Clinical chemistry

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Aspartate aminotransferase

39. For PFCAs, levels of AST were measured in 23 of the 50 studies reviewed (one of the ten acute studies, 21 of the 37 repeated dose studies and one of the three developmental studies).

40. No effect on AST was reported in the acute study in male rats following exposure to PFOA (Elcombe et al., 2010).

41. In the repeated dose studies, serum AST was only increased in three of the 21 studies, all with PFOA. (Elcombe et al. (2010) reported an increase in male rats following a 28-, but not 7-day, exposure. An increase in AST was also seen in male (Soltani et al., 2023; Zou et al., 2015) and female (Xu et al., 2022) mice.

42. In contrast, no effects were reported following exposure to PFBA for 28 or 90 days (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), PFOA (Butenhoff et al., 2002; Butenhoff et al., 2012a; Elcombe et al., 2010; Guo et al., 2019; Li et al., 2019; NTP., 2022b; Qazi et al., 2010a; Son et al., 2008; Zou et al., 2015), PFNA and PFDA (NTP., 2022b) and PFUnDA (Takahashi et al., 2014).

43. No studies that showed an increase in AST were carried out in both male and female animals so sex differences could not be evaluated.

44. For PFSAs, levels of serum AST were measured in 13 of the 25 studies reviewed (one acute study and 12 of the 25 repeated dose studies).

45. No effect on AST was reported in the acute study in male and female Cynomolgus monkeys following a single exposure to PFOS (Chang et al., 2017).

46. In the repeated dose studies, AST was only increased in two of the 12 studies, both of which reported an increase in male rats following exposure to PFOS (Han et al., 2018b; Kim et al., 2011).

47. In contrast, no effects were reported following exposure to PFBS (Lieder et al., 2009a; NICNAS., 2005; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; Elcombe et al., 2012; Han et al., 2018a; NTP., 2022a).

48. Differences in response were seen between sexes only following exposure to PFOS, where decreases in AST were only seen in male rats (Kim et al., 2011).

Alanine aminotransferase

49. For PFCAs, serum levels of ALT were measured in 25 of the 50 studies reviewed (one of the ten acute studies, 23 of the 37 repeated dose studies and one of the three developmental studies).

50. No effect on ALT was reported in the acute study in male rats following exposure to PFOA (Elcombe et al., 2010).

51. In the repeated dose studies, ALT was only increased in four of the 23 studies. Loveless et al. (2009) reported an increase in male rats following exposure to PFHxA. NTP. (2022b) and Soltani et al. (2023) showed increases in male rats and mice, respectively, following exposure to PFOA and Xu et al. (2022) reported an increase in ALT in female mice in the developmental study.

52. In contrast, no effects were reported following exposure to PFBA for 28 and 90 days (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; NTP., 2022b), PFOA (Botelho et al., 2015; Butenhoff et al., 2002; Butenhoff et al., 2012a; Elcombe et al., 2010; Guo et al., 2019; Li et al., 2019; NTP., 2022b; Qazi et al., 2010a; Son et al., 2008; Zou et al., 2015), PFNA and PFDA (NTP., 2022b), PFUnDA (Takahashi et al., 2014) and PFDoDA (Kato et al., 2014).

53. Differences in response were seen between sexes following exposure to PFHxA (Loveless et al., 2009) and PFOA (NTP., 2022b) where decreases in ALT were only seen in males.

54. For PFSAs, serum levels of ALT were measured in 14 of the 25 studies reviewed (one acute study and 13 of the 25 repeated dose studies).

55. No effect on ALT was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

56. In the repeated dose studies, ALT was increased in two of the 13 studies and was decreased in one study. An increase in ALT was seen male mice following exposure to PFHxS (He et al., 2022) and in male rats with PFOS (Han et al., 2018a), whereas a decrease was seen in female Cynomolgus monkeys after PFOS exposure (Seacat et al., 2002).

57. In contrast, no effects were reported following exposure to PFBS (Lieder et al., 2009a; NICNAS., 2005; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; Han et al., 2018b; NTP., 2022a).

