PFDA

In this guide

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In vivo toxicity data

Langley and Pilcher, 1985

196. Langley and Pilcher (1985) investigated the effect of perfluorodecanoic acid (PFDA) on TH levels in rats. Male Wistar rats (30/group) received a single intraperitoneal (i.p.) injection of 75 mg/kg bw PFDA. A control group of weight-matched rats received a single injection of vehicle 24 hours after treatment and was subsequently pair-fed with the PFDA treated group (called thereafter pair-fed controls). A further control group of eight rats were fed ad libitum (ad libitum controls). Groups of five rats (PFDA-treated or pair-fed) were sacrificed beginning 12 hours after treatment and thereafter at 1, 2, 4, 6 and 8 days. Blood was collected and TT4 and TT3 levels were measured. Control rats fed ad libitum were sacrificed on days 0, 1 and 2.

197. Body weight: The average body weight of PFDA-treated rats reduced over 8 days of treatment (statistical significance not determined). A similar trend was observed in the pair-fed control rats.

198. Thyroid hormone levels: TT4 levels were significantly reduced compared with pair-fed and ad libitum controls at all timepoints, reaching a minimum concentration at 2 days post-treatment. TT3 levels were significantly lower than pair-fed controls at 12 hours, 1 day and 2 days. After 2 days, serum TT3 levels were similar to pair-fed controls. The authors proposed that the TT4 findings in pair-fed controls indicate the depression in thyroid hormones in PFDA treated animals was not the result of reduced feed intake.

199. The authors concluded that following 4 days of pair-feeding, TT3 values were at the same level as that produced by PFDA treatment; however, TT4 levels in PFDA-treated rats were significantly lower than in those pair-fed throughout the study. These data indicate that the depression of thyroid hormones levels produced by PFDA is not solely a result of starvation.

200. NTP (2022a) investigated the effects of PFDA on thyroid weight, histopathology and TH levels in rats. In a repeated dose study, SD rats (10/sex/group) were administered PFDA at doses 0, 0.156, 0.312, 0.625, 1.25, or 2.5 mg/kg bw/day by gavage for 28 days. At necropsy on day 29, blood samples were collected for TT4, TT3, FT4, TSH and PFDA analysis, and thyroids were removed for histopathological evaluation.

201. Mortality: All rats survived to scheduled necropsy.

202. General toxicity and body weight: No clinical signs of general toxicity were observed. In males and females, terminal body weights were significantly reduced at 1.25 and 2.5 mg/kg bw/day, compared with controls.

203. Gross pathology: In males, relative thyroid weight:body weight was significantly increased at 1.25 and 2.5 mg/kg bw/day, compared with controls. Thyroid weights were unaffected by treatment. In females, thyroid weights were significantly increased at 0.312 mg/kg bw/day, 0.625 mg/kg bw/day and 1.25 mg/kg bw/day, and relative thyroid weight:body weight was significantly increased at ≥0.312 mg/kg bw/day.

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

205. Thyroid hormone levels: In males, TT4 levels were significantly decreased at 0.312 mg/kg bw/day, and FT4 levels were significantly decreased at ≥ 0.312 mg/kg bw/day, compared with controls. TT3 and TSH levels were unaffected by treatment. In females, FT4 and TT3 levels were significantly decreased at 1.25 and 2.5 mg/kg bw/day, respectively, and TT4 and TSH levels

were unaffected by treatment.

206. Plasma PFDA concentrations: In males, mean plasma PFDA concentrations on day 29 were 0.022 µg/mL (control), 8.505 µg/mL (0.156 mg/kg bw/day), 23.030 µg/mL (0.312 mg/kg bw/day), 42.720 µg/mL (0.625 mg/kg bw/day), 101.580 µg/mL (1.25 mg/kg bw/day) and 259.400 µg/mL (2.5 mg/kg bw/day). In females, concentrations were 0.042 (control), 11.208 µg/mL (0.156 mg/kg bw/day), 25.700 µg/mL (0.312 mg/kg bw/day), 50.290 µg/mL (0.625 mg/kg bw/day), 117.150 µg/mL (1.25 mg/kg bw/day) and 246.875 µg/mL (2.5 mg/kg bw/day).

