weight (Hirata-Koizumi et al., 2012); therefore, there is also the possibility that hepatic necrosis is one factor for inhibition of body weight gain.

As with PFOA and the other PFCAs, the primary target of PFDoA was the liver. Relative liver weights increased in both sexes in the 0.5 and 2.5 mg/kg/day groups. Various histopathological changes, including hepatocyte hypertrophy and necrosis, were observed in the liver in both sexes given 2.5 mg PFDoA/kg/day, and focal necrosis was also found in the liver of 2/12 females receiving 0.5 mg PFDoA/kg/day. These changes have been attributed, at least in part, to PPARα activation by PFDoA because PPARα is considered to mediate the biological effects of peroxisome proliferators, such as increases in liver weight due to hepatocyte hypertrophy and hyperplasia, transcriptional increases in enzymes involved in the metabolism of fatty acids, and hepatocarcinogenesis (Green, 1995; Holden et al., 1999; Corton et al., 2000). On the other hand, the following findings suggest that a different mechanism from PPARα activation is involved in the hepatotoxicity of PFDoA. The peribiliary infiltration of inflammatory cells, bilirubin deposition, and proliferation of the bile duct were observed in the 2.5 mg/kg/day group, and blood biochemical examinations revealed an increased level of T-Bil and γ-GTP activity at 2.5 mg/kg/day and increased ALP activity at 0.5 and 2.5 mg/kg/day. These changes indicate inflammatory cholestasis. Yellow brown discoloration of the liver and subcutis, and yellow mass and patch on the epididymis observed in some animals given 2.5 mg PFDoA/kg/day may have resulted from the accumulation of yellow bilirubin pigment. The dose-independent changes in serum T-Cho observed in males suggest that the hypocholesterolemic action of PFDoA via PPARα activation may have been countervailed by impaired cholesterol excretion associated with cholestasis in the high dose group.

Most of the other changes observed in the 2.5 mg/kg/day group may be secondary effects that occur with the pronounced reduction in body weight gain and food consumption. A reduction in motor activity and grip strength may reflect muscle weakness accompanying decreases in body weight rather than neurotoxicity. Atrophy of the lateral great muscle in the 2.5 mg/kg/day group supports this hypothesis. Histopathological changes observed in the stomach, thymus, pancreas, and bone marrow are known to be associated with nutrient deficiencies and/or stress. The prolonged administration of PFDoA, which had a marked influence on food consumption and body weight, must have been stressful for animals. On the other hand, atrophy of the adrenal gland cannot only be explained by changes in body weight and food consumption because previous food restriction studies demonstrated that the adrenal gland was hypertrophied (Moriyama et al., 2008; Shallie et al., 2012). Such atrophic changes in the adrenal gland were shown to be induced by adrenal steroidogenesis inhibitors such as 1-(o-chlorophenyl)−1-(p-chlorophenyl)−2,2-dichloroethane (o,p'-DDD), and α-[1,4-dioxido-3-methylquinoxalin-2-yl]-*N*-methylnitrone (DMNM) (Hamid et al., 1974; Rosol et al., 2001). Because PFDoA was demonstrated to inhibit steroidogenesis in the testis and ovary (Shi et al., 2007; Shi et al., 2009a,b; 2010a,b), it may also alter adrenal steroidogenesis to cause atrophy of the adrenal cortex.

PFDoA affected the male and female reproductive systems. In males, cell debris and a reduction in the number of spermatid or spermatozoa were observed in the testis and epididymis, and atrophic changes were identified in the prostate, seminal vesicle, and coagulating gland in the 2.5 mg/kg/day group. Although these changes may have been due to the inhibition of body weight gain, a previous study demonstrated that the oral administration of PFDoA to rats for 110 days at a dose as low as 0.2 mg/kg/day decreased serum testosterone levels without affecting body weight (Shi et al., 2009a). An *in vitro* study reported the dose-dependent inhibition of steroidogenesis in mouse Leydig tumor cells and primary rat Leydig cells (Shi et al., 2010a), which indicated that PFDoA directly affected testicular testosterone synthesis, and not via the hypothalamic-pituitary-testicular axis. Since decreased testosterone biosynthesis is known to result in the degeneration and reduction in the number of germ cells as well as decreased size of accessory sex glands (O'Connor et al., 2002; OECD, 2009), the histopathological changes observed in the male reproductive organs in this study were attributed, at least in part, to the disruption of steroidogenesis. Shi et al. (2007, 2009a) reported that levels of the steroidogenic acute regulatory protein (StAR), which is responsible for cholesterol transport to the inner mitochondrial membrane, and StAR mRNA were markedly decreased in the testes of rats exposed to PFDoA, and treatment with the hydrosoluble form of cholesterol, which readily enters the inner mitochondrial membrane without the help of StAR, to mouse Leydig tumor cells prevented the inhibitory effect of PFDoA on steroidogenesis (Shi et al., 2010a). These results suggest that StAR is one of the target proteins for PFDoA activity in Leydig cells. A recently conducted proteomic analysis on the testis of rats exposed to PFDoA indicated that alterations in multiple pathways, including mitochondrial disruption and oxidative stress, may be associated with the testicular toxicity of PFDoA in rats (Shi et al., 2010b). Decreased testosterone levels in the testes and/or blood was also caused by PFOA, perfluorononanonic acid (PFNA, C9) and perfluorodecanoic acid (PFDeA, C10) (Bookstaff et al., 1990; Biegel et al., 1995; Jensen et al., 2008; Feng et al., 2009; Feng et al., 2010), which may involve the same mechanism as PFDoA. Recent study on PFOA-induced disruption of testosterone biosynthesis suggests the involvement of PPARα (Li et al., 2011).

