Effects on gene expression

In this guide

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159. For PFCAs, liver-related gene expression was assessed in 21 studies (five acute studies, 15 repeated dose studies, and one developmental study), 20 of which (ten in both mice and rats) reported changes in liver-related gene expression.

160. Following acute exposure, Cheng and Klaassen (2008) reported increased mRNA levels of cytochrome P450 (Cyp450) 2B10, 3A11 and 4A14 in liver of male mice treated with 40 mg/kg bw PFOA and 80 mg/kg bw PFDA. However, in the range-finding experiment, 10 mg/kg bw PFDA only increased Cyp4A14. Das et al. (2017) also reported changes in mRNA of genes relating to

fatty acid, TG and cholesterol synthesis and omega oxidation in male mice.

161. For PFCAs, in the repeat dose studies, changes in mRNA expression were reported following exposure with PFBA, PFHxA, PFOA, PFNA, PFDA and PFDoDA.

162. Butenhoff et al. (2012a) reported an increase in mRNA of acyl-CoA oxidase 1 (Acox), uridine diphospho-glucuronosyl transferase (Ugt) 1A1 and CYP4A1 but a decrease in Cyp1A1, Ugt 1A6 and Ugt 2A in male rats following exposure to PFBA for 28 days. Similar results were reported after a 90-day exposure, with Acox, UGT1A1, CYP4A1, malic enzyme and cytochrome P450 oxidoreductase (Por) being increased and Cyp1A1 being decreased. No effects were seen in females. Foreman et al. (2009) reported an increase in Cyp4A10 and acyl-CoA oxidase (ACO) in male mice after PFBA exposure.

163. NTP. (2022b) reported increased expression of Acox1, Cyp4a1, Cyp2b1 and Cyp2b2 in male and Cyp2b1 and Cyp2b2 in female rats following PFHxA exposure.

164. Butenhoff et al. (2012a) reported an increase in mRNA of Acaca, Acox, Cyp4A1, Cyp2B2, Malic, Por, Fasn, Type 1 deiodinase, iodothyronine deiodinase type 1 (Dio1), Ugt 1A1, Ugt 1A6, Ugt 2B and Apolipoprotein (Apo) A1 in male rats following exposure to PFOA and an increase in Acox, Cyp3A1, Malic, Cyp7A1 in females.

165. Guruge et al. (2006) reported changes in the expression of genes involved in transport and metabolisms of fatty acids and lipids, cell communication, adhesion, growth, apoptosis, regulation of hormone, proteolysis and peptidolysis and signal transductionas well as apoptosis, regulation of hormone, metabolisms and G-protein coupled receptor protein signalling pathway in male rats.

166. Li et al. (2019) reported increased the expression of genes related to fatty acid metabolism (Cd36, Acox1, Sterol regulatory element-binding transcription factor 1 (Srebf1) and sterol regulatory element-binding transcription factor 2 (Srebf2), carnitine palmitoyltransferase 1A (Cpt-1A) and ApoB), Cyp2b10, Cyp3a11, Cyp4a10, constitutive androstane receptor (Car) and pregnane X receptor (Pxr), after 2 weeks, Cd36, Peroxisome proliferator-activated receptor (Ppar) -α, Ppar-γ, Cyp2b10, Cyp3a11, Car and Pxr after 8 weeks and Cd36, Fasn, Ppar-γ, Cyp2b10, Cyp3a11, Car and Pxr in male mice.

167. NTP. (2022) also demonstrated an increase in gene expression of Cyp4a1, Cyp2b1 and Cyp2b2 in male rats and Cyp2b1 and Cyp2b2 in females.

168. Son et al. (2008) showed that increased expression of mRNA for TNF-α, IL-1β and transforming growth factor (TGF) -β in the liver only occurred at 50-250 mg/kg bw/day PFOA in male mice. No changes were seen at the LOAEL.

169. PFNA was reported to decrease mRNA of Aldo-Keto Reductase 1C1 (AKR1C1), Ugt 2B15, Cyp2C11, Cyp1A2 and Cyp2B6 in male rats at the highest dose where toxicity was noted (Hadrup et al., 2016). In contrast, NTP. (2022b) reported increased gene expression of Acox1, Cyp4a1, Cyp2b1 and Cyp2b2 in males and female rats.

170. NTP. (2022b) also reported increased gene expression of Acox1, Cyp4a1, Cyp2b1 and Cyp2b2 in males following exposure to PFDA and Acox1, Cyp2b1 and Cyp2b2 in females.

171. Finally, Zhang et al. (2008) reported increased mRNA of PPAR-α/γ, Acox and CypA4 in male rats associated with PFDoDA exposure.

172. In the developmental study, Xu et al. (2022) reported an increase in mRNA of gene related to inflammation including toll-like receptor (Tlr)-4, Myeloid differentiation primary response 88 (Myd88), TNF receptor associated factor 6 (Traf6), IL1-β and Tnf-α following exposure to PFOA

173. For PFSAs, liver-related gene expression was assessed in 11 repeated dose studies, 10 of which (five in both mice and rats) reported changes in liver-related gene expression following exposure with PFBS, PFHxS and PFOS.

174. Bijland et al. (2011) observed changes in gene expression related to lipolysis, fatty acid uptake and transport, fatty acid binding and activation, fatty acid oxidation and very low density lipoprotein (VLDL) assembly in male mice following exposure to PFBS, PFHxS and PFOS.

175. NTP. (2022a) reported increased gene expression of Cyp4a1, Cyp2b1 and Cyp2b2 in males after PFBS, PFHxS and PFOS exposure whereas Cyp2b1, Cyp2b2 and Acox1expression was increased in female rats. Kim et al. (2011) also showed an increase in Cyp4A1 in male rats following exposure to PFOS.

176. Han et al. (2018b) saw increased expression of PCNA, c-Jun, c-MYC and CydD1 in male rats following PFOS exposure whereas a decrease in gene expression of APOA1, APOA2, PEPCK, G6PC was seen in male mice (Huck et al.,

2018).

177. In contrast, no effects were seen in male and female rats following exposure to PFOS (Bagley et al., 2017).