207. The authors concluded that FT4 was decreased, and TT4 was decreased in males only. TSH was unaffected and there were no histopathologic changes in the thyroid gland.

Van Rafelghem *et al*. 1987

208. Van Rafelghem *et al*. (1987) investigated the effect of PFDA on thyroid hormone levels and thyroid histology in rats. Adult male SD rats (8 – 16/group) received a single i.p. injection of 20, 40 or 80 mg/kg bw PFDA on Day 0. Two controls groups were used both receiving a single injection of the vehicle. One control group was pair-fed whilst the other was allowed to feed ad libitum. Body weights and feed intake were measured daily for 7 days following treatment.

209. Eight rats were sacrificed from each group on Day 7 after dosing. Blood was collected for thyroid hormone level analysis and thyroid glands for histopathological assessment. Free thyroxine index (FTI) was calculated as the product of the TT4 concentration and T3 uptake.

210. General toxicity and body weight: PFDA treatment resulted in a dose-dependent reduction in body weight and cumulative feed intake over the 7-day period. Both were significantly reduced at doses of 40 and 80 mg/kg bw when compared with ad libitum controls but were unaffected compared with pair-fed controls.

211. Gross pathology: Thyroid gland weights were significantly reduced in the 80 mg/kg bw group compared with ad libitum controls and pair-fed controls. Pair feeding with the 80 mg/kg bw treated group also significantly reduced thyroid weights, compared with ad libitum controls, leading the authors to propose that the reduced thyroid weight in treated rats was partly attributed to hypophagia (reduced ingestion of food).

212. Histopathology: There were no histological changes attributed to treatment.

213. Thyroid hormone levels: Treatment with PFDA significantly decreased TT4 levels in a dose-dependent manner from 20 mg/kg bw, compared with both pair-fed and ad libitum controls. Controls that were pair-fed with the 80 mg/kg bw treated group also showed a significantly reduced TT4 level compared with ad libitum controls. TT3 levels in PFDA-treated rats were unaffected compared with ad libitum controls at 80 mg/kg bw, whereas controls that were pair-fed with the 80 mg/kg bw treated group had significantly reduced TT3 levels. T3 uptake was significantly reduced at 80 mg/kg bw, compared with ad libitum controls, however no effects were seen in pair-fed controls. The authors state the treatment-related effects on FTI were similar to those for TT4 (data not provided).

214. The authors concluded that reductions in TT4 concentration and FTI at a low dose of PFDA (20 mg/kg bw) indicate that PFDA-induced hypothyroxinemia can be dissociated from its overtly toxic effects (i.e., severe hypophagia and body weight loss) observed at higher doses. Although PFDA caused a dose-dependent decrease in thyroid gland weight (not completely paralleled by pair feeding), thyroid histology was unremarkable. These results suggest that despite alterations in plasma thyroid hormone levels there is no consistent pattern of effects on functional thyroid status which could explain the overt toxicity of PFDA.

Table 1 *In vivo* thyroid toxicity effects following acute exposure to PFSAs

*Derived by contractor; NR – not reported; NA – not applicable.

Substance	Species / sex / number	Dose / route of administration / duration (mg/kg bw)	Serum concentration (µg/mL)	Observed effects at LOAEL	Published NOAEL / LOAEL (mg/kg bw)	Referenc

PFOS (potassium salt).	SD rats / female / 5 – 15/group.	15 / gavage / single dose.	At 15 mg/kg bw 37.28 ± 8.49 at 2 hours 66.90 ± 9.00 at 6 hours 61.58 ± 8.81 at 24 hours.	Serum ↑ FT4 at 2 – 6 hrs but not at 24hrs ↓ TSH at 2 – 6 hrs ↓ TT4 at 2 – 24 hrs. Liver ↑ ME mRNA at 2 hrs ↑ ME activity at 24 hrs ↑ UGT1A mRNA at 2 – 6 hrs.	NA / 15.	Chang *et al*. (2008)
PFOS (potassium salt).	SD rats / male and female / 4/group (male), 5/group (female).	15 / gavage / single dose.	NR.	↓ TT4 at 24 hrs) ↓ ^{125}I in serum and liver) ↑ ^{125}I in urine and faeces).	NA / 15*.	Chang *et al*. (2008)
PFOS (potassium salt).	Cynomolgus monkeys / male and female / 6/group.	Group 1: 0 or 9 / gavage / single dose on day	At 9 mg/kg bw on day 113. 67.7 ± 7.5 in males 68.8 ± 2.5 in Females.	No adverse effects on thyroid status.	9 / NA*.	Chang *et al*. (2017)

