CASWELL FILE

Reviewed By: William Dykstra, Ph.D. William Dykstra 7/21/92
Section I, Toxicology Branch I (H7509C)
for Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hurley 7/22/92
Section I, Toxicology Branch I (H7509C)

# DATA EVALUATION REPORT

Study Type: Acute and Subacute Inhalation Toxicity Studies of Neo-Pynamin Forte in Rats

TOX Chem. No.: 844

MRID No.: 421464-01

Accession No.: N/A

Test Material: Neo-pynamin forte (Lot No. 7911-02; 95.6% purity)

Synonym: Neopynamin

Study Number: IT-10-0144

Sponsor: Sumitomo Chemical Company, Ltd.

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

Title of Report: Acute and Subacute Inhalation Toxicity Studies of Neo-Pynamin Forte in Rats

Author: T. Suzuki et al.

Report Issued: March 20, 1981

Conclusions:

The Acute $LC_{50}$ > 1180 mg/$m^3$ (both sexes) with an acute NOEL of 26 mg/$m^3$. Toxic signs were bradypnea, hyperexcitability, salivation, ataxia, limb paralysis. Dose levels were 0, 26, 131, 243, 595, and 1180 mg/$m^3$.

Subacute NOEL = 49 mg/$m^3$ (mid-dose)

LEL = 87 mg/$m^3$ (high-dose): Effects were toxic signs in both sexes, decreased water consumption in females, increased leucocyte counts in females and decreased eosinophils in females. Dose levels were 0, 0 (kerosene only), 26, 49, and 87 mg/$m^3$ for 3 hours/day, 7 days/week, for 4 weeks.

Classification: Core-Supplementary

The individual data were not provided. In addition, the exposure period for the acute inhalation study was only 3 hours and the animals were not tested at high enough dose levels to allow for calculation of the $LC_{50}$.

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

Review:

Acute and Subacute Inhalation Toxicity Studies of Neo-Pynamin Forte in Rats (Sumitomo Lab # IT-10-0144; March 20, 1981)

Quality Assurance Statement was signed by T. Kadota and dated February 20, 1981.

Test Material - NP-F. Lot No. 7911-02; 95.6% purity.

1. Acute Inhalation Toxicity - Randomized groups of 10 male and 10 female 5-week old Sprague-Dawley rats, 5/cage, were exposed to test material dissolved in deodorized Kerosene which was atomized at the air pressure of 1.0 $kg/cm^2$, the injection rate of 0.21 mL/min, and the air flow rate of 50 L/min. This method produced a mist (median particle size: 1.23-1.51 uM) which was applied at doses of 0, 26, 131, 243, 595, and 1180 $mg/m^3$ of test material in the air (50% of the maximum mist concentration) for a duration of 3 hours to 10/sex/dose. The aerodynamic diameter of particles and the number of particles per unit volume were measured by means of a Microscopic Sedimentation Analyzer.

   Observations were for 14 days. Body weight was taken on day 0, 3, 7, and 14. All dead and surviving animals were necropsied.

   Results

   Toxic Signs and Mortality - No raw data were presented.

   26 $mg/m^3$ - No toxic signs or deaths.

   113 $mg/m^3$ and above - hyperexcitability, salivation, decrease of spontaneous activity, bradypnea, hyperpnea, ataxia, and limb paralysis. Ten percent of female rats in the 1180 $mg/m^3$ group died.

   $LD_{50}$ > 1180 $mg/m^3$ (both sexes)

   NOEL = 26 $mg/m^3$

   Body weight was comparable between control and treated rats.

   Necropsy results did not reveal any notable changes in any dose groups.

Classification: Core-Supplementary

Individual animal data were not provided, and the dose levels and exposure period were such that an $LC_{50}$ could not be calculated.

2. Subacute Inhalation Toxicity Study - Randomized groups of 10 male and 10 female 4-week old (60-75 g, both sexes) Sprague-Dawley rats, 5/cage, were exposed, as in the acute study, to a mist containing 0, 0 (Kerosene only), 26, 49, and 87 $mg/m^3$ of test material in air continuously for 3 hours/day, 7 days/week for 28 days (4 weeks). Particle size was measured as in the acute study.

Toxic signs were observed daily, body weight was measured twice a week and water and food consumption per cage was measured weekly. Following the final exposure, fresh urine was examined, and blood was collected for hematology and clinical chemistry determinations. Animals were sacrificed, examined grossly and absolute weight of several organs were measured. Extracted organs and tissues were fixed, embedded, stained, and examined microscopically (see Table reproduced from study report for list of specific items examined).

The Student's t-test was used to compare means of treated groups to negative control group and base (Kerosene only) combined group for quantitative measurements. Histopathological results were analyzed by Chi-Square test.

Result:

Toxic Signs - Although raw data were not reported, the report states that slight bradypnea, irregular respiration and salivation were observed in male and female animals of the 87 $mg/m^3$ group only. These toxic signs were observed after every exposure, but there was no cumulative effect.

Body Weight - Negative control male animals had slightly larger body weights than male animals in the base controls or the treated groups. The body weight gain for males for the 28 days was 173, 184, 171, 178, and 167 g for base control, negative control, low-, mid-, and high-dose groups, respectively. In females, the body weight gain during the 4-week study was 93.1, 96.1, 90.9, 98.3, and 91.7 g for the base control, negative control, low-, mid-, and high-dose groups, respectively. There did not appear to be any effect on body weight gain in any of the treated groups.

Food Consumption - Male negative controls consumed more food (g/rat/day) during weeks 2 and 3 than the base control or treated groups. There were no other statistically significant differences between control and treated groups of both sexes at other times.

Water Consumption - Although there were sporadic significant differences in water consumption in treated low- and mid-dose males, the findings were not dose-related. In females, water consumption at the high-dose was significantly decreased at week 3 and 4 in comparison to controls. At week 3, water consumption (mL/rat/day) was 35.8, 32.6, 32.0, 35.3, and 30.1* and at week 4, the values were 42.6, 32.0*, 36.0, 40.3, and 34.9* for base control, negative control, low-, mid-, and high-dose groups, respectively, for both weeks. The decreased water consumption in high-dose females at week 3 and 4 may be compound-related. (*$p < 0.05$)

Urinalysis - Although individual data were not present, the summary data showed that there were no compound-related effects in occult blood, ketones, glucose, bilirubin, protein, and pH.

Hematology - In comparison to female base controls, the mean mid- and high-dose females had total leucocyte counts which were elevated significantly. The high-dose female lymphocyte count was increased only by 4%, which is not probably toxicologically significant, and the high-dose eosinophil count was decreased in comparison to controls. These high-dose findings in females may be compound-related. Other significantly increased or decreased values in males and females were not dose-relate and were not considered related to treatment.

Clinical Chemistry - In males, SGOT was significantly decreased at the low- and high-dose male groups, but these findings are not toxicologically significant. There were also significant decreases in male cholinesterase measurement at the low-, mid-, and high-dose but the changes were not dose-related.

Other clinical chemistry parameters did not show dose-related or compound-related significant findings.

Organ Weights - Absolute and relative organ weights did not display significant dose-related or compound-related effects. The organs weighed were brain, lung, heart, spleen, liver, testes, ovary, pituitary, thyroid, and adrenal.



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Gross Pathology - No raw data were presented but the report states that no gross findings were related to treatment.

Histopathology - There were no compound-related histological lesions in males or females.

Classification - Core-Supplementary

Individual animal data were not provided.

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