58. Differences in response were seen between sexes only following exposure to PFOS where decreases in ALT were only seen in female monkeys (Seacat et al., 2002).

Alkaline phosphatase

59. For PFCAs, serum levels of ALP were measured in 17 of the 50 studies reviewed (all of which were repeated dose studies).

60. In the repeated dose studies, ALP was increased in five of the 17 studies. Butenhoff et al. (2012a) reported increases in male rats following exposure to PFBA for 28 and 90 days.

61. PFOA increased ALP in male and female rats (NTP., 2022b) and in male mice (Qazi et al., 2010a; Zou et al., 2015) and PFDoDA increased ALP in male mice (Kato et al., 2014).

62. In contrast, no effects were reported following long term exposure to PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), PFOA (Butenhoff et al., 2012a), PFNA and PFDA (NTP., 2022b), PFUnDA (Takahashi et al., 2014) and PFTeDA, PFHxDA and PFPDA (Hirata-Koizumi et al., 2015).

63. Differences in response were seen between sexes following exposure to PFBA (Butenhoff et al., 2012a) and PfDoDA (Kato et al., 2014) where a decrease in ALP was only seen in male rats.

64. For PFSAs, serum levels of ALP were measured in 10 of the 25 studies reviewed (one acute study and nine of the 25 repeated dose studies).

65. No effect on ALP was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

66. In the repeated dose studies, ALP was only increased in female Cynomolgus monkeys following exposure to PFOS (Seacat et al., 2002).

67. In contrast, no effects were reported following long term exposure to PFBS (NICNAS., 2005; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; Elcombe et al., 2012; NTP., 2022a)

68. Differences in response were seen between sexes following exposure to PFOS where increases in ALP were only seen in female monkeys (Seacat et al., 2002).

Triglycerides

69. For PFCAs, serum or plasma TG levels were measured in 15 of the 50 studies reviewed (five of the ten acute studies and 18 of the 37 repeated dose studies).

70. In the acute studies, four of the five studies reported an increase in serum TG. Das et al. (2017) reported an increase with PFOA and PFNA in male mice, and Kawashima et al. (1995) reported an increase with PFOA and PFDA in male rats. No effect was seen in male mice following exposure to PFOA (Elcombe et al., 2010).

71. In the repeated dose studies, TG was decreased in five of the 18 studies. Elcombe et al. (2010) reported a decrease in male rats following a 7- and 28-day exposure to PFOA in male rats. A decrease was also reported by NTP. (2022b) in male rats and by Qazi et al. (2010a) in male mice. In contrast, Wu et al. (2018) reported an increase in TG in male mice following PFOA exposure. PFNA also decreased TG in male rats (NTP., 2022b).

72. In contrast, no effects were reported following exposure to PFBA for 28 or 90 days (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; NTP., 2022b), PFOA (Botelho et al., 2015; Butenhoff et al., 2012a), PFDA (NTP., 2022b), PFDoDA (Kato et al., 2014; Zhang et al., 2008), PFTeDA and PFHxDA (Hirata-Koizumi et al., 2015) and PFODA (Hirata-Koizumi et al., 2012).

73. Differences in response were seen between sexes following exposure to PFOA and PFNA (NTP., 2022b) where a decrease in TG was only seen in male rats.

74. For PFSAs, serum or plasma TG levels were measured in 16 of the 25 studies reviewed (one acute study and 15 of the 25 repeated dose studies) and hepatic TG levels were measured in seven repeated dose studies.

75. No effect on TG was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

76. In the repeated dose studies, serum or plasma TG was decreased in four of the 15 studies and increased in one study. A decrease in TG was seen in male mice after exposure to PFBS, PFHxS and PFOS (Bijland et al., 2011) and in male rats with PFOS (Kim et al., 2011), whereas an increase was seen in male Cynomolgus monkeys after PFOS exposure (Seacat et al., 2002).

77. Hepatic TG was increased in male mice following exposure to PFHxS (Bijland et al., 2011; Das et al., 2017; He et al., 2022) and PFOS (Bijland et al., 2011; Chen et al., 2022)

78. In contrast, no effects were reported following exposure to PFBS (Bijland et al., 2011; Chen et al., 2022; Lieder et al., 2009a; NICNAS., 2005; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; Elcombe et al., 2012; Huck et al., 2018; NTP., 2022a).

