg/kg/day. There were no abnormal clinical signs, body weight or food intake effects, clinical chemistries, hematological abnormalities or any pathological changes due to the

administration of the sumilarv to the skin.

Conclusions: NOEL for dermal and systemic toxicity were greater than 1000 mg/kg, the highest dose tested.
Classification: Core guideline.
Special Review Criteria (40 CFR 154.7) There are not trigger considerations based on this study.

The DER for this study is attached.

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Reviewed by: Stanley B. Gross, Ph.D., DABT, CIH
Section 2, Toxicology Branch 1 (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, PhD
Section 2, Toxicology Branch 1, (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 21 Day Dermal Subchronic Study in Rats

TOX. CHEM NO: New Chemical

ACCESSION NUMBER: D196985 MRID NO.: 430041-01

TEST MATERIAL: Sumilarv Technical; PC #1029032

SYNONYMS: (2-[1-methyl-2-(4-phenoxyphenoxy) ethoxy] pyridine. S-31183.

STUDY NUMBER: GLN 82-2.

SPONSOR: Sumitomo Chemical Co., Osaka, Japan.

TESTING FACILITY: Hazelton Laboratories Washington, Vienna, VA.

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AUTHOR(S): Micheal R. Moore, PhD, DABT

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EXECUTIVE SUMMARY:

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Conclusions: The NOEL for dermal and systemic toxicity was greater than 1000 mg/kg, the highest dose tested.
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Special Review Criteria (40 CFR 154.7) There are no trigger considerations based on this study.

*A. MATERIALS:

*A.1. Test compound: Description: Solid white crystalline; Batch #007024; Purity - 97.2%; obtained from Sumitomo Chem.
Vehicle: Corn oil lot 86202 obtained from Dukes Pure Corn Oil, Richmond, VA; 100% assumed.

*A.2. Test animals: Species: Rats. Strain: Sprague-Dawley, Crl::CDBR from Charles River Labs., Kingston, NY. Age: 55 days at start of study. Weight: Males 204-263 gm; Females 170 to 208 gm.

Species Justification: Rats are typically used in these studies.

*B. STUDY DESIGN:

*B.1. ANIMAL ASSIGNMENTS. From 64 animals originally obtained from supplier, animals were randomly assigned to four experimental groups (5/sex/group) as shown in the following table:

GROUP ASSIGNMENTS

GROUP	Dose (mg/k/day)*	Male	Female
G1 Control	0	5	5
G2 Low (LDT)	100	5	5
G3 Mid (MDT)	300	5	5
G4 High (HDT)	1000**	5	5

* Applied to the skin in 2 mg/kg/day corn oil.
** Limit test dose.

Dose Selection. The dose selections are based on a 7 day range finding study involving the same dosing concentrations used in the 21 day study. The techniques used in the 7 day study were similar to the definitive study. The test material was administered to 3 rats/sex at dose levels of 100, 300 and a limit dose of 1000 mg/kg/day. A concurrent control of 3 rats/sex received daily application of corn oil. Parameters evaluated were mortality, clinical observations, dermal irritation scores, body weights, food consumption, hematology, organ weights and necropsy findings. No toxicity to the animals, gross organ pathology, body weight changes, food consumption changes, skin irritation or behavior were observed in the 7 day study. Therefore the same dose levels were chosen for the 21 day study.

*B.2. HUSBANDRY. The animals were acclimatized for 14 days prior to assignment to the study. They were housed two per cage under standard laboratory conditions of 72 ± 6°F and humidity, 50 ± 20%. Purina Certified Rodent Chow #5002 and water was made available ad libitum.

*B.3. STATISTICS Means and standard deviations were applied to many of the data using statistical significance based on 5% confidence limits. Other statistical procedures included a Leven's test for homogeneity using several transformation procedures; Dunnett's test for significance; ANOVA, etc.

*.B.4. QUALITY ASSURANCE. A quality assurance statement was included in the report and was signed by Lauryn E. Eisenhower, 1/11/93. Protocol deviations did not affect the technical integrity of the study.

*C. METHODS.

*C.1. PREPARATION OF THE TEST MATERIAL. The sumilarv was melted overnight at 50-60° and then mixed with corn oil to make solutions of 50, 100 and 150 mg/ml. These solutions were referred to as "first mix" solutions. Aliquots of the first mix solutions were further mixed in vials with corn oil to make up solution concentrations for skin applications to the animals at constant solution volumes of 2 ml/kg/day.

The homogeneity and stability analyses of the test material were carried out during the 7 day range-finding study using the lowest and highest dosing concentrations applied to the animals. Concentration verifications were made by analyzing the "first mix solutions" of all dose levels in duplicate using gas chromatography methods.

*C.2. ADMINISTRATION OF TEST MATERIAL. An area of skin 5 x 5 cm around the trunk of each animal was clipped using electric clippers one week prior and again one day prior to the application of the test substance. Additionally clipping was done as needed during the next 21 days. The sumilarv corn oil solution was applied to the skin daily in volumes of 2 ml/kg/day applied to the clipped skin area with a glass rod and the area then covered with gauze was held in place with sterile surgical tape (3M brand), wrapped around the shaved truck. At the end of daily 6 hour exposure period, the dressing was removed; the site washed with distilled water; and wiped with a facial tissue.

Collars. In order to minimize preening of the application site, each rat was fitted with a plastic collar (Laboratory Rodent Collar SAF-T Shield, Ejay International, Inc., Glendora, CA). The collar was applied to each animal 5 days prior to the start of the 21 day application period in order to acclimate the animals to the collars.

