Agency is currently examining these postulated modes of action in detail. The following summaries are not meant to be a detailed review of the literature, but simply summarize the current scientific evidence.

### 3.8.2.1 Liver Tumors

It has been well documented that APFO is a potent peroxisome proliferator, inducing peroxisome proliferation in the liver of rats and mice (e.g., Ikeda et al., 1985; Pastoor et al., 1987; Sohlenius et al., 1992). A sex-related difference in the induction of liver peroxisome proliferation exists in rats (Kawashima et al., 1989), but not in mice (Sohlenius et al., 1992). The higher induction of liver peroxisome proliferation in male rats was shown to be strongly dependent on the sex hormone testosterone (Kawashima et al., 1989). Like many other peroxisome proliferators, APFO has also been shown to cause hepatomegaly (an early biomarker of peroxisome proliferator hepatocarcinogenesis) in rats (Takagi, et al., 1992; Cook, 1994) and mice (Kennedy, 1987), and induce oxidative DNA damage in liver of rats (Takagi et al., 1991). The totality of these data appears to suggest that the liver toxicity and carcinogenicity of APFO may be related to induction of peroxisome proliferation. Meanwhile, estrogen has been shown to promote hepatocarcinogenesis in rats (Yager and Yager, 1980; Cameron et al., 1982); an increase in estrogen levels after APFO exposure (discussed below) may also play a role in hepatocarcinogenesis in rats. Recently, IARC (1995) concluded that the liver tumors induced in rodents by PPAR-alpha agonists are unlikely to be operative in humans based on our current understanding of the animal mode of action.

### 3.8.2.2 Leydig Cell Tumors

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.

Although significant increases in LH were not seen in Sprague-Dawley rats after treatment of APFO in the 14 day-studies, it appears that increase in LH levels cannot be ruled out to be involved (in addition to increased estradiol level) in the induction of LCT by APFO. In these studies, significant increase in hepatic aromatase (which converts testosterone to estradiol) activities associated with decreased serum testosterone levels and increased estradiol levels were observed in the treated rats. Testosterone is synthesized and secreted by the Leydig cells, and is regulated by LH; testosterone and LH form a closed-loop feedback system in the HPT axis. In order to maintain adequate testosterone plasma levels, reduced testosterone levels (caused by increased aromatase activity) are expected to lead to increased LH levels through the negative feedback mechanism. It has been pointed out that increases in LH may not always be seen in all studies of chemicals for which the proposed mode of action calls for elevated LH, and that compensation may have occurred to restore homeostasis and inappropriate timing of sampling are some of the explanations for failing to detect changes in LH levels (Clegg et al., 1997).

3.8.2.3 Mammary Gland Tumors

Estradiol has also been shown to stimulate the secretion of TGF α by mammary epithelial cells and the overexpression of TGF α has been suggested as one possible factor in producing sustained cell proliferation of mammary tumor cells and the subsequent development of neoplasia (Liu et al., 1987). Hence, it is possible that the APFO-induced elevation of estradiol levels may also be responsible for the development of mammary fibroadenomas in Sprague Dawley rats in addition to LCT (discussed above). In fact, this is consistent with the mechanism by which spontaneous mammary neoplasms were developed in aging female Sprague Dawley rats. It has been demonstrated that the early appearance and high spontaneous incidence of mammary gland tumors in untreated, aging female Sprague-Dawley rats is due to increased exposure to endogenous estrogen and prolactin as a result of an accelerating effect on normal, age-related perturbations of the estrous cycle in this strain of rat (Cutts and Noble, 1964; Chapin et al., 1996).

3.8.2.4 Pancreatic Tumors

The mechanism by which APFO induced pancreatic acinar cell tumors is unknown. A number of other peroxisome proliferators also produce pancreatic acinar cell tumors in rats. Available data suggest that the pancreatic acinar cell tumors are related to an increase in serum cholecystokinin (CCK) level secondary to hepatic cholestasis (Cook et al., 1994; Obourn et al., 1997). CCK is a