79. Differences in response were seen between sexes following exposure to PFOS where a decrease in TG was only seen in male rats (Kim et al., 2011) and an increase was seen in male Cynomolgus monkeys (Seacat et al., 2002).

Cholesterol

80. For PFCAs, serum total cholesterol levels were measured in 22 of the 50 studies reviewed (three of the ten acute studies and 19 of the 37 repeated dose studies).

81. No effect on cholesterol was reported in the acute study in male rats following exposure to PFOA (Elcombe et al., 2010; Kawashima et al., 1995) or PFDA (Kawashima et al., 1995).

82. In the repeated dose studies, cholesterol was decreased in 11 of the 19 studies.

83. A decrease was reported in male rats following exposure to PFBA for 28 days (Butenhoff et al., 2012a), in male rats (Chengelis et al., 2009; NTP., 2022b) after exposure to PFHxA, in male rats following exposure to PFOA (Elcombe et al., 2010; NTP., 2022b; Qazi et al., 2010a), and in male rats PFNA and PFDA (NTP., 2022b). Takahashi et al. (2014) also reported decreases cholesterol in male and female rats following exposure to PFUnDA and Kato et al. (2014) noted decreases in male rats with PFDoDA.

84. In contrast, no effects were reported following exposure to PFBA for 90 days (Butenhoff et al., 2012a), PFHxA (Loveless et al., 2009), PFOA (Butenhoff et al., 2002; Butenhoff et al., 2012a), PFDoDA (Zhang et al., 2008), PFTeDA and PFHxDA (Hirata-Koizumi et al., 2015) and PFODA (Hirata-Koizumi et al., 2012).

85. Differences in response were seen between sexes following exposure to PFBA (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; NTP., 2022b), PFOA,

PFNA and PFDA (NTP., 2022b), and PFDoDA (Kato et al., 2014), where a decrease in cholesterol was only seen in male rats.

86. For PFSAs, serum total cholesterol levels were measured in 14 of the 25 studies reviewed (one acute study and 13 of the 25 repeated dose studies).

87. No effect on cholesterol was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

88. In the repeated dose studies, cholesterol was decreased in seven of the 13 studies and increased in one study. NTP. (2022a) reported an increase in male rats following exposure to PFBS. In contrast, a decrease was observed in male mice (Bijland et al., 2011) and rats (Butenhoff et al., 2009; NTP., 2022a) following exposure to PFHxS, and in female rats (Butenhoff et al., 2012b), male rats (Elcombe et al., 2012; NTP., 2022a) and male and female Cynomolgus monkeys following exposure to PFOS (Seacat et al., 2002).

89. Plasma non-high-density lipoprotein (HDL) and HDL cholesterol were decreased in male mice following exposure to PFHxS and PFOS (Bijland et al., 2011).

90. In contrast, no effects were reported following exposure to PFBS (Bijland et al., 2011).

91. Sex differences were seen following exposure to PFBS, PFHxS and PFOS (NTP., 2022a) and PFOS (Butenhoff et al., 2012b) where an increase in cholesterol was seen in males with PFBS and a decrease was seen in males with PFHxS and PFOS.

Total protein

92. For PFCAs, serum TP levels were measured in 16 of the 50 studies reviewed (all of which were repeated dose studies.

93. In the repeated dose studies, TP was decreased in three of the 16 studies and increased in two studies.

94. A decrease was reported in male rats following exposure to PFBA for 90 days (Butenhoff et al., 2012a) and in male and female rats following exposure to PFNA and PFDA (NTP., 2022b), whereas PFOA increased TP in male mice (Guo et al., 2019) and male rats (NTP., 2022b).

95. In contrast, no effects were reported following exposure to PFBA for 28 days (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), PFOA (Butenhoff et al., 2002; Butenhoff et al., 2012a), PFUnDA (Takahashi et al., 2014), PFDoDA (Kato et al., 2014), PFTeDA and PFHxDA (Hirata-Koizumi et al., 2015) and PFODA (Hirata-Koizumi et al., 2012).