*C.3. OBSERVATIONS: The animals were inspected twice daily for signs of toxicity and mortality. Hands-on-physical examinations and scoring of each of the application areas were made daily, one hour prior to application of the test agent for that day. Body weights were measured prior to the start of the 21 day application period and weekly there after. Food consumption was measured weekly.

*C.4. CLINICAL CHEMISTRY AND HEMATOLOGY. Routine clinical chemistry and hematology were carried out at the end of the exposure period. Blood was obtained by orbital sinus puncture

using capillary tubes after the animals were anesthetized with an intramuscular injection of ketamine hydrochloride.

Hematology. The following hematological measurements (as checked) were carried out:

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*	X	Reticulocyte count
-	Blood clotting measurements (Thromboplastin time) (Clotting time) (Prothrombin time)		

* Required of chronic studies.

Clinical Chemistry. The following clinical chemistry determinations (as checked) were carried out:

	Electrolytes:		Other:
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
-	Magnesium*	x	Blood urea nitrogen*
x	Phosphorous*	x	Cholesterol*
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	Enzymes	x	Total Bilirubin*
-	Alkaline phosphatase	x	Total Protein*
-	Cholinesterase	x	Triglycerides
-	Creatinine phosphokinase*		
-	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		

* Required of chronic studies.

*C.7. NECROPSY. Prior to sacrifice, all animals were fasted overnight, then weighed on the day of scheduled necropsy, given an intraperitoneal injection of sodium pentobarbital, and exsanguinated. Necropsies included the examination of the external condition of the body and gross examination of all organs and cavities of the body.

The following organs were examined grossly:

ORGANS TAKEN AT NECROPSY.

Digestive system	Cardiovasc./Hemat.	Neurologic
Tongue	Aorta*	Brain*, W
Salivary glands*	Heart*	Periph. nerve*
Esophagus*	Bone marrow*	Spinal cord *

Stomach*	Lymph nodes*	Pituitary*
Duodenum*	Spleen	Eyes (optic n.)*
Jejunum*	Thymus*	Glandular
Ileum*	Urogenital	Adrenal gland* W
Cecum*	Kidneys*+ W	Lacrimal gland
Colon*	Urinary bladder*	Mammary gland*
Rectum*	Testes*+ W	Parathyroids*
Liver *+ W	Epididymides	Thyroids*
	Prostate	
Pancreas*	Seminal vesicle	Bone*
Respiratory	Ovaries*+ W	Skeletal muscle*.
Trachea*	Uterus*	Skin*
Lung*		All gross lesions
Nose		and masses*
Pharynx	Harderian glands	
Larynx		

* Required for chronic studies.
+ Organ weight required in chronic studies.

Organ Weights. Organs weights were obtained only for kidneys, livers and testes.

Histopathology. Selected tissues from control and high dose groups were preserved, stained with hematoxylin and eosin, and examined histologically. Selected tissues included: liver and kidneys and treated and untreated skin, skin from perimeter of treated sites and from perimeter of the treated site (two control females).

*D. RESULTS.

*D.1. Concentration Analyses. Stability and homogeneity was based on the analytical concentrations from the 7 day range-finding study. The first mix test solutions of sumilarv in oil (50 and 500 mg/ml) were analyzed by gas chromatography using duplicate sampling at the top middle and bottom of the dosing solutions. The results were within 97% of the target solutions for the three dosing sites. Duplicate sampling of these concentrations after 24 hours were within 4% of the target doses.

*D.2. Clinical Observations. There were no mortalities during the study. The only abnormalities were skin irritations observed on a limited number of animals. These were peripheral to the application sites and were assumed to be due to the irritation of the surgical tape applications.

Body Weights. Body weight gains in the treatment groups were comparable or in excess of the control animals over the 21 day period. This is seen in the body weight data in the table

below.

SELECTED BODY WEIGHT DATA

Week	Control	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
		(Body wt. M/F, gm)		
Week 1 (Beginning)	240/187	227/180	243/190	245/195
Week 4 (End)	338/237	339/237	326/245	356/255

Food Consumption was not adversely effected by the sumilarv treatment.

*D.3. Clinical Pathology Aspartate aminotransferase values for low dose group of males were decreased compared to controls. Mean cell volumes in mid dose group males were significantly decreased and mean cell hemoglobin values in the high dose females were significantly increased. None of these changes reflected biologically adverse changes or changes which were related to the dosing with sumilarv.

*D.4. Terminal Studies

Gross Findings. There were very few abnormal findings and the only findings relatable to the dermal treatment with sumilarv was due to irritation surrounding the application sites. Skin sores were observed at the perimeter of the shaved area in three Group 3 males, two females each of Groups 1 and 2, and one female in Group 3.

Organ Weights. Mean absolute organ weights and organ-to-body-weight ratios were similar between controls and sumilarv treated groups.

Histopathology. There were no adverse effects relative to the liver and kidney analyses. Histopathological assessments of the sumilarv treated areas were unremarkable. Two control females showed slight inflammation (localized hyperkeratosis in one rat and small shallow ulcerated area in the other) ~~were from~~ in the area of contact with the surgical tape used to secure the dressings covering the areas of topical exposure.

*D. DISCUSSION:

*D.1. Design Objectives. The study was generally well designed, executed and reported.

The histopathological assessment of the lung for the control and high dose groups was omitted, but because of the lack of pathological effects, this omission will be ignored.

8

*D.2. Lack of Adverse Effects. Sumilarv caused no toxicological effects during this 21 day dermal application study. Any findings of adverse effects were incidental or was due to the surgical tape irritation use to apply the chemical.

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