were collected for histopathology: adrenal (2), aorta, brain, cecum, colon, duodenum, epididymis (2), esophagus, eyes [preserved in Davidson's fixative (2)], femur with bone marrow (articular surface of the distal end), gallbladder, heart, ileum, jejunum, kidneys (2), lesions, liver, lung, mesenteric lymph node, mammary gland, pancreas, pituitary, prostate, rectum, salivary gland [mandibular (2)], sciatic nerve, seminal vesicle (2), skeletal muscle (thigh), skin, spinal cord (cervical, thoracic, and lumbar), spleen, sternum with bone marrow, stomach, testis [(2) preserved in Bouin's solution, thymus, thyroid (2) with parathyroid, trachea and urinary bladder.

Two animals, one male from the 30/20 mg/kg/day dose group and one male from the 3 mg/kg/day dose group, were sacrificed in moribund condition during the study. The male in the 30/20 mg/kg/day dose group was sacrificed on day 29. This animal exhibited signs of hypoactivity, weight loss, few or no feces, low or no food consumption and the entire body was cold to the touch before death. Necropsy revealed esophageal and gastric lesions that were indicative of an injury that occurred during dosing and liver lesions that were presumed to be treatment related. The animal from the 3 mg/kg/day dose group was sacrificed on day 137. This animal showed clinical signs of limited use and paralysis of the hind limbs, ataxia and hypoactive behavior, few feces and no food consumption. The cause of death was not determined, but APFO treatment could not be ruled out.

Males given 30 mg/kg/day from days 1-11 had clinical signs of few feces and low food consumption and they lost weight during week 1 of treatment. Based on these signs, treatment was stopped on day 11 and was not resumed until day 22. When treatment was resumed, the dose was lowered to 20 mg/kg/day; this group was then designated the 30/20 mg/kg/day group. Of the remaining animals in this group, only 2 tolerated this dose level for the remaining 23 weeks of treatment. Treatment of three males given 30/20 mg/kg/day was halted on days 43 (week 7), 66 (week 10), and 81 (week 12) respectively. Clinical signs in these animals included thin appearance, few or no feces, low or no food consumption, and weight loss. The animals appeared to recover from compound-related effects within 3 weeks after cessation of treatment.

Mean body weight changes were notably lower during weeks 1 and 2 for males receiving 30 mg/kg/day. During week 2, this change was statistically significant. Treatment was stopped on day 11 and when it was resumed at 20 mg/kg/day on day 21, mean body weight changes were significantly lower than controls during weeks 7, 9 and 24. Overall mean body weight changes through week 27 were notably lower for the males in the 30/20 mg/kg/day group. There was an increased incidence of low or no food consumption for animals in the 30/20 mg/kg/day group that was considered to be treatment related.

There were no consistent or clearly dose-related effects on estrone, estradiol, estriol, thyroid stimulating hormone, or testosterone that were seen in any treatment group over time. In general, thyroid hormones were decreased beginning on day 35 in animals in the 10 or 30/20 mg/kg/day groups. Triiodothyronine remained depressed through day 183 in the 30/20 mg/kg group. Total thyroxin was decreased beginning on day 35 in animals administered 10 or 30/20 mg/kg APFO. The effect on thyroxin was most pronounced at day 35 in animals administered 10 mg/kg/day and day 66 in animals administered 30/20 mg/kg/day. Thereafter, the effect began