

# PFAS/2023/02 Annex 3

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## Summaries

When writing summaries of the data, how do members want the data presented?

1. Summary per sensitive endpoint (e.g. liver weight, clinical chemistry, thyroid hormones).
2. Summary per individual PFAS.
3. Summary per group or sub-group of PFAS (e.g. PFCA or PFSA).

Examples of each option are given below. (To note these are made of illustrative data rather than data taken from studies).

### Example of a summary per endpoint

Evidence from repeated dose toxicity oral studies in rats, mice, and monkeys indicate that the liver is a sensitive target for PFHxA, PFOA, PFNA and PFDA, as well as PFBS, PFHxS, PFOS and PFDODA.

The effects seen included increases in changes in clinical chemistry parameters (ALT), liver weight, hepatocellular hypertrophy, and decreases in serum lipid levels.

### ALT

Fifty-seven out of 88 studies measured liver enzyme ALT of which four reported increases following exposure to PFHxA (1 study; rats), PFOA (1 study; mice), and PFOS (2 studies; mice and monkeys). In contrast, one study reported a decrease in ALT in rats following exposure to PFOS.

For PFHxA, ALT was significantly increased in male and female rats following exposure to 20 mg/kg bw/day for 90 days ( $63 \pm 64$  U/L) compared with controls ( $27 \pm 3$  U/L) (Loveless *et al.* 2009).

A statistically significant increase in ALT was also seen in male rats following exposure to 10 mg/kg bw/day PFOS for 21 days compared with controls (approx. 600 U/L vs 350 U/L in controls; data taken from figures) (Elcombe *et al.*, 2010). A transient increase was seen in male and female monkeys following treatment with 0.15 mg/kg bw/day on day 37 ( $37 \pm 12$  U/L vs  $34 \pm 15$  U/L in controls) and day 62 ( $50 \pm 24$  U/L vs  $39 \pm 2015$  U/L in controls) but not at later time points (Seacat *et al.*, 2002).

PFOA also caused a significant increase in ALT in male mice following exposure to 5 mg/kg bw/day for 21 days ( $35 \pm 12$  U/L vs  $22 \pm 4$  U/L for treated and control mice, respectively) (Wu *et al.*, 2018).

Overall, the lowest dose that cause an increase in ALT was 0.15 mg/kg bw/day PFOS (male and female monkeys), followed by 5 mg/kg bw/day PFOA (mice male) and 20 mg/kg bw/day PFHxA (male and female rats).

## **Example of a summary per PFAS**

PFHxS was investigated in five repeat dose toxicity studies (Butenhoff *et al.*, 2009b; Gilbert *et al.*, 2021; NTP, 2022b and Romhoj *et al.*, 2018 and 2020). Overall, a decrease in thyroid hormones was seen in all studies with the exception of the study by Butenhoff *et al.*, 2009b, in which no effects were reported in male and female SD rats following exposure to 3 mg/kg bw/day.

Decreases in TT4, TT3 and FT4 in serum were reported in two studies in rats (Gilbert *et al.*, 2021; NTP, 2022b). In the study by Gilbert *et al.*, decreases in TT4, TT3 and FT4 were seen in Long-Evans female rats following exposure to 50 mg/kg bw/day from GD 6 to GD 21 (TT4; 10 ng/ml vs 17 ng/ml for treated and controls, respectively. TT3; 40 ng/ml vs 50 ng/ml. FT4; 1.5 ng/dl vs 1.75 ng/dl). NTP (2022b) reported a decrease in TT4, TT3 and FT4 in serum, in SD male and female rats compared to controls, following exposure to 0.625 mg/kg bw/day (TT4; 22 ng/ml vs 45 ng/ml for treated and controls, respectively. TT3; 45 ng/ml vs 55 ng/ml. FT4;

5 ng/dl vs 7 ng/dl).

In contrast, only TT4 (Romhoj *et al.*, 2018) and TT3 (Romhoj *et al.*, 2020) were decreased in female Wistar rats following exposure to 25 mg/kg bw/day from GD 7 to PND 22 and (TT4; 15 ng/ml vs 45 ng/ml for treated and controls, respectively. TT3; 41 ng/ml vs 56 ng/ml).

PFHxS also increased the incidence of minimal to moderate hypertrophy and hyperplasia of follicular epithelial cells in the thyroid of male SD rats following exposure to 3 mg/kg bw/day (Butenhoff *et al.*, 2009b)

### **Example of a summary per group or sub-group of PFAS (e.g. PFCA or PFSA)**

Data on thyroid toxicity are available for PFCAs, namely PFHxA, PFOA, PFNA and PFDA.

All studies, with the exception of Loveless *et al* (2009) noted a decrease in TT4 and FT4. NTP (2022a) reported a decrease in male rats following exposure to 62.6 mg/kg bw/day PFHxA (TT4 -  $3.4 \pm 0.23$  ng/ml vs  $4.26 \pm 0.15$  ng/ml in treated and controls, respectively; FT4 -  $2.16 \pm 0.17$  pg/ml vs  $2.88 \pm 0.09$  pg/ml), 0.625 mg/kg bw/day PFOA (TT4 -  $5.2 \pm 0.45$  ng/ml vs  $4.26 \pm 0.15$  ng/ml; FT4 -  $6.25 \pm 0.17$  ng/ml vs  $2.88 \pm 0.09$  ng/ml) and PFNA (TT4 -  $3.2 \pm 0.68$  ng/ml vs  $4.26 \pm 0.15$  ng/ml; FT4 -  $5.55 \pm 0.18$  ng/ml vs  $2.88 \pm 0.09$ ), and 0.312 mg/kg bw/day PFDA (TT4 -  $3.25 \pm 0.165$  ng/ml vs  $4.26 \pm 0.15$  ng/ml; FT4 -  $2.39 \pm 0.21$  ng/ml vs  $2.88 \pm 0.09$  ng/ml) for 28 days. Similarly a decrease was seen in male and female rats following exposure to 10 mg/kg bw/day PFOA from GD8 to PND2 (TT4 -  $16.2 \pm 0.9$  ng/ml vs  $29.1 \pm 1.0$  ng/ml; FT4 -  $25.9 \pm 2.0$  pg/ml vs  $42.2 \pm 7.7$  pg/ml) (Conley *et al*, 2022).

Increased thyroid weight was only seen in female rats following exposure to 0.312 mg/kg bw/day PFDA for 28 days (NTP, 2022a), and in males and females following exposure to 500 mg/kg bw/day PFHxA for 92 or 93 days (Loveless *et al.*, 2009). In the latter study, an increase in minimal hypertrophy of thyroid follicular epithelium was also reported.