Batracyclin Toxicology Abstract
Division of Cancer Treatment and Diagnosis
National Cancer Institute

Batracylin was administered by the oral route of administration in all toxicity studies. In the single dose toxicity study in mice, no mortality occurred in the male mice throughout the study, whereas mortality in the females was delayed and occurred between days 9 and 18 in mice receiving doses of ≥1900 mg/kg. Clinical signs included diarrhea, soft and/ or yellow stool, rough hair coat, lethargy, hunched posture, emaciation, and dehydration. In daily x9 study in mice, which is the most efficacious schedule, the LD10 was about 120 mg/kg/day (360 mg/m^2/day). Lethality was delayed, occurring between days 8 through 16. The data from the single and nine daily dose studies with batracylin indicate that the combined LD_{50} for a single dose (2,623.8 mg/kg) is 11 times higher than that for nine daily doses (232.3 mg/kg/day).

Rats were found to be much more sensitive than mice to batracylin. At 1/10 the MELD10, the prospective clinical trial starting-dose, significant toxicity was observed on both the single dose and daily x 9 schedule. Single doses of 48 mg/kg (1/20 MELD10) or higher and nine daily doses of 16.2 mg/kg/day (1/4 MELD10) were lethal to all the rats. The toxic effects, which were severe and occurred at doses as low as 1/30 MELD10, included bone marrow atrophy; gastrointestinal atrophy, necrosis, degeneration, and inflammation; renal tubular necrosis; seminiferous tubular necrosis in males; ovarian degeneration in females; and bile duct hyperplasia. There were also decreased white cells and platelets and changes in blood and urine chemistries. The safe dose of batracylin in rats was estimated to be 1/30 to 1/60 the MELD10 on the daily x 9 schedule.

In dogs, little toxicity (i.e., slight diarrhea, some anorexia, body weight loss, and mild white cell depression) was observed at 9 daily doses of up to 36 mg/kg/day (2 x MELD10). The only histological lesion, duodenal mucosal gland dilation, was of unknown toxicologic significance.

In conclusion, IND-directed, GLP-compliant toxicology studies of batracylin (NSC320846) were conducted in 3 mammalian species: mice, rats, and dogs. Batracylin was dosed orally, once per day for 9 consecutive days. The variation in tolerated doses across species was most striking, with an MTD range of at least 60-fold. In mice, the MTD was 150 mg/m^2/day. In rats, the MTD was 30-fold lower, 12 mg/m^2/day. The MTD was not reached in dogs at 720 mg/m^2/day. In all species tested, sublethal toxicity was fully reversible after cessation of dosing. The major toxicities were myelosuppression in all species. Renal, hepatic, testicular, ovarian, gastrointestinal, and lethargy were found in different degrees among the various species. Pharmacology studies of batracylin in vivo and in vitro indicate that rats extensively acetylate batracylin to produce N-acetyl batracylin. Mice produce relatively small amounts and dogs do not generate this metabolite. Published data indicate that N-acetyl-batracylin is a highly-toxic metabolite.