PFOS (potassium salt).	Cynomolgus monkeys / male and female / 4-6/sex/dose.	0, 14, 14.8 / 17.2 (male/female) and 11 / gavage / single doses on day 43, day 288 and day 358 followed by 62 days recovery.	At 14 mg/kg bw/day on day 50 104.8 ± 502 in males 96.5 ± 6.2 in Females. At 14.8/17.2 bw/day on day 288 141.0 ± 13.1 in males 147.6 ± 17.5 in Females. At 11 mg/kg bw on day 365 160.8 ± 14.2 in Males 165.0 ± 6.7 in Females.	No adverse effects on thyroid status ↓ TT4 but values within normal Range.	Males: NA / 13.3 (average dose) Females: NA / 14.	Chang *et al*. (2017).

Table 2 *In vivo* thyroid toxicity effects following acute exposure to PFCAs

*Derived by contractor; NR – not reported; NA – not applicable.

Substance	Species / sex / number	Dose / route of administration / duration (mg/kg bw)	Serum concentration (µg/mL)	Observed effects at LOAEL	Published NOAEL / LOAEL (mg/kg bw)	Reference
				↓ TT4		
PFDA	Wistar rats / male / 30/group.	75 / i.p. / single dose.	NR.	↓ TT3 (transient ≤ 2 days) ↓ Body weight (BW).	NA / 75*.	Langley and Pilcher (1985).
PFDA	SD rats / male / 8 – 16/group.	0, 20, 40 or 80 / i.p. / single dose.	NR.	↓ TT4 ↓ FTI.	NA / 20*.	Van Rafelghem *et al*. (1987).

Table 3 *In vivo* thyroid toxicity effects following repeated exposure to PFSAs

*Derived by contractor; ** calculated according to EFSA. (2012); NR – not reported; NA – not applicable.

Substance	Species / sex / number / study type	Dose / route of administration / duration (mg/kg bw)	Serum concentration (µg/mL)	Observed effects at LOAEL	Published NOAEL / LOAEL (mg/kg bw)	Ref

PFBS (potassium salt).	ICR mice / female / 10/group / developmental study.	0, 50, 200 or 500 / gavage / GD1 – 20.	At 50 mg/kg bw/day Maternal serum: 0.074 ± 0.022. At 200 mg/kg bw/day Maternal serum: 0.332 ± 0.053.	Maternal: ↓ TT4, TT3 and FT4 ↑ TSH. Offspring: ↓ BW in females at all ages ↓ TT4 and TT3 in all ages ↑ TSH on PND30 ↑ Trh mRNA in hypothalamus on PND30.	Maternal: 50 / 200. Offspring: 50 / 200.	Fen (20
PFBS	SD rats / male and female / 10/group / repeated dose study.	0, 62.6, 125, 250,500 or 1000 / gavage / 28 days.	At 62.6 mg/kg bw/day Plasma:2.222 ± 0.477 in males 0.154 ± 0.048 in Females.	↓ TT4, FT4 and TT3.	NA / 62.6.	NTP (20
PFHxS (potassium salt).	SD rat / male and female / 15/sex/group / developmental study.	0, 0.3, 1, 3 or 10 / gavage / day 1 – day 43 (males); day 1 – PND21 or GD25 (females).	At 1 mg/kg bw/day on day 42 Serum: 89.1 ±0.80 in males. At 3 mg/kg bw/day on day 42 Serum: 128.67 ± 10.30 in males.	↑ Hyperplasia of thyroid follicular cells in males.	1 / 3.	But *et a* (20

