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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Discussion paper for the EFSA Public Consultation on the draft Opinion on the risks to human health related to the presence of perfluoroalkyl substances in food

Introduction

1. The European Food Safety Authority (EFSA) was asked, by the European Commission, to prepare an Opinion on the risks to human health related to the presence of perfluoroalkylated substances (PFASs) in food, and to consider existing hazard assessments and available occurrence data. This is currently out for public consultation.

2. In their current Opinion EFSA consider 27 PFASs covering 9 groups (Table 1).

Table 1. Chemical name and acronym of the 27 PFASs reviewed in the current EFSA Opinion

Chemical name	Acronym
Perfluoroalkyl carboxylic acids (PFCAs)	
Perfluorobutanoic acid	PFBA
Perfluoropentanoic acid	PFPeA
Perfluorohexanoic acid	PFHxA
Perfluoroheptanoic acid	PFHpA
Perfluorooctanoic acid	PFOA
Perfluorononanoic acid	PFNA
Perfluorodecanoic acid	PFDA
Perfluoroundecanoic acid	PFUnDA
Perfluorododecanoic acid	PFDoDA
Perfluorotridecanoic acid	PFTrDA
Perfluorotetradecanoic acid	PFteDA
Perfluoropentadecanoic acid	PFPeDA
Perfluorohexadecanoic acid	PFHxDA
Perfluorooctadecanoic acid	PFODA
Perfluoroalkane sulfonic acids (PFSAs)	
Perfluorobutane sulfonic acid	PFBS
Perfluorohexane sulfonic acid	PFHxS

Perfluoroheptane sulfonic acid	PFHpS
Perfluorooctane sulfonic acid	PFOS
Perfluorodecane sulfonic acid	PFDS
Perfluoroalkane sulfinic acids (PFSIAs)	
Perfluorooctane sulfinic acid	PFOSI
N:2 fluorotelomer alcohols (n:2 FTOHs)	
8:2 Fluorotelomer alcohol	8:2 FTOH
n:2 polyfluoroalkyl phosphoric acid esters (PAPs)	
8:2 Fluorotelomer phosphate monoester	8:2 monoPAP
8:2 Fluorotelomer phosphate diester	8:2 diPAP
Perfluoroalkane sulphonamides (FASAs)	
Perfluorooctane sulfonamide	FOSA
N-ethyl perfluoroalkane sulphonamides (EtFASAs)	
N-ethyl perfluorooctane sulfonamide	EtFOSA
N-ethylperfluoroalkane sulfonamidoethanols (EtFASEs)	
N-ethyl perfluorooctane sulfonamidoethanol	EtFOSE
Perfluoroalkyl phosphate	
Ammonium bis[2-[N-ethyl(hepatodecafluorooctane)sulphonylamino]ethyl]phosphate	FC-807

3. The CONTAM Panel has recommended a TWI of 8 ng/kg bw for the sum of four PFASs (PFOA, PFOS, PFNA and PFHxS).

Background

Previous evaluations

4. EFSA considered evaluations on PFOS and PFOA that had been carried out since their Opinion from 2018 and previous risk assessments for PFASs other than PFOS and PFOA.

5. The 2018 EFSA Opinion (EFSA, 2018) included tolerable weekly intakes (TWIs) of 13 and 6 ng/kg bw per week for PFOS and PFOA, respectively. These were based on human epidemiological studies. For PFOS, the increase in serum total cholesterol in adults, and the decrease in antibody response at vaccination in children were identified as the critical effects. Increase in serum total cholesterol was the critical effect identified for PFOA. Reduced birth weight was also considered for both compounds and increased prevalence of high serum levels of the liver enzyme alanine aminotransferase (ALT) for PFOA.

6. Risk assessments have also been carried out by:

- the Swedish Environmental Protection Agency (2012) which assessed 23 PFASs () in Sweden (Swedish Environmental Protection Agency, 2012)

- the Danish Environmental Protection Agency (2015) which reviewed FOSA (Danish EPA, 2015)

- the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) published an opinion on PFBA, PFHxA, PFBS and PFHxS (ANSES, 2015).

- the German Human Biomonitoring (HBM) Commission established drinking water guide values for PFBA, PFHxA, PFHpA, PFOA, PFNA, PFBS, PFHxS, PFOS and Health-based orientation values for PFPeA, PFHpA, PFDA, PFHPs and FOSA. (Bundesgesundheitsblatt 2017, 60:350-352).

- Food Safety Australia New Zealand (FSANZ) published a hazard assessment report for PFOS, PFOA and PFHxS (FSANZ, 2017).

- The Department of Environmental Protection (New Jersey, US) developed a Health-based Maximum Contaminant level for PFOA (DEP, 02/2017), PFOS (DEP, 11/2017) and PFNA (DEP, 10/2017).