A previous study demonstrated that PFDoA decreased serum estradiol levels in female rats following a 28-day oral administration period at a dose that affected body weight (Shi et al., 2009b). Alterations in the ovarian expression of genes responsible for cholesterol transport and steroidogenesis (StAR protein, cholesterol side-chain cleavage enzyme, and 17-beta-hydroxysteroid dehydrogenase) were also found

in this previous study. Such effects on the ovarian steroidogenesis may explain why continuous diestrous was observed in the recovery group in this study because estrogen and progesterone, which are steroid hormones synthesized from cholesterol in the ovary, play an important role in controlling the estrous cycle (OECD, 2009). Continuous diestrous indicates at least the temporary and possibly permanent cessation of follicular development and ovulation, and thus temporary infertility (Parker, 2006). In this study, the lack of an effect on the copulation and fertility indices was consistent with the findings that the abnormal estrous cycle was observed after the 27th day of the administration period in the recovery group and not found during the 14-day premating period in the main group. Considering that continuous diestrous was induced around the same time as changes in body weight and food consumption became apparent, the disruption of energy homeostasis could be a factor in the abnormal estrous cycles observed in this study. Food restriction in rats has been shown to result in weight loss and constant diestrous (Kotsuji et al., 1986; Narita et al., 2011). Recent evidence has suggested that many of the central and peripheral endocrine signals that govern energy homeostasis are involved in the control of reproductive function by acting at different levels of the hypothalamic-pituitary-gonadal axis (Narita et al., 2011). Effects on estrous cyclicity have not been reported for the other PFCAs, which may be because the reproductive toxicity of the other PFCAs were not examined at doses causing severe inhibition of body weight gain as observed in the 2.5 mg/kg/day PFDoA group.

PFDoA exerted no effects on the copulation and fertility indices or on the number of corpora lutea and implantation; however, only one of twelve pregnant females delivered live pups in the 2.5 mg/kg/day group. As mentioned above, PFDoA has been reported to disrupt ovarian steroidogenesis (Shi et al., 2009b). Since pregnancy is maintained under the control of estradiol and progesterone (Ogle et al., 1990; Bartholomeusz et al., 1999), PFDoA may affect pregnancy by disrupting steroidogenesis. Another possible factor is impaired fetal development, which could affect the maintenance of pregnancy and normal delivery. Live pups delivered from one pregnant female in the 2.5 mg/kg/day group had markedly lower body weights than those of the controls. The effects of PFDoA on fetal development could be attributed to secondary effects due to maternal toxicity; however, the lipophilic properties of PFDoA (Inoue et al., 2012) also indicate the possibility that it was transferred via the placenta and directly affected the fetuses.

In this study, some of the changes observed during and at the end of the administration period were detected even after the 14-day recovery period, including reductions in body weight, hypertrophy of hepatocytes, bilirubin disposition, peribiliary infiltration of inflammatory cells and bile duct proliferation in the liver, and atrophy of the adrenal cortex. Although no data are currently available on the toxicokinetics of PFDoA, previous studies demonstrated that PFCAs with a longer carbon chain were eliminated more slowly from the body; the elimination half-life was shown to be 6.38 h for perfluorobutanoic acid (C4), 2.4 h for perfluoroheptanoic acid (C7), 135–185 h for PFOA (C8), 710 hours for PFNA (C9), and 958 h for PFDeA (C10) in male rats intravenously administered PFCAs (Kudo et al., 2002; Kemper, 2003; Ohmori et al., 2003; Chang et al., 2008). Therefore, incomplete recovery of the toxic effects caused by PFDoA may be attributed to its slow elimination from the body.

In summary, 42- to 47-day oral gavage administration of PFDoA mainly affected the liver, causing hypertrophy, necrosis, and inflammatory cholestasis, at 0.5 and 2.5 mg/kg/day. In the 2.5 mg/kg/day group, body weight gain was markedly inhibited, and various changes, mostly viewed as secondary effects, were observed in the bone marrow, spleen, thymus, and adrenal gland. These toxic effects did not recover completely during the 14-day recovery period. Regarding reproductive/developmental toxicity, various histopathological changes, including decreased spermatid and spermatozoa counts, were observed in the male reproductive organs, and continuous diestrous was found in females in the 2.5 mg/kg/day group. Seven of twelve females receiving 2.5 mg/kg/day died during late pregnancy while four other females in this group did not deliver live pups. Based on these findings, the NOAELs of PFDoA were concluded to be 0.1 mg/kg/day for repeated dose toxicity and 0.5 mg/kg/day for the reproductive/developmental toxicity.

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