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Section I, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

Study Type: 82-1; Subchronic Feeding - Rat

TOX Chem. No.: 844

Accession No.: N/A

MRID No.: 421464-02

Test Material: Neopynamin forte tech.

Synonym: Neopynamin

Study Number: IT-10-0140

Sponsor: Sumitomo Chemical Company, Ltd.

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

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

Author: S. Hosokawa, et al.

Report Issued: December 21, 1981

Conclusions:

The NOEL is 200 ppm (HDT) (males only). Doses were 0, 25, 50, 100, and 200 ppm for 3 and 6 months in male Sprague-Dawley rats. Criteria evaluated were clinical signs, body weight, food and water consumption, ophthalmology, urinalysis, hematology, clinical chemistries, necropsy, organ weights, and histopathology. No treatment-related effects were observed.

Classification: Core-Supplementary

Individual animal data were not provided, only one sex was tested and incomplete microscopic examinations were conducted.

Special Review Criteria (40 CFR 154.7): N/A

Review:

Additional Six Month Subchronic Toxicity Study of Neo-Pynamin - Forte in Male Rats (Sumitomo Project No. # IT-10-0140; December 21, 1981)

A Quality Assurance Statement was not provided.

Test Material - Neopynamin Forte; yellowish brown viscous liquid; Lot No. 7911-02; purity 95.6%;

Animals - Four-week old Sprague-Dawley male rats, obtained from Charles River, Japan, were acclimated for 1 week. Randomized groups of 12 rats/dose for 13 weeks (satellite group) and 21 rats/dose for 6 months were fed diets containing 0 (without corn oil), 25, 50, 100, and 200 ppm of test material. The rats were housed 3 per cage and offered respective diets, prepared fresh once every 4 weeks and kept refrigerated, and tap water ad libitum. The concentration of the compound in the diet was checked before use.

Methods - Animals were observed twice daily for toxic signs, moribundity and deaths. Body weight was measured once a week and food and water consumption was done for 3 consecutive days every week. Urinalysis was tested semi-quantitatively in the final week. Ophthalmoscopic examinations were performed on all rats in the final week. After fasting for 16 hours, all surviving animals at 3 and 6 months were sacrificed by abdominal aorta blood sampling. Hematology and clinical chemistry determinations were performed.

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

Clinical Chemistry - Albumin, SAP, bilirubin, BUN, serum ChE, cholesterol, creatine, glucose, SGOT, SGPT, leucine aminopeptidase, LDH, total protein, creatinine phosphokinase, triglyceride, phospholipid, Na, K, Ca, and A/G ratio.

Necropsy - Necropsy was performed on all rats and the following organ weights were taken: brain, lungs, heart, spleen, kidneys, liver, testes, pituitary, thyroids, and adrenals. Following fixation, histopathological examination was carried out on brain, lungs, heart, liver, kidneys, spleen, testes, pituitary, thyroid, adrenal, and all gross lesions.

Statistics - Body weight, food and water consumption, hematology, clinical chemistry, and organ weights were analyzed by t-test and urinalysis were analyzed by U-test. Gross and microscopic results were analyzed by Chi-Square (with Yates Correction) and, if necessary, by Fisher's Exact Test. The level of significance was $p < 0.05 < 0.01$.

2

Results:

1. Dietary Analysis: Concentration analysis of nine dietary preparations had mean values of < 1, 23.7, 48.0, 94.0, and 186 ppm for the various groups. Diets were stable for 2 weeks at room temperature and 6 weeks at 4 °C.

2. Clinical Signs - No raw data were presented but the report states that no deaths or clinical signs related to treatment were observed.

3. Body Weight - There were no significant differences between control and treated male rats over the 6 month period. Body weight gain at 13 weeks for satellite groups was 372, 391, 384, 384, and 382 grams for 0, 25, 50, 100, and 200 ppm groups, respectively.

   For the main groups, body weight gain at 26 weeks was 483, 474, 453, 448, and 438 grams for the 0, 25, 50, 100, and 200 ppm groups, respectively.

4. Food Consumption and Water Intake - There were no consistently significant differences between control and treated groups in food consumption measured or g/kg/body weight/day for 6 months.

5. Ophthalmology - Although no raw data were presented, the report states that no compound-related effects were observed.

6. Compound Intake - Compound intake averaged 1.31, 2.64, 5.29, and 10.75 mg/kg/day for the 25, 50, 100, and 200 ppm groups, respectively.

7. Urinalysis - No compound-related effects in main groups of treated rats in comparison to controls.

8. Hematology - No dose-related significant findings at 13 weeks. Although at 50 ppm there were decreased RBC, Ht, and Hg and increased WBC, the results were not dose-related. At 6 months, WBC was significantly increased at 200 ppm, although differential WBC did not show any significant intergroup differences. Since increased WBC was not observed in previous studies up to 3000 ppm, the results of this study are not considered compound-related.

9. Clinical Chemistry - In the 3-month assay, triglyceride was decreased in a dose-related manner and was significantly decreased at 200 ppm. Phospholipid was decreased at 100 and 200 ppm, significantly. Other

changes were not dose-related. In the 6-month assay, triglycerides and phospholipid were comparable between control and treated rats which is in contrast to the 3-month results.

10. Organ Weights - At 3 months, there were no dose-related significant changes in organ weights between control and treated rats. At 6 months, at 200 ppm, absolute testes weight was significantly decreased and absolute thyroid weight was significantly decreased at 100 and 200 ppm. At 3 months, relative thyroid weight was significantly decreased at 200 ppm.

    Absolute and relative liver weight at 3 and 6 months were comparable between control and treated rats.

    At 6 months, relative weights of lungs at 50, 100, and 200 ppm were increased, relative weight of heart was increased at 100 and 200 ppm, relative weight of testes was decreased at 200 ppm, and relative weight of thyroid was decreased at 25 and 200 ppm.

    Since these absolute and relative organ weights were not observed in other studies at higher doses, they were not considered compound-related.

11. Gross Necropsy - No compound-related statistically significant effects at 3 and 6 months.

12. Histopathology - No compound-related statistically significant effects at 3 and 6 months.

Discussion: This study is graded core-supplementary because there were no individual animal data, only one sex was tested and limited microscopic examinations were conducted. The NOEL is 200 ppm (HDT).

4

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