Discussion - PFAS/2023/04

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83. Ten PFAS are considered in this paper, comprising three PFSAs (PFBS, PFHxS and PFOS) and seven PFCAs (PFBA, PFHxA, PFOA, PFNA, PFDA, PFHxDA and PFTeDA).

84. Table 1 and Table 2 below present the lowest point of departure (POD) for PFSAs and PFCAs, respectively, based on thyroid effects. For PFBS, PFHxA and PFOA, only a LOAEL was determined, as effects were seen at the lowest dose tested.

85. THs were measured in a total of 38 studies in adult animals, being the most frequently studied thyroid-related endpoint and the most sensitive endpoint on which the majority of the N/LOAELs have been determined.

86. In repeated dose and developmental toxicity studies there were consistent decreases in TH levels observed with PFSAs (PFBS, PFHxS and PFOS) and PFCAs (PFBA, PFDA, PFOA and PFNA), mainly FT4, TT4, TT3. In general, these decreases were not associated with compensatory increases in TSH. Therefore, the results

are not generally indicative of a classical induced hypothyroid state following exposure to PFAS, where decreased T4 and T3 levels would be associated with increased TSH. The five studies where recovery was assessed suggest that changes in TH levels are transient, and have the potential to return to control values, although this was not seen consistently.

Table 1 Lowest POD for PFAS based on thyroid effects - PFSAs

*Derived by contractor; NA – not applicable.

87. Thyroid histopathology was assessed in 25 studies. At lower PFAS doses, histopathological changes were seen less frequently than changes in TH levels. Notable changes in histopathology were identified at the LOAEL in only four studies, with PFHxS, PFBA, PFHxA and PFOA, and included increased incidence of hypertrophy and/or hyperplasia of follicular epithelial cells and increased thyroid follicular epithelial cell height. Loveless *et al*. (2009) noted that thyroid hypertrophy, as seen in their study with PFHxA, is a common finding in rats, associated with the induction of hepatic microsomal enzymes, leading to increased biliary excretion of T4 and elevation of TSH, which results in hypertrophy of follicular epithelial cells. It should be noted that this discussion by Loveless *et al*. (2009) is not supported by any measurements of THs in their study. In their 92/93-day study with PFHxA, thyroid follicular epithelial hypertrophy was seen only at doses that also produced liver hypertrophy. The authors also stated that due to the species-specific short half-life for T4 in rodents, rats are uniquely sensitive to thyroid hormone perturbation in association with induction of liver enzymes (Capen, 1997 cited in Loveless *et al*. (2009)), concluding that whilst the observed thyroid follicular cell hypertrophy is potentially adverse, it is unlikely that this effect is relevant to non-rodent species (Alison *et al*., 1994 cited in Loveless et al. (2009)). The three studies where recovery was assessed suggest that thyroid follicular hypertrophy may be transient, although this was not seen consistently.

88. Thyroid weight was measured in 17 studies, where an increased weight was seen at the LOAEL with PFBA, PFHxA, PFDA and PFHxDA. Increases were generally only seen at doses higher than those causing changes in THs. The three studies in which recovery was assessed suggest that changes in thyroid weight may be transient.

89. Sex-specific differences were seen with effects on THs, with changes more frequently seen in male than in female animals at comparable doses. No clear sex-specific effect was evident regarding histopathological changes or thyroid weight.

90. Serum/plasma PFAS levels will be evaluated further in subsequent papers considering the toxicokinetics of PFAS

91. It may be relevant to note the approach taken by two authoritative bodies, namely the ATSDR (ATSDR, 2021) and the United States Environmental Protection Agency (USEPA) (USEPA, 2023), in selecting thyroid effects as the basis for setting human health criteria values. These opinions will be explored in future papers.

92. Overall, the *in vivo* evidence indicates that low doses of PFSAs and PFCAs can produce adverse effects on levels of THs (typically without affecting TSH levels), and that higher doses can produce histopathological alterations in the thyroid and an increase in thyroid weight. However, some of these findings are inconsistent, and some endpoints appear to be sex-specific (with males being more sensitive than females).

93. Interpretation of the *in vivo* evidence with respect to adversity and human relevance is problematic and will be explored in future papers.

Questions on which the views of the Committee are sought

94. Members are invited to consider the following questions:

i). Are there any specific papers that the subgroup would like to review in more detail?

ii). Recovery is assessed in a minority of studies. Should the N/LOAEL be based on effects seen at the end of treatment or after the recovery period?

iii). Thyroid effects seen in developmental studies are presented for dams and offspring. The N/LOAELs are based on effects in the dam only. Does the subgroup agree with excluding effects seen in offspring, which will be reported in subsequent papers?

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