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

SEP 30 1986

005528 OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 10308-3. Pynamin Forte. Chronic/ Oncogenicity Feeding Study in Rats. Allethrin Data Call-In.
Tox. Chem. No. 25
Project No. 1617

TO: Arturo Castillo (PM #17)
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Record No. 170855

Action Requested and Background:

Sumitomo Chemical Company, Ltd. has submitted a chronic/oncogenicity study on Pynamin Forte in rats in response to a data call-in notice from the USEPA. The Toxicology Branch has been requested to review the submitted study.

Response:

The Toxicology Branch (TB) has determined that Pynamin Forte did not prove to be an oncogen under the conditions of the study. Chronic effects related to the administration of the chemical consisted mainly of decreases in body weight gain in males and females (HDT) and in females (mid-dose, LOEL), increases in liver weights in males and females (HDT) and in males (mid-dose, LOEL), the presence of histiocyte phagocyting crystals in the livers of females (mid- and high doses) and possible increases in kidney weights in males at the high dose level.

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): male and female F344/DuCrj rats
Age: 4 weeks (5 weeks at start of test)
Weight(s): 70-84 g (females), 72-103 g (males) - main study
70-85 g (females), 84-105 g (males) - satellite groups
Source(s): Charles River Japan, Inc.
Housing: 5 animals/cage

3. Procedure:

a. Dietary Preparation (if applicable): Test compound mixed in pulverized diet (CE-2, Clea Japan Inc.), weight/weight for 30 minutes.

Frequency of preparation: Intervals < 4 weeks
Storage conditions: Not given
Stability Analyses: Maximal preparing interval set at 4 wks on basis of data obtained from sponsor (data not given)
Homogeneity Analyses: Samples collected from top, middle and bottom layers of diet at each concentration and analyzed (once)
Concentration Analyses: Pynamin content analyzed 1x/month for each level

b. Basis For Selection of Dosage Levels: A 5-week subacute study was conducted with dietary levels of 10000, 5000, 2500, 1250, 625 and 0 ppm. The NOEL was 625 ppm and the LOEL was 1250 ppm based upon body weight gain, liver weights, swelling of liver cells and narrowing tendency of sinusoids. The highest dose level was set at 2000 ppm for the chronic study.

c. Animal Assignment and Dose Levels:

Test Group	Dose Administered (ppm)	Main Study 123 weeks		Interim Sac. 26 weeks		Interim Sac. 52 weeks		Interim Sac. 78 weeks	
		male	female	male	female	male	female	male	female
Contr.	0	50	50	10	10	10	10	10	10
1	125	50	50	10	10	10	10	10	10
2	500	50	50	10	10	10	10	10	10
3	2000	50	50	10	10	10	10	10	10

d. Procedures for Studies Other Than Feeding and/or Additions, Changes in Feeding Study: N/A

e. Clinical Observations and Mortality: All animals examined daily for mortality and general behavior. Palpations at time of body weight recordings.

f. Body Weight Determinations: Every week during first 14 weeks, biweekly thereafter.

g. Food and/or Water Consumption: Two-day food consumption/cage weekly for first 14 weeks, biweekly thereafter. Food efficiencies calculated for all groups except satellite groups. Water intake measured at same intervals as food consumption.

h. Ophthalmological Examinations (if applicable): Not done

i. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals): Ten males and ten females/dose group killed at 26, 52 and 78 weeks and all survivors at 123 weeks. Animals fasted from day prior to sacrifice. Blood taken from abdominal aorta after laparotomy under ether anesthesia.

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*	x	Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*	x	Mean corpustular HGB conc.(MCHC)
x	Leukocyte count (WBC)*	x	Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*	x	Prothrombin times
x	Platelet count*		
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

Collection times and animals same as those for hematology.

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorus*	x	Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	Enzymes:		Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
	Creatinine phosphokinase*	x	Uric acid
	Lactic acid dehydrogenase	x	A/G ratio
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines.