PFHxS (potassium salt).	Long-Evans rats / female / 6 – 9/group / developmental study.	0 or 50 / gavage / GD6 - PND21.	NR	Maternal: ↓ TT4, TT3 and FT4. Offspring: ↓ TT4, TT3 and FT4↓ TT4 in brain tissue (PN 0 only).	Maternal: NA / 50*.- Offspring: NA / 50*.	Gilb *al*.
PFHxS (potassium salt).	SD rats / male and female / 10/group / repeated dose study.	0, 0.625, 1.25, 2.5, 5 or 10 (males), 0, 3.12, 6.25, 12.5, 25 or 50 (females) / gavage / 28 days.	At 0.625 mg/kg bw/day Plasma: 66.76 ± 3.518 in Males.	↓ TT4, FT4 and TT3 in males.	NA / 0.625*.	NTP (20
PFHxS (potassium salt).	Wistar rats / female / 8/group / developmental study.	0, 25 or 45 / gavage / GD7 – PND22.	At 25 mg/kg bw/day Maternal serum: 139 on PND22 (SD not given).	Maternal and offspring: ↓TT4.	Maternal: ND / 25. Offspring: ND / 25.	Ran *al*.
PFHxS (potassium salt).	Wistar rats / female / 16 – 20/group / developmental Study.	0, 0.05, 5 or 25 / gavage / GD7 – PND22.	NR	Maternal and offspring: ↓TT4.	0.05 / 5.	Ran *al*.

PFHxS (potassium salt).	Wistar rats / female / 16 – 20/group / developmental study.	0, 0.05, 5 or 25 /gavage / GD7 – PND22.	NR	Maternal ↓TT3. Offspring: ↓ Thyroid weight in females.	Maternal: 5* / 25*. Offspring: 0.05* / 5*.	Ran *al*. (
PFOS (potassium salt).	SD rats / male and female / 60 – 70/dose / repeated dose study.	0, 0.5, 2, 5 or 20 ppm equivalent to 0, 0.024, 0.098, 0.242, 0.984 or 1.144 (recovery group) (males) or 0, 0.029, 0.120, 0.299, 1.251 or 1.385 (recovery group) (females) / diet / 104 Weeks.	At 0.984 mg/kg bw/day Serum: 69.3 ± 0.351 in Males.	No adverse effects on thyroid status.	0.984* / NA.	But *et a* (20
PFOS (potassium salt).	SD rats / male / 6/group / repeated dose Study.	0 or 3 / gavage / 7 days.	NR	↓ TT4 and TT3.	NA / 3*.	Cha . (2

PFOS (potassium salt).	SD rats / female / 25/group / developmental study.	0, 0.1, 0.3 and 1.0 / gavage / GD0 - PND20.	NR	Maternal: No adverse effects on thyroid status ↓ BW. Offspring: Possible effect on thyroid epithelial cells in females on GD20.	Maternal: 1.0* / NA. Offspring: NA / 1.0.	Cha . (2
PFOS (potassium salt).	SD rats / female / 5/dose / repeated dose study.	0, 0.1, 0.3, 1, 2 / gavage / GD8 – PND2.	At 0.1 mg/kg bw/day on PND2 Serum: 2.2 ± 0.1.	Maternal: ↓ TT4 on PND2. Offspring: ↓ TT4 on PND2.	Maternal: NA / 0.1*. Offspring: NA/ 0.3*.	Cor *al*.
PFOS	SD rats / male and female /	0, 2, 20, 50 or 100 ppm	At 0.14 mg/kg bw/day in males	↓ TT4.	Males: 0.14 / 1.33.	Cur *al*.

