A large number of non-genotoxic compounds of diverse chemical structures have been reported to induce Leydig cell tumors (LCT) in rats, mice, or dogs. A review of the available information on LCT induction in animals led a workshop panel to classify these compounds into seven groups based on their modes of action (Clegg et al., 1997). The common theme in the mode of action for most compounds is that these compounds affect the hormonal control of Leydig cell growth by disrupting the hypothalamic-pituitary-testicular axis at various points that result in increasing the serum levels of luteinizing hormone (LH). It has been postulated that in addition to stimulating the production of testosterone, LH may also play a mitogenic role in the Leydig cells; a sustained increase in circulating LH levels and chronic stimulation of Leydig cells by growth-stimulating mediators such as IGF-1, TGF-β, leukotrienes and various free radicals can lead to LCT development (*rev. in*: Clegg et al., 1997).

A series of studies have been conducted to investigate the mechanism of tumor formation in male Sprague-Dawley (CD) rats exposed to APFO (Cook et al., 1992; Biegel et al., 1995; Liu et al., 1996). No significant increases in LH were seen in the rats after treatment of APFO at various dose levels for 14 days. However, serum and testicular levels of estradiol were significantly increased and testosterone levels were significantly decreased. It was postulated that the elevated estradiol levels may cause Leydig cell hyperplasia and tumor formation by acting as a mitogen and/or enhancing growth factor secretion; the transforming growth factor α

(TGF α), which binds to the epidermal growth factor (EGF) receptor and stimulated cell proliferation, for instance, has been detected in Leydig cells (Teerds et al., 1990). Subsequent experiments have shown that APFO increased the levels of estradiol by inducing cytochrome P450 XIX (aromatase), which converts testosterone to estradiol. Peroxisome proliferators are known to induce β-oxidation and cytochrome P-450 monooxygenases by binding to the peroxisome proliferation activation receptor α (PPAR α; a subfamily of steroid hormone receptors). It is believed that APFO induces cytochrome P450 XIX (aromatase) by binding to and activating the PPARα.