Discussion

In this guide

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

56. Competitive binding studies show that PFAS can compete with T4 for binding to serum transport proteins and so disturb TH homeostasis, with binding affinities to TTR stronger than to TBG. Binding affinity to TTR is associated with PFAS carbon chain length and the charged end group.

57. Results from the study by Long *et al*. (2013) indicated that only the longer chain PFAS with alkyl chains of 10 to 12 carbon atoms appear to have the ability to interact with AhR and influence gene expression profiles of key factors involved in thyroid function.

58. Evidence from cell proliferation and cell viability studies show that PFAS can decrease both, although this is not consistently seen across different cell types (rat or human cells) with the same PFAS.

59. Disruption of iodide homeostasis in thyroid cells may be a one of the potential mechanisms for the thyroid-disrupting effects of some PFAS, but this was not seen consistently across the PFAS studied.

60. Decreases in cAMP production was also not seen consistently across the PFAS studied.

61. A deeper understanding as to which PFAS may present greater impacts upon the thyroid and why PFAS may differ in their ability to bind to critical targets involved in the regulation of thyroid function may be gained from relative potency estimates seen in the studies by Ren *et al*. (2016) and Weiss *et al*. (2009), supported by molecular docking simulations (not presented in this paper). PFOS, PFHxS and PFOA displayed the highest relative potencies in these studies, although depending on the study the most potent of these three PFAS varied.

62. In vitro studies on new generation PFAS (C6O4 and F-53B) are presented, comprising different test models and endpoints. C6O4 is reported to have no effect on FRTL-5 or NHT cell viability or apoptosis (Coperchini et al., 2021) and to increase iodide uptake in cells following TSH stimulation and decrease intracellular cAMP levels, with no effect on NIS and TPO gene expression (De Toni *et al*., 2022). The study by Deng *et al*. (2018), on F-53B demonstrated that F-53B is a strong TH agonist.

63. Taken together, the in vitro evidence reviewed for various PFSAs and PFCAs, and new generation PFAS, shows that in vitro exposure of thyroid cells (rat or human) and of thyroid relevant proteins can have various thyroid-disrupting effects. These are not always consistent, but do, in some cases, support the findings on thyroid function displayed in in vivo studies where consistent decreases in THs are seen.

Questions on which the views of the Committee are sought

64. Members are invited to consider the following questions:

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

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