96. Differences in response were seen between sexes following exposure to PFBA (Butenhoff et al., 2012a), where a decrease in cholesterol was only seen in male rats.

97. For PFSAs, serum TP levels were measured in eight of the 25 studies reviewed (one acute study and seven of the 25 repeated dose studies).

98. No effect on TP was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

99. In the repeated dose studies, TP was increased in two of the seven studies in male (NTP., 2022a) and female (NICNAS., 2005) rats following exposure to PFBS.

100. In contrast, no effects were reported following exposure to PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) or PFOS (Butenhoff et al., 2012b; NTP., 2022a).

101. Differences in response were seen between sexes in both studies with PFBS as NTP. (2022a) reported an increase in TP in males but not females, but NICNAS. (2005) reported increases in females but not males.

Bilirubin

102. For PFCAs, serum bilirubin levels were measured in 12 of the 50 studies reviewed (all of which were repeated dose studies).

103. In the repeated dose studies, bilirubin was decreased in one of the 12 studies and increased in one study.

104. A decrease was reported in male and female rats following exposure to PFBA for 90 days (Butenhoff et al., 2012a) but increased in male and female Cynomolgus monkeys following exposure to PFOA (Butenhoff et al., 2002).

105. In contrast, no effects were reported following exposure to PFBA for 28 days (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; Loveless et al.,

2009; NTP., 2022b), PFOA (Butenhoff et al., 2012a; NTP., 2022b), PFNA and PFDA (NTP., 2022b), PFUnDA (Takahashi et al., 2014) and PFDoDA (Kato et al., 2014).

106. No differences in response were seen between sexes as effects were seen in both male and female rats with PFBA (Butenhoff et al., 2012a) and Cynomolgus monkeys with PFOA (Butenhoff et al., 2002).

107. For PFSAs, serum bilirubin levels were measured in 10 of the 25 studies reviewed (one acute study and nine of the 25 repeated dose studies).

108. No effect on bilirubin levels was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

109. In the repeated dose studies, bilirubin was decreased in one of the 12 studies, in male Cynomolgus monkeys following exposure to PFOS (Seacat et al., 2002).

110. In contrast, no effects were reported following exposure to PFBS (Lieder et al., 2009a; NICNAS., 2005; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; NTP., 2022a).

111. Differences in response were seen between sexes following exposure to PFOS where decreases in bilirubin were only seen in male Cynomolgus monkeys (Seacat et al., 2002).

Albumin

112. For PFCAs, serum albumin levels were measured in 17 of the 50 studies reviewed (all of which were repeated dose studies).

113. In the repeated dose studies, albumin was increased in one study in male mice following exposure to PFOA (Guo et al., 2019).

114. In contrast, no effects were reported following exposure to PFBA for 28 or 90 days (Butenhoff et al., 2012a), PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), PFOA (Butenhoff et al., 2002; Butenhoff et al., 2012a; NTP., 2022b), PFNA and PFDA (Kennedy Jr, 1987; NTP., 2022b), PFDA (NTP., 2022b), PFUnDA (Takahashi et al., 2014), PFDoDA (Kato et al., 2014), PFTeDA and PFHxDA (Hirata-Koizumi et al., 2015) and PFODA (Hirata-Koizumi et al., 2012).

115. No studies that showed an increase in albumin were carried out in both male and female animals so sex differences could not be evaluated.

116. For PFSAs, serum albumin levels were measured in nine of the 25 studies reviewed (one acute study and eight of the 25 repeated dose studies).

117. No effect on albumin levels was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

118. In the repeated dose studies, albumin was increased in one of the eight studies in which a decrease was reported in female rats following exposure to PFBS for 90 days (NICNAS., 2005).

119. In contrast, no effects were reported following exposure to PFBS (Lieder et al., 2009a; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; NTP., 2022a).

120. Differences in response were seen between sexes following exposure to PFBS where increases in albumin were only seen in female mice (NICNAS., 2005).

Globulin

121. For PFCAs, serum globulin levels were measured in 9 of the 50 studies reviewed (all of which were repeated dose studies).