(potassium salt).	20/group / repeated dose study.	equivalent to 0,0.14, 1.33, 3.21 or 6.3 (males) and 0, 0.15, 1.43, 3.73 or 7.58 (females) / diet / 28 days.	Serum: 0.95 ± 0.13. At 1.33 mg/kg bw/day in males Serum: 13.45 ± 1. 48. At 0.15 mg/kg bw/day in females Serum: 1.50 ± 0.23. At 1.43 mg/kg bw/day in females Serum: 15.40 ± 0.56.	N/A	Females: 0.15 / 1.43.	N/A
PFOS (potassium salt).	SD rats / male / 40/group / repeated dose study.	0, 20 or 100 ppm equivalent to 1.93 or 9.65 / diet / 7 days.	At 1.93 mg/kg bw/day Serum: 39.49 ± 7.76 on day 1 15.49 ± 1.60 on day 28 8.03 ± 1.14 on day 56 4.38 ± 0.72 on day 84.	No adverse effects on thyroid status ↓ BW.	NA / 1.93*.	Elco *al*. (
PFOS (potassium salt).	SD rats / female / 17 – 28/group / developmental Study.	0, 1, 2, 3, 5 or 10 / gavage / GD2- GD21.	NR	Offspring: ↓ TT4 and FT4.	Offspring NA / 1*.	Lau (20

PFOS (potassium salt).	CD-1 mice / female / 21 – 22/group / developmental Study.	0, 1, 5, 10, 15 or 20 / gavage / GD1 – GD17.	NR	Offspring: No adverse effects on thyroid hormones Mortality.	Offspring: NA / 15*.	Lau (20
PFOS (potassium salt).	SD rats / female / 20/group / two generation reproductive Study.	0, 0.4, 0.8, 1.0, 1.2, 1.6 or 2.0 / gavage / 42 days prior to mating through to PND4.	NR	Maternal: ↓ TT4. Offspring: ↓ TT4 and TT3.	Maternal: NA / 0.4. Offspring: 0.8* / 1.0*.	Lue *al*.
PFOS	SD rats / male and female / 10/group / repeated dose study.	0, 0.312, 0.625, 1.25, 2.5 or 5 / gavage / 28 days.	At 0.312 mg/kg bw/day. Mean plasma: 23.73 ± 1.114 in Males. 30.53 ± 0.918 in Females.	↓ TT4 and FT4.	NA / 0.312.	NTP (20

PFOS (potassium salt).	Cynomolgus monkeys / male and female / 4-6/group / repeated dose study.	0, 0.03, 0.15 or 0.75 / gavage / 182 days.	At 0.75 mg/kg bw/day on day 183. Serum: 173 ± 37 in males 171 ± 22 in Females. At 0.15 mg/kg bw/day on day 183. Serum: 82.6 ± 25.2 in males 66.8 ± 10.8 in Females.	↓ TT3 and FT3 ↑ TSH ↓ BW gain. ↑ Mortality.	0.15 / 0.75.	Sea *al*.
PFOS (potassium salt).	SD rats / female / 25 – 50/group / developmental Study.	0, 1, 2, 3, 5 or 10 / gavage / GD2 – GD20.	ND	↓ TT4 and FT4 on GD7 – 21 ↓ T3 on GD21.	NA / 1.	Thil *et a* (20
PFOS (potassium salt).	SD rats / female / 6 – 8 /group / repeated dose.	0, 3, 5 / gavage / 20 days.	ND	↓ TT4 and FT4 on day 3 – 20 ↓ T3 on day 7 – 20 ↑ TSH on day 7.	NA / 3*.	Thil *et a* (20
PFOS (potassium salt).	CD mice / female / 60 – 80/group / developmental study.	0, 1, 5, 10, 15 or 20 / gavage / GD1 – GD17.	At 10 mg/kg bw/day on GD18 Maternal serum: 190 ± 7.	↓ TT4 on GD6.	15 / 20.	Thil *et a* (20