X	Digestive system
x	Tongue
xx	Salivary glands*
x	Esophagus*
x	Stomach*
x	Duodenum*
x	Jejunum*
x	Ileum*
x	Cecum*
x	Colon*
x	Rectum*
xx	Liver*
	Gall bladder*
x	Pancreas*
	Respiratory
x	Trachea*
xx	Lung*
x	Nasal cavity
x	Larynx

X	Cardiovasc./Hemat.
x	Aorta*
xx	Heart*
x	Bone marrow*
x	Lymph nodes*
xx	Spleen*
xx	Thymus*
	Urogenital
xx	Kidneys*
x	Urinary bladder*
xx	Testes*
	Epididymides
x	Prostate
x	Seminal vesicle
xx	Ovaries
x	Uterus*
x	Vagina

X	Neurologic
xx	Brain*
x	Periph. nerve*
x	Spinal cord (3 levels)*
xx	Pituitary*
	Eyes (optic n.)*
	Glandular
xx	Adrenals*
x	Lacrimal gland
x	Mammary gland*
x	Parathyroids*
xx	Thyroids*
	Other
x	Bone*
x	Skeletal muscle*
x	Skin and subcutaneous tissue
x	All gross lesions and masses
x	Ear + Zymbal's gland
x	Eyeballs
x	Harder's gland

1. Statistical Analyses: Significance of differences between control and treated groups were determined by Student's t test for means and by Fisher's exact test for frequency. Differences considered significant at levels of 1% ($p<0.01$) and 5% ($p<0.05$).

B. RESULTS:

1. Dietary Preparation: Homogeneity - The analysis revealed that the amount of Pynamin Forte in the feed sample ranged from 89-100% of the expected value at the 125 ppm level, from 86-96% of the expected value at the 500 ppm level and from 87-97% of the expected value at the 2000 ppm level. Concentration Analyses - The content of Pynamin Forte was consistently lower than the desired values. For the lowest dose level, the mean amount of the test chemical was 87.6% of the expected value, for the mid-dose level it was 86.3% of the expected value and for the high dose it was 88% of the expected value. These values, however, were not so low that it was considered necessary to alter the conclusions reached concerning the NOEL's and LOEL's for the chemical. The mean intake of the test compound in mg/kg/day

6. Hematology: Statistically significant observations for specific hematological parameters were scattered throughout the treated groups at all of the scheduled sacrifice times. None of these findings were biologically significant, however, because there were no dose-related trends and there was no consistency in the observations within successive scheduled sacrifices.

7. Clinical Chemistry: In males, statistically significant decreases in GOT, GPT and alkaline phosphatase were observed at the highest dose level at 26 and 52 weeks (decreased GPT was also noted at the mid-dose level at 26 weeks). GPT was significantly increased at the terminal sacrifice in high dose males. There were other statistically significant observations as well, however, none of these appear to be biologically significant because there were no dose-related trends and because there was no consistency in the observations within successive scheduled sacrifices.

8. Urinalysis: At 26 weeks, males in all groups had a slight increase in pH, and in protein and crystalline components of urinary sediments. At 52 weeks, males in the mid- and high dose levels again exhibited a slight increase in protein. At week 78, findings in treated and control animals were similar. At week 123 (termination), all treated male groups and the 500 ppm group of the females exhibited greater urinary specific gravity. Other findings in all the treated groups at all the scheduled sacrifice times appeared to be similar to controls.

9. Gross Pathology: In general, gross observations were similar in all treated groups when compared to controls. This was true for animals examined at scheduled sacrifices as well as for those necropsied which either died or were sacrificed in extremis during the course of the study. Sporadic findings in the older animals included swelling of various organs and tissues, granular surfaced livers and kidneys, discoloration of various organs, atrophy of the testes, cyst formation of the ovaries, tumors on the skin and subcutaneous tissues, alopecia and turbidity in the eyes.

