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REPEATED DOSE (28 DAYS) ORAL TOXICITY STUDY IN RATS, BASED ON THE PROTOCOL (OECD TEST GUIDELINE NO. 407) TO SCREEN ENDOCRINE-DISRUPTING CHEMICALS

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Abstract In association with the international validation project to establish a test protocol for the "Enhanced OECD Test Guideline 407", we performed a 28-day repeated-dose toxicity study of vinclozolin (VCZ), an androgen antagonist, and ketoconazole (KCZ), a biosynthesis inhibitor of testosterone (T), and assessed the sensitivity of new parameters for detecting endocrine-related effects of endocrine-disrupting chemicals. Seven-week-old SD rats, each group consisting of 10 males and 10 females, were administered test materials by oral gavage. Male rats were killed 1 day after the 28th administration, and female rats on the day they entered the diestrus status in the estrous cycle after the last treatment. Male rats receiving VCZ at dose of 200 mg/kg/d increased serum T and estradiol levels, although they were not significantly different, and decreased weight of the reproductive organs (seminal vesicle, epididymides etc). KCZ-treated male rats decreased T and increased LH. Both test materials in male rats caused a decrease in T3 (T4) levels with an increase of TSH and enlargement of thyroid gland. A chronic administration of these compounds may cause increase thyroid hormone metabolism with compensation via increased TSH production. Dose-related changes were not detected by spermatogenesis and sperm analysis. In females, a significant prolongation of the estrous cycle was observed in the 100 mg/kg KCZ-treated group. In conclusion, among the parameters tested in the present study the weight of endocrine-linked organs, and their histopathological assessment, serum hormone levels and estrous cycle stage allowed the detection of endocrine-related effects of VCZ and KCZ.

keyword : Endocrine Disruptor, Enhanced OECD Test Guideline 407, Ketoconazole, Vinclozolin, Rat