PFOS (potassium salt).	Wistar rats / female / 3 – 9/group / developmental study.	0, 3.2 and 32 mg/kg diet equivalent to 0.38 and 3.8** / diet / GD1 – PND14.	At 0.38 mg/kg bw/day Maternal serum: 2.29 ± 0.15 on PND1 4.16 ± 0.04 on PND7 3.15 ± 0.21 on PND14. Offspring serum: 5.85 ± 0.33 on PND1 3.65 ±0.23 on PND7 4.89 ± 0.29 on PND14.	Maternal and offspring: ↓ TT4 and TT3.	NA / 0.38*.	Wa (20
PFOS (potassium salt).	Wistar rats / female / 20/group / developmental study.	0 or 3.2 mg/kg diet equivalent to 0.29** / diet / Prenatal exposure GD0 – PND0; Postnatal exposure PND1 – 35; Combined prenatal and	At 0.29 mg/kg bw/day in offspring (Prenatal exposure) on PND35 Serum: 0.41 ± 0.02 in males.	Offspring: ↓ TT4 in all exposure groups.	NA / 0.29*.	Yu (20

			1.02 ± 0.08 in Females.			
		postnatal group GD0 – PND35.	At 0.29 mg/kg bw/day in offspring (postnatal exposure) on PND35 Serum: 7.04 ± 0.59 in females. At 0.29 mg/kg bw/day in offspring (Combined prenatal and postnatal exposure) on PND35 Serum: 11.53 ± 0.28 in females on PND35.			

Table 4 *In vivo* thyroid toxicity effects following repeated exposure to PFCAs

*Derived by contractor; NR – not reported; NA – not applicable.

Substance	Species / sex / number / study type	Dose / route of administration / duration (mg/kg bw/day)	Serum / plasma concentration (µg/mL)	Observed effects at LOAEL	Published NOAEL / LOAEL (mg/kg bw/day)	Refe

PFHxA (sodium salt).	Crl:Cd SD rats / male and female / 10/sex/group / repeated dose study.	0, 20, 100 or 500/ gavage / 92/93 days (males/females.	NR.	↑ Thyroid follicular epithelial hypertrophy (females) ↑ thyroid weight (males and females) ↓ BW (males).	100 / 500.	Lovel *al*. (2
PFHxA	SD rats / male and female / 10/group / repeated dose study.	0, 62.6, 125, 250, 500 or 1000 / gavage / 28 days.	At 62.6 mg/kg bw/day Plasma:0.378 ± 0.178 in Males.	↓ TT4, FT4 and TT3 in males.	NA / 62.6.	NTP (2022
PFOA (ammonia salt).	SD rats / female / 5/dose / repeated dose study.	0, 10, 30, 62.5, 125 or 250 / gavage / GD8 – PND2.	At 10 mg/kg bw/day on PND2 Maternal serum: 31.8 ± 1.1.	Maternal: ↓ TT4, TT3, FT4 and FT3 on PND2. Offspring:↓ birthweights↓ TT3, TT4 and↓ rT3 on PND2.	Maternal: NA / 10*. Offspring: NA/ 10*.	Conle *al*. (2
PFOA	SD rats / male and female / 10/group / repeated dose study.	0, 0.625, 1.25, 2.5, 5 or 10 (males), 0, 6.25, 12.5, 25, 50, or 100 (females) / gavage / 28 days.	At 0.625 mg/kg bw/day. Plasma: 50.690 ± 2.207 in Males.	↓ TT4, FT4 and TT3 in males.	NA / 0.625.	NTP (2022

PFNA	SD rats / male and female / 10/group / repeated dose study.	0, 0.625, 1.25, 2.5, 5 or 10 (males), 0, 1.56,3.12, 6.25, 12.5 or 25 (females) / gavage / 28 days.	At 0.625 mg/kg bw/day Plasma:56.730 ± 1.878 in Males.	↓ TT4 and FT4 in males.	NA / 0.625.	NTP (2022
PFDA	SD rats / male and female / 10/group / repeated dose study.	0, 0.156, 0.312, 0.625, 1.25, or 2.5 / gavage / 28 days.	At 0.156 mg/kg bw/day Plasma:8.505 ± 0.578 in males. 11.208 ± 0.436 in Females. At 0.312 mg/kg bw/day Plasma:23.030 ± 1.771 in males 25.700 ± 1.048 in Females.	↓ TT4 and FT4 in males. ↑ thyroid weight and relative thyroid weight: body weight in females.	Males: 0.156* / 0.312*. Females: 0.156 / 0.312.	NTP (2022