Biostability of Batracylin: Incubation of batracylin in mouse and human plasma for as long as 48 h did not produce significant degradation. In addition, there was no evidence of appearance of N-acetylbatracylin or the acid-catalyzed open-ring product in plasma. Time dependent formation of N-acetyl-batracylin was observed in the whole blood of the rodents.

Mouse and rat pharmacokinetics: Plasma concentration of batracylin in mice was higher following i.p. administration of 350 mg/kg (1050 mg/m$^2$) than that observed following p.o. administration, and the relatively high concentrations following i.p. dosing appeared to be maintained for somewhat longer periods of time (Mayo report, 1989). Plasma concentrations of batracylin administered at 590 mg/m$^2$ were consistently higher in mice than in rats. Based on plasma AUC values, the mean batracylin systemic exposure to the rat was 14.9% of that to the mouse. 24-h urinary recovery of batracylin in both species was <2% of the dose. Urinary recovery of batracylin was greater in mice than in rats, consistent with the plasma data. Calculation of plasma AUC values for N-acetyl-batracylin following oral administration of batracylin (590 mg/m$^2$) to mice and rats revealed that systemic levels of N-acetyl-batracylin in the rat was 8.8 times greater than in the mouse. Urinary recovery of N-acetyl-batracylin was very low in both species (<2%) as was the case for batracylin. However, urinary recovery of N-acetyl-batracylin was much greater in the rat than in the mouse, consistent with the plasma data.

Absence of bioavailability or toxicity of oral N-acetyl-batracylin in rats: Toxicokinetics of N-acetyl-batracylin was assessed following oral administration in rats and mice. Interestingly, N-acetyl-batracylin was not toxic following oral administration at a dose of 600 mg/kg (3,600 mg/m$^2$) in rats, or a 2,400 mg/kg (7,200 mg/m$^2$) dose in mice. Oral administration of N-acetyl-batracylin to rats at a dose of 750 mg/kg (4,500 mg/m$^2$) exhibited almost no N-acetyl-batracylin in rat plasma (<50 ng/mL). It was estimated that the relative bioavailability of N-acetyl-batracylin following an oral administration of 750 mg/kg (4,500 mg/m$^2$) to rats was less than 5% of that following oral administration of 108-125 mg/kg (650-750 mg/m$^2$) of batracylin. Based on the AUC ratio, one may speculate that the lack of toxicity observed following oral administration of N-acetyl-batracylin to mice and rats reflects the very poor bioavailability of the compound.

Pharmacokinetics in dogs: Pharmacokinetic patterns of batracylin following oral administration in dogs fit best in a two-compartment model with first-order absorption and biphasic elimination. Lag time in oral absorption of batracylin ranged from ~11 min (50 mg/kg, or 1000 mg/m$^2$) to 50-57 min (150 and 300 mg/kg, or 3000 and 6000 mg/m$^2$). Batracylin administered at 50, 150 and 300
mg/kg (1,000, 3,000, and 6,000 mg/m$^2$) reached its mean C$_{max}$ 161, 365, and 3100 ng/mL at T$_{max}$ 65, 118 and 120 min, respectively. The absorption t$_{1/2}$ of batracylin in suspension (37-60 min) seemed longer than in gelatin capsules (28-35 min). The AUC values of batracylin for 50, 150 and 300 mg/kg (1,000, 3,000, and 6,000 mg/m$^2$) were 20946, 64225 and 526501 ng/mL·min. AUC following 300 mg/kg (6000 mg/m$^2$) was about 9-fold greater than that following 150 mg/kg (3000 mg/m$^2$), due to higher peak plasma concentration and longer elimination t$_{1/2}$ (566 min) at the 300 mg/kg (6000 mg/m$^2$) level. The chromatographic profile of dog plasma revealed a metabolite eluted near the solvent front with chromatographic retention characteristics (retention time ~1.8min) similar to that observed in mouse pharmacokinetic studies. This product may be N-(2,5-diaminobenzyl) phthalimide produced from acid-hydrolyzed ring-opening of batracylin although no structure identification was performed. It is important to mention that the chromatographic peak of N-acetyl-batracylin apparently observed in rat plasma was absent in dog plasma.