PFCAs

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PFHxA

In vivo toxicity data

Loveless *et al*. 2009

160. Loveless *et al*. (2009) investigated the effects of sodium perfluorohexanoate (NaPFHxA) on thyroid weight and histopathology. In the main study, adult Crl:Cd Sprague Dawley (SD) rats (10/sex/group) were administered NaPFHxA daily by gavage at doses of 0, 20, 100, or 500 mg/kg bw/day for 92 days (males) or 93 days (females). Two further groups (10/sex/group) were designated for either a 90-day recovery (0, 20, 100, or 500 mg/kg bw/day) or 30-day recovery (0 and 500 mg/kg bw/day). This study conformed to the OECD Guideline 408 (Repeated Dose 90 Day Oral Toxicity Study in Rodents).

161. Mortality: No deaths were attributed to treatment.

162. General toxicity and body weight: No clinical signs of general toxicity were observed. Mean body weight was significantly decreased from day 42 to 105 in male rats treated with 500 mg/kg bw/day with a 90-day recovery period, compared with controls with the same recovery period. No treatment-related effects on either body weight or body weight gain were observed in any female group, or males from the main study or 30-day recovery. Terminal weights of males and females at the end of either a 30- or 90-day recovery (i.e, day 122-123 or 182-183, respectively) were unaffected.

163. Gross pathology: Thyroid weights were significantly increased in female rats treated with 500 mg/kg bw/day following the 30-day recovery period, compared with controls with the same recovery period. There were no significant changes observed in females in either the main study or 90-day recovery group, or in males at any time point or dose.

164. Histopathology: In the main study, minimal hypertrophy of the thyroid follicular epithelium was observed in both male and female rats exposed to 500 mg/kg bw/day, and one male rat exposed to 100 mg/kg bw/day. In the 30-day recovery group, minimal hypertrophy of the thyroid follicular epithelium was present in males and females exposed to 500 mg/kg bw/day. In the 90- day recovery group, minimal hypertrophy of the thyroid follicular epithelium was only observed in males exposed to 500 mg/kg bw/day.

165. Authors noted that since hypertrophy of the thyroid follicular epithelium was present primarily in rats exposed to 500 mg/ kg bw/day in the main study and in the 30- and 90-day recovery groups, the increased thyroid weights observed in females in the 30-day recovery group may be adverse and treatment related. Thyroid follicular cell hypertrophy was also potentially adverse albeit minimal and likely to be secondary and related to liver hypertrophy and induction of metabolic liver enzymes, which were also seen at 500 mg/kg bw/day. The authors also commented this response may not be relevant to non-rodent species.

166. The authors concluded that the administration of NaPFHxA by gavage for approximately 90 days was associated with adverse changes at 500 mg/kg bw/day that included thyroid pathology.

NTP, 2022a

167. The National Toxicology Program (NTP, 2022a) investigated the effects of PFHxA on thyroid weight, histopathology and TH levels in rats. In a

repeated dose study, SD rats (10/sex/group) were administered PFHxA at doses 0, 62.6, 125, 250, 500 or 1000 mg/kg bw/day with half the dose being administered twice daily by gavage for 28 days. At necropsy on day 29, blood samples were collected for TT4, TT3, FT4, TSH and PFHxA analysis, and thyroids were removed for histopathological evaluation.

168. Mortality: All rats survived to scheduled necropsy.

169. General toxicity and body weight: No clinical signs of general toxicity were observed. In males, terminal body weights were significantly reduced at 1000 mg/kg bw/day, compared with controls. In females, terminal body weights were unaffected by treatment.

170. Gross pathology: Thyroid weights in males and females were unaffected by treatment.

171. Histopathology: Histopathology in males and females was unaffected by treatment.

172. Thyroid hormone levels: In males, TT4, FT4 and TT3 levels were significantly decreased at ≥ 62.6 mg/kg bw/day compared with controls. TSH was unaffected by treatment. No effects were seen in females.

173. Plasma PFHxA concentrations: In males, mean plasma PFHxA concentrations were 0.378 µg/mL (62.6 mg/kg bw/day), 0.503 µg/mL (125 mg/kg bw/day), 1.297 µg/mL (250 mg/kg bw/day), 3.339 µg/mL (500 mg/kg bw/day) and 10.899 µg/mL (1000 mg/kg bw/day). In females, mean plasma PFHxA concentrations were 0.129 µg/mL (62.6 mg/kg bw/day), 0.292 µg/mL (125 mg/kg bw/day), 0.475 µg/mL (250 mg/kg bw/day), 1.668 µg/mL (500 mg/kg bw/day) and 6.712 µg/mL (1000 mg/kg bw/day). No PFHxA was seen in controls.

174. Overall TT4 and FT4 were decreased (males only), while TSH was unaffected in males or females. There were no histopathologic changes in the thyroid gland.