Liver histopathology

In this guide

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143. For PFCAs, histopathology was carried out in 37 of the 50 studies reviewed (three of the ten acute studies, 33 of the 37 repeated dose studies and one of the three developmental studies).

144. In acute studies, no effects on liver histopathology were reported in male rats following exposure to PFOA (Elcombe et al., 2010) and in male mice with PFOA and PFNA (Das et al., 2017).

145. In the repeated dose studies, histopathological changes were seen in 14 of the 33 studies.

146. An increased incidence of hepatocellular hypertrophy was seen in male rats following exposure to PFBA for 90 days (Butenhoff et al., 2012a). PFOA caused hypertrophy of centrilobular hepatocytes in male mice (Botelho et al., 2015), hepatocellular hypertrophy and fatty vacuolation in male rats and hepatocellular hypertrophy and hepatocellular hyperplasia (Elcombe et al., 2010), hepatocellular hypertrophy in male mice (Guo et al., 2019), centrilobular hepatocellular hypertrophy, with elevated numbers of cytoplasmic acidophilic granules in male mice (Qazi et al., 2010a), mild lymphocytic infiltration around the central vein in male mice (Son et al., 2008), visible vacuoles around liver portal area in male mice (Wu et al., 2018) and deranged liver architecture, marked oedema, vacuolar degeneration, hepatocellular necrosis, and inflammatory cell infiltration in male mice (Zou et al., 2015).

147. PFNA also caused hepatocytic cytoplasmic alterations in male and female rats and hepatocyte hypertrophy in males (NTP., 2022b). Takahashi et al. (2014) also reported hepatocyte centrilobular hypertrophy in male and female rats after exposure to PFUnDA, and Hirata-Koizumi et al. (2012) observed centrilobular liver hypertrophy and steatosis in males and females with PFTeDA, centrilobular liver hypertrophy in males and females with PFHxDA and centrilobular liver hypertrophy in males with PFODA.

148. Xu et al. (2022) also reported hepatocyte hypertrophy, disarrangement, cytoplasmic loss, nuclear migration, acidophil bodies and inflammatory cell infiltration in female mice in the developmental study with PFOA.

149. In contrast, no effects were seen on liver histopathology with PFBA following 28 days exposure (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), PFOA (Butenhoff et al., 2002; Butenhoff et al., 2012a; Li et al., 2019; NTP., 2022b; Soltani et al., 2023), PFNA (Fang et al., 2012; Hadrup et al., 2016), PFDA (Frawley et al., 2018; NTP., 2022b) and PFDoDA (Kato et al., 2014; Zhang et al., 2008).

150. Differences in response were seen between sexes following exposure to PFBA for 90 days (Butenhoff et al., 2012a), PPFA (NTP., 2022b) and PFODA (Hirata-Koizumi et al., 2012) where histopathological changes were only seen in males.

151. For PFSAs, histopathology was carried out in 17 of the 25 repeated dose studies reviewed and histopathological changes were seen in 11 of the 16 studies.

152. Following exposure to PFBS, Chen et al. (2022) reported increased apoptosis in male mice and Lieder et al. (2009b) observed hepatocellular hypertrophy in male rats.

153. Hepatocellular hypertrophy was also seen in male mice following exposure to PFHxS (Chang et al., 2018; Das et al., 2017) and with PFOS in male and female mice (Bagley et al., 2017), male rats (Butenhoff et al., 2012b; Elcombe et al., 2012; Han et al., 2018b), female rats (Kim et al., 2011; NTP., 2022a) and male and female Cynomolgus monkeys (Seacat et al., 2002).

154. Other histopathological effects observed following PFOS exposure included cytoplasmic alterations in males and necrosis in male and female mice (Bagley et al., 2017), cystic hepatocellular degeneration in male rats and hepatocellular periportal vacuolation in females (Butenhoff et al., 2012b), lipid droplets, inflammation and apoptosis in male mice (Chen et al., 2022), apoptosis in male rats (Kim et al., 2011) and centrilobular vacuolation and lipid droplet accumulation in male and female Cynomolgus monkeys (Seacat et al., 2002).

155. In contrast, no effects were seen with PFBS (Lieder et al., 2009a; NICNAS., 2005; NTP., 2022a), PFHxS (He et al., 2022; NTP., 2022a) and PFOS (NTP., 2022a).

156. Differences in response were seen between sexes following exposure to PFBS (Lieder et al., 2009b) where hepatocellular hypertrophy was only seen in male rats.

Recovery

157. Following the 90-exposure to PFBA, all parameters observed after treatment (TP, bilirubin and histopathological changes) were comparable to controls after recovery (Butenhoff et al., 2012a).

158. Following the 90 day exposure to PFBS, the increased liver weight that was observed after treatment was comparable to controls after the recovery period (NICNAS., 2005). No data on liver weight were reported in Cynomolgus monkeys following exposure to PFOS for 182 days and a 90-day recovery period (Seacat et al., 2002).