CASWELL FILE

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DATA EVALUATION REPORT

Study Type: 82-1 - 6 Month Rat Feeding Study
TOX Chem No.: 844
Accession No.: N/A
MRID No.: 421464-03

Test Material: Neopynamin forte tech.

Synonym: Neopynamin

Study Number: IT-00-0139

Sponsor: Sumitomo Chemical Company, Ltd.

Testing Facility: Laboratory of Biochem. and Tox., Hyogo, Japan

Title of Report: Six-Month Subchronic Toxicity Study of Neopynamin Forte in Rats

Author: S. Hosokawa, et al.

Report Issued: September 28, 1981

Conclusions: Male and female Sprague-Dawley rats were fed neopynamin forte in the diet for a period of 3 or 6 months at the following dose levels: 0, 100, 300, 1000, or 3000 ppm.

The NOEL is 100 ppm, and the LEL is 300 ppm. The effects were increased cholesterol in both sexes at 3 and 6 months, increased absolute relative liver weights in males at 6 months and increased relative liver weights in males at 6 months. Microscopic examination revealed a decrease in the grade of fatty change and cytoplasmic vacuolation of the liver. These were considered to be adaptive changes, which may also be true of the other effects noted above.

Classification: Core-Supplementary

Individual animal data were not provided.

Special Review Criteria (40 CFR 154.7)

Review:

Six Month Subchronic Toxicity Study of Neo-Pynamin-Forte in Rats (Sumitomo Lab I.D. # IT-00-0139; September 28, 1981)

Quality Assurance statement was signed by T. Kadota on September 24, 1981.

Test Material - Neopynamin Forte (Lot No. 7911-02); purity 95.6%; yellowish brown color.

Animals - Four-week old Sprague-Dawley rats, purchased from Charles River Japan, Inc. were used in the study. Animals were quarantined for 1 week and acclimatized, housed four per cage. Animals were fed fresh Clea diet, Clea Japan Company, and tap water ad libitum. Diet was prepared fresh once every 4 weeks and kept refrigerated. The concentration of the compound in the diet was checked before use. Stability of the compound in the diet was checked after 6 weeks and the concentrations were found to be 93-94% of the initial measurement. Stability was also checked after storage for 2 weeks at room temperature and the concentrations were found to be 90-97% of the initial measurements.

Methods - Randomized groups of 32 male and 32 female young Sprague-Dawley rats were fed diets containing 0, (corn oil) 100, 300, 1000, and 3000 ppm of test material. The groups consisted of a main group of 20/sex/dose and a satellite group of 12/sex/dose. The main group received diets for 6 months and the satellite group received diet for 3 months. Clinical observations for morbid and dead rats was conducted twice a day. Animals were palpated and weighed once a week. Food and water consumption per cage was measured for 3 continuous days per week. In the final week of study, urinalysis was performed on each animal. Parameters measured were pH, occult blood, ketones, glucose, bilirubin (3-month period only), and protein.

All animals were subject to an ophthalmological examination on the day before terminal sacrifice.

At the termination of feeding, all survivors were fasted for 16 hours and sacrificed. Blood was collected for hematology and clinical chemistry determination.

Hematology - RBC, total WBC, platelets, Hg, Ht, MCV, and differential WBC were measured.

Clinical Chemistry - Albumin, SAP, total bilirubin, BUN, serum ChE, cholesterol, creatine, glucose, SGOT, SGPT, leucine aminopeptidase, LDH, total protein, A/G ratio Na, K, Ca and albumin/globulin ratio were measured.

2

Necropsy and Organ Weights - All sacrificed animals were necropsied and the weight of brain, lungs, heart, spleen, kidneys, liver, testes or ovaries, pituitary, thyroid, and adrenals were taken. Animals that died moribund did not have organ weights.

Histopathology - The following organs and tissues were examined microscopically: brain, lungs, heart, spleen, kidneys, liver, testes or ovaries, pituitary, thyroid, adrenals, parathyroid, bladder, gross abnormal lesions, eyes*, spinal cord*, trachea*, bone marrow*, femoral bone*, mesenteric lymph node*, thymus*, esophagus*, stomach*, small intestine*, large intestine*, salivary gland*, pancreas*, prostate*, uterus*, femoral muscles*, tongue**, preputial gland**, seminal vesicles**, epididymis**, sciatic nerves**, mandibular lymph node**, and skin**.

*Organs examined only in the control and the highest dose of satellite groups.
**Organs examined only in the main groups.

Statistics - The t-test was used for body weight, food and water consumption, hematological and clinical chemistry determinations, and organ weights. Urinalysis was analyzed by U-test. Pathology results were analyzed by Chi-Square or U-test. The $p < 0.05$ was considered significant.

