Discussion

In this guide

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180. Ten PFCAs (PFBA, PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFDODA, PFTeDA, PFHxDA and PFPDA) and three PFSAs (PFBS, PFHxS and PFOS) are considered in this paper.

181. Table 1 and Table 2 below present the lowest point of departure (POD) based on liver effects. For PFHxA, PFOA, PFDA and PFHxS, only a LOAEL was determined, as effects were seen at the lowest dose tested.

182. Clinical chemistry parameters, liver weight and histopathological changes (hepatocellular hypertrophy) were the most sensitive endpoints on which the majority of the N/LOAELs have been determined. Changes in gene expression

were also noted in some studies.

183. In repeated dose and developmental toxicity studies there were some changes in ALT, ALP, TP, bilirubin, albumin, globulin and albumin/globulin ratio and cholesterol, although for most parameters, there was a lack of consistency of the direction of effect across studies and with different PFAS. For example, PFOA and PFNA decreased serum TG male rats (NTP., 2022b) and in male mice (Qazi et al., 2010a) whereas Wu et al. (2018) reported an increase in male mice. However, the majority of studies did not show any effect on such parameters. Several studies show increases in AST, ALP or ALT at the LOAEL, which, in some cases, was accompanied by histopathological changes but overall, there were limited signs of overt hepatotoxicity observed.

184. The most prevalent effect observed as the decrease in serum cholesterol, which was observed in a number of studies, mainly in male rats after treatment with both PFCAs and PFSAs. Seacat et al. (2002) also noted that the decrease in serum cholesterol observed in Cynomolgus monkeys was the earliest reliable clinical response to PFOS.

185. An increase in liver weight was reported in multiple studies, which was generally accompanied by hepatocellular hypertrophy, due to the increased hepatic enzyme induction and hepatocellular function in response to the chemical exposure. In general, such effects appeared transient as they returned to control levels during a recovery period following cessation of treatment.

186. In rats and cynomolgus monkeys treated with PFBA and PFOA, respectively, Butenhoff et al. (2002 and 2012) noted that the increased liver weight did not appear to be a result of hepatocellular hyperplasia (no increase in nuclear DNA) and correlated it with increases in peroxisomes, endoplasmic reticulum, and mitochondria in both short term and chronic studies. Moreover, despite deriving a NOAEL of 6 mg/kg bw/day based on hepatocellular hypertrophy, increased liver weights, and slight clinical biochemistry changes at 30 mg/kg bw/day, Butenhoff et al. (2012a) noted that the NOAEL was conservative as such changes did not constitute clear functional or morphological deficits. NTP noted that increased absolute and relative liver weights were commonly seen with two or more PFCAs and PFSAs which correlated with histopathologic changes in the liver such as hepatocellular hypertrophy, and in some cases hepatocellular degeneration and necrosis, and that such changes often were seen at the lowest dose tested (NTP., 2022b). Other histological lesions in the liver varied across PFAS and between sexes.

187. Sex-specific differences were seen with effects on clinical chemistry parameters, with changes more frequently seen in male than in female animals at comparable doses. Similarly, histopathological changes or increased liver weight was more common in male animals.

188. Serum/plasma PFAS levels will be evaluated further in subsequent papers considering the toxicokinetics of PFAS.

189. It may be relevant to note the approach taken by two authoritative bodies, namely the ATSDR (ATSDR, 2021) and the United States Environmental Protection Agency (USEPA) (USEPA, 2023), in selecting liver effects as the basis for setting human health criteria values. These opinions will be explored in future papers.

190. Overall, the in vivo evidence indicates that doses of PFSAs and PFCAs can produce affect clinical chemistry parameters, can produce histopathological alterations in the liver and an increase in liver weight. However, some of these findings are inconsistent, and some endpoints appear to be sex-specific (with males being more sensitive than females).

191. The biological relevance and adverse nature of the most sensitive endpoints seen in the liver following PFSA exposure will be further explored in future papers.