Summary and Abbreviations

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Summary

215. This paper presents an overview of the *in vivo* data for thyroid toxicity. It does not contain an overall summary and conclusions as these will be provided once the review of *in vitro* and epidemiological data has taken place. A review of authoritative body opinions and evaluation of adversity will also be undertaken. Nevertheless, some key points to note are discussed below.

216. All seven PFAS showed decreases in TH levels (including in offspring) but generally without an associated rise in TSH levels, and there were sex differences in response. There is disagreement between researchers about the biological significance of these findings.

217. Thyroid morphology was examined in 18 of the 27 studies on the seven PFAS, but adverse findings (follicular epithelial cell hyperplasia and hypertrophy) were only found in four studies on four different PFAS, of which only one study measured TH and showed it to be reduced. The significance of these morphological changes in these studies is uncertain as it is suggested that they could be secondary to liver hypertrophy and the induction of metabolic liver

enzymes leading to an increase in T4 and TSH. Moreover, as T4 in rodents has a short half-life, they are more sensitive, hence this effect may not be relevant to non-rodent species.

218. Authoritative bodies such as the Agency for Toxic Substances and Disease Registry (ATSDR) based their point of departure (POD) on effects on thyroid pathology, while the United States Environmental Protection Agency (US EPA) consider reduced TH levels to be an indication of adverse effects. These opinions will be explored in future papers.

219. Overall, the in vivo evidence indicates that low doses of PFAS can produce adverse effects on levels of thyroid hormones (without affecting TSH levels), and at higher doses, can produce morphological alterations in the thyroid. However, some of the findings are inconsistent, sex-specific and difficult to interpret in terms of adversity and human relevance.

Questions on which the views of the Committee are sought

220. Members are invited to consider the following questions:

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

iii) Would a discussion of adversity and human relevance be useful at this stage, or should this await a consideration of epidemiological data?

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August 2023 List of Abbreviations and Technical terms

ApoA1	Apolipoprotein A1
BDE-47	2,2’,4,4’-tetrabromodiphenyl ether
Dio1	Type 1 deiodinase, iodothyronine deiodinase type 1

EFSA	European Food Safety Authority
FT3	Free triiodothyronine
FT4	Free thyroxine
FTI	Free thyroxine index
GD	Gestational day
HBGV	Health-based guidance value
HPT	Hypothalamic–pituitary–thyroid
i.p.	Intraperitoneal
K^+PFBS	Potassium perfluorobutanesulfonate
K^+PFHxS	Potassium perfluorohexanesulfonate
K^+PFOS	Potassium perfluorooctane sulfonate
LOEL	Lowest observed effect level
Mdra1	Multidrug resistance 1
ME	Malic enzyme
mRNA	Messenger ribonucleic acid
NA	Not applicable

NAM	New approach methodology
NaPFHxA	Sodium perfluorohexanoate
ND	Not detected
nis	Sodium-iodide symporter
Nkx2.1	NK2 homeobox 1 (TTF-1)
NOAEL	No observed adverse effect level
NR	Not reported
NTP	National Toxicology Program
Pax8	Paired box 8
PFBS	Perfluorobutane sulfonate
PFCA	Perfluoroalkyl carboxylic acid
PFDA	Perfluorodecanoic acid
PFHxA	Perfluorohexanoate / Perfluorohexanoic acid
PFHxS	Perfluorohexanesulfonate/Perfluorohexanesulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid

PFOS	Perfluorooctane sulfonate
PFSA	Perfluorosulfonic acids
PND	Postnatal day
Por	P450 oxidoreductase
RNA	Ribonucleic acid
rT3	Reverse triiodothyronine
SD	Sprague Dawley
Slc5a5 (NIS)	Solute carrier family 5
Spot14	Thyroid hormone-inducible hepatic protein, or THRSP
T3	Triiodothyronine
T4	Thyroxine
TT3	Total triiodothyronine
TT4	Total thyroxine
TH	Thyroid hormone
Tpo	Thyroid peroxidase (also threoperoxidase)
TR	Thyroid hormone receptor

Trh	Thyrotropin releasing hormone
TRα	Thyroid hormone receptor α
TRα-LBD	Thyroid hormone receptor α ligand-binding domain
TRβ	Thyroid hormone receptor β
TSH	Thyrotropin also thyroid stimulating hormone
Tshr	Thyroid stimulating hormone receptor
ttf-1	Thyroid transcription factor 1
TTR	Transthyretin
TWI	Tolerable weekly intake
UGT1A	UDP-glucuronsyltransferase 1A
UGT1A1	Uridine diphosphoglucuronosyl transferase 1A1
UGT1A6	Uridine diphosphoglucuronosyl transferase 1A6