Results:

1. Clinical Findings and Mortality - No raw data for clinical findings and mortality were presented. However, the report states that there were no compound-related clinical signs. One female rat of the high-dose group died in week 23 due to malocclusion of incisors resulting in an inability to consume food. The report also stated that "sparse hair of gena, swelling of auricle, and general rough hair coat were occasionally observed in all treated groups from around the 7th week."

2. Body Weight - Body weight and body weight gain were statistically significantly decreased in both sexes of the high-dose. However, at no time were the mean body weights of either high dose groups less than 90% of the control values. Decreased body weight gain was 6.7 and 8.1 percent for high-dose males at weeks 13, and 26 when compared to controls. In females, decreased body weight gain was 6.6 and 3.8 percent for high dose females in weeks 13 and 26 when compared to controls. Since none of these values were less than 90% of the control values at any time point, the decreases in body weight and body

weight gains are not considered to be biologically significant.

3. Food Consumption and Water Intake - There were no consistent differences between control and treated groups of both sexes in food consumption and water intake. As presented in Table 6 in the report, the following average amounts of food and compounds ingested are shown below:

Dietary Level ppm	Food Consumption g (kg) day		Compound mg/kg/day	
	male	female	male	female
0	56.4	72.2	--	--
100	58.3	70.8	5.83	7.08
300	56.9	71.4	17.1	21.4
1000	57.9	71.4	57.9	71.4
3000	59.4	71.2	178	214

4. Ophthalmological Examination - No raw data were presented. The report states that at the 3-month examination, one 1000 ppm female had intra retinal hemorrhage and one 1000 ppm female had indistinct eye ground vessels. These findings are not considered compound-related.

5. Urinalysis - Bilirubin was increased in both sexes of all treated groups in comparison to controls, but when the diazo method of measurement was replaced by the method of Harrison, no compound-related findings were observed at 3 months. Bilirubin was not measured at 6 months. Urinary protein tended to increase in both sexes at 3 and 6 months at 1000 and 3000 ppm, but the changes were not statistically significant.

6. Hematology - There were no consistent, dose-related significant effects in either sex at 3 or 6 months.

7. Clinical Chemistry - Dose-related, statistically significant increases in cholesterol were seen in both sexes at 3 and 6 months at 1000 and 3000 ppm. Calcium levels were significantly increased in males at 3 and 6 months at 300, 1000, and 3000 ppm. Glucose was significantly increased at 6 months in all treated male groups. It is unlikely that the increases in glucose are toxicologically significant, because they were not seen at 3 months. It is also unlikely that the increases in calcium values are toxicologically

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significant because the differences are within 10% of control values at all dose levels.

8. Organ Weights - At 3 months, absolute liver weight was significantly increased in males at 3000 ppm. At 6 months, absolute liver weight was significantly increased in males at 300, 1000, and 3000 ppm and in females at 1000 and 3000 ppm. With respect to relative liver weight, at 3 months, there were increased relative liver weights at 1000 and 3000 ppm in males and females. At 6 months, relative liver weight was increased at 100, 300, 1000, and 3000 ppm in males and 1000 and 3000 ppm in females. The percent increases in relative weight in males was 6.9, 9.8, 23.5, and 32.4 percent for the 100, 300, 1000, and 3000 ppm groups, respectively.

   Additionally, relative kidney weight was significantly increased males at 1000 and 3000 ppm and females at 3000 ppm. Also, relative weights of heart and testes in high-dose males and spleen in high-dose females were significantly increased.

   The 6.9 percent increase in relative liver weight of 100 ppm male rats at 6 months is not considered toxicologically significant.

9. Necropsy Observations - There were no unusual necropsy results at the 3-month sacrifice. At 6 months, swelling and luster surface of the liver was observed 1/20, 0/20, 0/20, 2/20, and 12/20 males and 2/20 high-dose females.

   The 12/20 liver necropsy findings at 3000 ppm are considered compound-related.

10. Histopathology - In the liver of males in the 1000 and 3000 and females of 3000 ppm groups for the 3 and 6 months sacrifices, there was a significant decrease in the grade of fatty change and cytoplasmic vacuolation. Additionally, for 3 and 6 month groups, there was an increased incidence in the kidney of eosinophilic body in tubular epithelial cells for males at 1000 and 3000 ppm. The changes observed in the livers are considered as adaptive changes since no cytotoxicity to parenchymal cells was observed.

Discussion: This study is graded core-supplementary because there were no individual animal data. The effects seen mostly involved the liver and were probably adaptive changes. The NOEL is 100 ppm and the LEL is 300 ppm based upon increased cholesterol levels in both sexes at 3 and 6

months and increased absolute and relative liver weights in males at 6 months. In addition, microscopic examination revealed a decrease in the grade of fatty change and cytoplasmic vacuolation of the liver in both sexes.

6