10. Organ Weights: The liver was the one organ which consistently had a higher absolute and relative weight in treated animals, both male and female when compared to controls. The following tables summarize the mean absolute and relative liver weight data for all the sacrifice times, including those animals which died or were sacrificed in extremis and whose organs were not severely autolyzed.

The significant increase in liver weights at the lowest dose level in males was not supported by any other biological parameters, was not different from historical control values in the same strain of rat from the same laboratory, and therefore was not considered to be biologically significant. Thus, the data indicates that there were significant increases in liver weights in males at the mid and high dose levels and in females at the high dose level. The kidney in the high dose male animals was the only other organ weight which may have significantly increased over control animals. At 78 weeks the mean absolute kidney weights were significantly increased in the high dose males ($p=0.01$), and at 52, 78 and 123 weeks (terminal sacrifice) the mean relative kidney weights were also significantly increased in high dose males over the controls ($p=0.01$, 0.01 and 0.05, respectively). Changes in weights of other organs were not consistent and thus were not biologically significant.

11. Histopathology:

a. Nonneoplastic lesions: The presence of histiocyte infiltration in association with separation of crystals in the livers of females of the 2000 ppm and 500 ppm groups was consistently observed at all sacrifice times (see the following table). This effect was also observed in 2 males which died during the study (2000 ppm group).

Histiocyte Phagocyting Crystals in the Liver

Time of Sacrifice	Females				Males			
	0ppm	125ppm	500ppm	2000ppm	0ppm	125ppm	500ppm	2000ppm
26 Weeks	0/10[a]	0/10	2/10	5/10	0/10	0/10	0/10	0/10
52 Weeks	0/10	0/10	7/10	10/10	0/10	0/10	0/10	0/10
78 Weeks	0/10	0/10	10/10	10/10	0/10	0/10	0/10	0/10
Term. - 123 Weeks	0/23	0/23	14/28*	31/35*	0/23	0/19	0/13	0/24
Animals which died during study	0/27	0/27	14/22*	14/15*	0/27	0/31	0/37	2/26

a Number of Observations per Number Examined. *Significant ($p<0.01$)

No other nonneoplastic lesions were considered to be attributable to the test material. The following table summarizes the incidences of nonneoplastic lesions for selected tissues.

Summary of Nonneoplastic Lesions from Selected Rat Tissues
Pynamin Forte Rat Chronic Feeding Study (Continued)

Organ and Findings	Female				Male			
	0ppm	125ppm	500ppm	2000ppm	0ppm	125ppm	500ppm	2000ppm
Pancreas	(50)	(50)	(50)	(49)	(50)	(49)	(50)	(50)
Normal	31	25	40	34	27	24	26	26
Atrophy of acinar cells	12	17	8	12	12	15	15	18
Islet-cell hyperplasia	0	0	1	0	2	4	3	1
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Normal	20	12	12	1	5	4	1	3
Lymphocytic accumulations	3	0	4	8	3	4	1	0
Fatty metamorphosis	5	14	7	9	3	8	8	7
Granuloma	4	1	10	4	0	1	0	0
Necrosis	2	1	4	1	3	8	2	4
Histiocytes phagocyting crystals	0	0	28**	45**	0	0	0	2
Bile duct proliferation	2	8	8	7	32	35	43	36
Kidney	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Normal	5	3	7	2	0	5	6	3
Calcification	38	36	34	45	1	0	0	0
Chronic nephropathy	8	8	13	17	40	36	33	40
Proteinaceous cast	11	11	6	8	10	7	10	4
Testis					(50)	(50)	(50)	(50)
Normal					0	1	0	0
Atrophy					2	4	11	1
Interstitial cell hyperplasia					2	0	0	0
Prostate					(49)	(46)	(47)	(48)
Atrophy					48	38	44	43
Inflammation					4	14	8	12
Epididymis					(49)	(47)	(50)	(50)
Atrophy					48	45	48	48
Seminal vesicle					(50)	(48)	(47)	(49)
Atrophy					44	42	44	41

**Statistically significant over controls $p<0.01$

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