INTRODUCTION

Ammonium perfluorooctanoic acid is non-genotoxic but has induced liver tumours when administered to rats. APFO is a peroxisome proliferator activated receptor (PPARα and PPARγ) ligand, and has previously been shown to elicit hepatomegaly in rats. Peroxisome proliferators have been shown to generally increase hepatocellular replicative DNA synthesis (S-phase) and to inhibit apoptosis. The objective of this study was to characterise APFO-induced hepatomegaly.

METHODS

APFO (300ppm) was administered in the diet to male Sprague Dawley rats (7-8 weeks old) for 1, 7 and 28 days. Wy14,643 (50ppm) was administered to other groups of rats as a positive control. Rats were implanted with osmotic pumps containing BrdU five days before termination. Rats exposed to diet for one day were administered BrdU (sc) two hours prior to sacrifice. On days 2, 8 and 29 rats were killed by exposure to a rising concentration of CO2. The livers were excised, weighed and samples fixed and processed for H&E staining. BrdU IHC and TUNEL. The number of BrdU positive nuclei was quantified using a microscope. Cytokeratin 19 staining was performed on liver sections. BrdU labelling index was calculated as the percentage of BrdU positive nuclei.

RESULTS

Administration of APFO decreased body weights after 7 and 28 days of exposure (90% and 85% of controls respectively). This effect was not observed in rats receiving Wy14,643. No adverse clinical observations were made. The mean ingested doses of APFO and Wy14,643 were 23.25 ± 0.11 and 3.66 ± 0.02 mg / kg bwt / day respectively. Absolute liver weights were increased with time following exposure to both APFO and Wy14,643 (Figure 1). Administration of APFO or Wy14,643 increased β-oxidation at all times (Fig 2).

APFO-induced hepatomegaly is characterised by hypertrophy (proliferation of peroxisomes and SER) and hyperplasia (increased S-phase and hepatocyte proliferation).

Unlike other peroxisome proliferators APFO appears not to inhibit apoptosis. This observation may be confounded due the simultaneous activation of PPARα (decreased apoptosis) and PPARγ (increased apoptosis). Unlike most peroxisome proliferators that are ligands for PPARα only, APFO is a ligand for both receptors. There is evidence to suggest that, in the rat liver, activation of PPARα and PPARγ decreases and increases apoptosis respectively.

CONCLUSIONS

APFO is a promiscuous ligand. The study presented suggests that APFO interacts with other receptors such as CAR (CYP2B induction, phenobarbitone-like) and PXR (CYP3A induction, dexamethasone-like) in addition to the PPARs.