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C-102

Sixty rats were divided into ten comparable groups of three males and three females each. Only six animals per level were used due to the limited amount of material. The average initial weight of the groups ranged between 77 and 84 grams. C-102, suspended in a 20 percent solution of polyvinylpyrrolidone, was administered to nine of the groups at logarithmic dose levels of 10.0, 17.8, 31.6, 56.3, 100.0, 178.0, 316.0, 563.0, and 1000.0 mg/kg. The tenth group served as controls. Animals were weighed (Appendix) and observed for symptoms as required (Table VII). Symptom dose-50's were calculated by the method of Litchfield and Fertig (Table VIII), where warranted, and a 24 hour weight gain suppression curve was determined (Figure V).

No objective symtoms were observed at the lowest level.

C-102, administered orally, produced a hypoactive effect at all but the two lowest levels within 0.5 to 1.5 hours. The number of hypoactive animals increased from three at the 31.6 mg/kg level to six at all levels above 100.0 mg/kg. Animals remained in a hypoactive state for about 6 hours at the 31.6 mg/kg level to as long as 48 hours at the 1000.0 mg/kg level. Although hypoactive, the animals at all but the 1000.0 mg/kg level were easily aroused and

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alerted by external stimuli. Handling the animals, or a sudden movement or noise, would cause an increase in activity for approximately 1 minute, after which the animals would again return to their hypoactive states. Hypoactive animals at the highest level became lethargic and were not easily aroused. During the period of hypoactivity, one to three animals at all but the lowest level were observed to intermittently wash themselves more than normal for periods ranging from 1 to 5 hours.

An excessive chewing phenomenon was exhibited by two animals at each of the 31.6, 56.3 and 100.0 mg/kg levels, three animals at the 178.0 mg/kg level, and all animals above 178.0 mg/kg. This symptom increased in degree of effect as the dosage increased until one-half the animals per level at the three highest levels would come to and chew on paper held six to twelve inches away.

Hypersensitivity to touch was observed in two and one animals, respectively, at the 31.6 and 56.3 mg/kg levels. A maximum number of five hypersensitive animals was observed at the 563.0 mg/kg level. The hypersensitivity occurred 1 to 4 hours after administration and lasted for 2.5 hours at the lowest observed level to a maximum of about 24 hours at the higher levels.

A decreased respiratory rate was observed at all but the

10.0 mg/kg level with increasing frequency and duration, and with a decreasing onset time. One animal at the 17.8 mg/kg level was observed to have a decreased respiratory rate within 1.25 hours, while all animals at the 1000.0 mg/kg level had slow respiration within 1 hour. The symptom persisted for 4.75 hours at the 17.8 mg/kg level to more than 1 day at the 1000.0 mg/kg level.

Ataxia, while it did not appear at the three lowest levels, was present at all levels above 31.6 mg/kg. While only two animals showed the inability to walk the dowel rod at the 56.3 mg/kg level, the symptom increased in frequency until all animals at the three highest levels were ataxic. Animals became ataxic 0.5 to 2.0 hours after administration. The duration of ataxia increased from 1 to 2 hours at the 56.3 mg/kg level to 24 hours at the highest level.

Poor equilibrium was present only at the four highest levels, with two animals at the 178.0 mg/kg level, five at the 316.0 mg/kg level, and all animals at the 563.0 and 1000.0 mg/kg levels showing the symptom. The duration of effect was shorter, and the onset time slightly longer, than for ataxia.

Animals at the four highest levels staggered within 0.75 to 2 hours after receiving C-102. In addition to staggering, the animals, at levels of 100.0 through 1000.0 mg/kg, walked with awkward gaits, such as: 1) walking with all limbs in a stiffened position; and 2) dragging

the hind quarters of the body with forelimbs in a stiffened position. These symptoms increased in frequency and amplitude as the dosage increased and were exhibited by animals at the 1000.0 mg/kg level for as long as 1 day. Animals exhibiting the awkward gait would stop in unusual positions with forelimbs extended anteriorly and hindlimbs extended posteriorly.

Both diarrhea and diuresis were observed in one to three animals per level at all but the lowest dosage level, but were not proportional to the dosage.

A low peripheral temperature, observed in one animal at the 178.0 mg/kg level, increased in frequency to a maximum of five animals at the highest level. The low peripheral temperature occurred from 2.25 to 5 hours after administration and had a duration of less then 24 hours in all cases.

No deaths occurred at any of the levels tested. Symptom dose 50's (Table VIII) were calculated by the method of Litchfield and Fertig. The 24 hour suppression of weight gain (Figure V) determined as described in the April report, varied between zero and 188 percent for females and zero and 198 percent for males. The 24 hour 50 percent weight gain suppression was 27.07 mg/kg with a slope of 283 for females, and 63.1 mg/kg with a slope of 288 for males. The suppression of weight gain was proportional to dosage level up through the 316.0 mg/kg level.

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