122. In the repeated dose studies, globulin was decreased in two of the nine studies and increased in two studies.

123. A decrease was reported in male and female rats following exposure to PFNA but only in males treated with PFDA (NTP., 2022b), but increased in male rats (NTP., 2022b) and male mice (Guo et al., 2019) following exposure to PFOA.

124. In contrast, no effects were reported following long term exposure to PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), and PFOA (Butenhoff et al., 2002).

125. Differences in response were seen between sexes following exposure to PFOA and PFDA (NTP., 2022b), where the changes in globulin were only seen in male rats.

126. For PFSAs, serum globulin levels were measured in nine of the 25 studies reviewed (one acute study and eight of the 25 repeated dose studies).

127. No effect on globulin levels was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

128. In the repeated dose studies, globulin was increased in one of the eight studies in which a decrease was reported in male rats following exposure to PFBS (NTP., 2022a).

129. In contrast, no effects were reported following exposure to PFBS (Lieder et al., 2009a; NICNAS., 2005), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (Butenhoff et al., 2012b; NTP., 2022a).

130. Differences in response were seen between sexes following exposure to PFBS where increases in albumin were only seen in male rats (NTP., 2022a).

Albumin/globulin ratio

131. For PFCAs, serum albumin/globulin ratio was measured in 11 of the 50 studies reviewed (all of which were repeated dose studies).

132. In the repeated dose studies, albumin/globulin ratio was decreased in three of the 11 studies and increased in two studies.

133. An increase was reported in male and female rats following exposure to PFDA (NTP., 2022b) and PFUnDA (Takahashi et al., 2014). In contrast, NTP. (2022b) reported an increase in male and female rats with PFNA and in male rats with PFOA, and Kato et al. (2014) noted an increase in female rats with PFDoDA.

134. In contrast, no effects were reported following long term exposure to PFHxA (Chengelis et al., 2009; Loveless et al., 2009; NTP., 2022b), PFTeDA and PFHxDA (Hirata-Koizumi et al., 2015) and PFODA (Hirata-Koizumi et al., 2012).

135. Differences in response were seen between sexes following exposure to PFOA (NTP., 2022), and PFDoDA (Kato et al., 2014), where increases in albumin/globulin ratio were only seen in male and female rats, respectively.

136. For PFSAs, serum albumin/globulin ratios were measured in eight of the 27 studies reviewed (one acute study and seven of the 25 repeated dose studies).

137. No effect on albumin/globulin ratio was reported in the acute study in male or female Cynomolgus monkeys following exposure to PFOS (Chang et al., 2017).

138. No effects were also reported in the repeat dose toxicity studies with PFBS (Lieder et al., 2009a; NICNAS., 2005; NTP., 2022a), PFHxS (Butenhoff et al., 2009; Chang et al., 2018; NTP., 2022a) and PFOS (NTP., 2022a).

Other endpoints

139. An increase in serum thiobarbituricacid (TBA), tumour necrosis factor (TNF)-α, interleukin (IL)-6, but not cholinesterase (CHE) was in male rats following exposure to PFOS (Han et al., 2018a; Han et al., 2018b).

140. PFOS decreased serum levels of SBA in male but not female Cynomolgus monkeys, decreased CK in males, increased CK in females and decreased sorbitol dehydrogenase (SDH) in male and females following exposure to PFOS (Seacat et al., 2002).

Recovery

141. Following the 28-day exposure to PFBA and a 3-week recovery period, cholesterol levels were comparable to controls in male rats although TP increased after the 3-week recovery period. No other parameters were measured after recovery. Similar results were seen following the 90-exposure where all parameters observed after treatment (TP, bilirubin) were comparable to controls after recovery (Butenhoff et al., 2012a).

142. Similar results were seen following the 7-day exposure to PFOS where all parameters observed after 1, 28 or 56 days after treatment were comparable to controls after 84 days (Elcombe et al., 2012). Seacat et al. (2002) also reported that changes to levels of cholesterol and histopathological changes seen at the end of exposure were comparable to controls after a one-year recovery period.