- The ATSDR (2018) has prepared a draft for public comment on the Toxicological profile of 14 PFASs (PFOS, PFOA, PFBA, PFHxA, PFHpA, PFNA, PFDA, PFUnDA, PFDoDA, PFBS, PFHxS, FOSA, 2-(N-methyl-perfluoroocatanesulfonamido)acetic acid and 2-(N-ethyl-perfluorooctane-sulfon-amido)acetic acid.

- RIVM (2018) published a Relative Potency Factor approach for 19 PFASs (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFHxDA, PFODA, PFBS, PFPeS, PFHxS, PFHpS and PFOS.

- Michigan Science Advisory Workgroup recommended Health-based Drinking Water Values for six PFASs (PFHxA, PFOA, PFNA, PFBS, PFHxS and PFOS). (Michigan Science Advisory Workgroup71, 2019).

Summary of 2020 EFSA evaluation

Toxicokinetics

7. This new Opinion reviews data on the toxicokinetics of PFASs in animals and humans. PFOS and PFOA toxicokinetics studies published prior to 2017 are included in previous EFSA Opinions. Additional studies published since 2017 are analysed and reported in the 2020 Opinion.

Experimental animals

8. Most of the information on the fate of PFSAs and PFCAs is based on PFOS and PFOA, respectively. These compounds are readily absorbed in the gastrointestinal (GI) tract in mammals and distribute predominantly to the plasma and liver. PFOS and PFAO are not metabolised and are excreted in both urine and faeces. They may be subject to extensive enterohepatic recirculation. Serum elimination half-lives for PFOS in rats and mice were slightly longer than one month and in rabbits and monkeys were 3-4 months. Significant sex differences are observed in the elimination of PFOA in some species such as rats, for which half-lives may vary from a few hours in females, to several days in males. These differences in biological half-lives are mainly due to differences in renal clearance. For both PFOS and PFOA, maternal transfer occurs prenatally to the foetus through placental transfer and postnatally through the consumption of maternal milk.

Humans

9. Based on the high concentrations of PFASs observed in the blood of individuals exposed to contaminated water and by what is known for PFSO and PFOA, it may be assumed that the GI absorption of most of the PFASs occurs to a significant extent in humans. PFASs are widely distributed with the highest concentrations found in blood, liver and kidney. PFASs in blood bind to albumin. PFSA and PFCA metabolism has never been observed, however, precursor compounds such as FTOHs and PAPs can be biotransformed in humans to PFCAs and other metabolites. PFASs are eliminated in urine and faeces and breast milk is also a substantial route of excretion. Shorter chain PFCAs are preferentially excreted in urine, whereas longer chain PFASs are preferentially eliminated through the bile and faeces. Extensive uptake from enterohepatic circulation and reabsorption by organic anion transporters (OATs) in the kidneys are believed to be more active processes in humans compared to rodents, slowing down the excretion of these substances. Short chain PFASs were found to have half-lives ranging from a few days to approximately one month, whereas PFHxS, PFOS, PFOA and PFNA estimated half-lives can exceed 3 years.

Toxicity

Observations in animals

10. Studies on effects following repeated exposures to PFOS and PFOA published prior to 2017 have been reviewed in previous EFSA Opinions. This

cover paper summarises the toxicity of PFOS, PFOA, PFNA and PFHxS where the information is available or more generally for PFCAs and PFSAs. Some toxicity data are available for other PFASs. More detail on all of these studies are covered in the EFSA Opinion and in more detail in Appendix E to the opinion.

Effects following repeated exposure

11. The most consistent and sensitive endpoint for PFCAs following repeated exposures was increased relative liver weight, especially in male rodents. Disturbances in lipid metabolism, hepatotoxic effects and signs of cholestasis were mostly evident at higher doses concentrations. For some PFCAs increased relative kidney weight, alterations of the nasal cavity and olfactory epithelium and disturbed thyroid hormone levels were among the most sensitive endpoints.

12. The most sensitive endpoint for perfluorobutane sulfonic acid (PFBS), PFHxS and PFOS was an elevated absolute and relative liver weight. At higher dose levels, disturbed lipid metabolism, necrosis and inflammation in the liver were observed. Alterations in the kidney and disturbed thyroid hormones were repeatedly documented.

Developmental and reproductive toxicity

13. The 2018 EFSA Opinion documented reproductive and developmental toxicity studies for PFOS and PFOA published between 2008 and 2016. These studies are included in Appendix F of the current (2020) Opinion (Table F.6 – F.8). Also included in these tables are some key studies evaluated by EFSA in their 2008 Opinion on PFOS and PFOA (EFSA, 2008).

14. Developmental studies on PFOS show effects in offspring at doses similar to, or below, those showing maternal toxicity. Among effects observed in rats and/or mice are high mortality early after birth, reduced fetal weight, reduced postnatal growth, increased liver weight, anasarca, impaired immune effects, cardiac abnormalities, cleft palate, delayed ossification of bones and a decrease in placental weight and capacity. The most sensitive endpoints were increase in liver weight, effects on placental physiology and aspects of glucose homeostasis.

15. The most sensitive developmental outcome for PFOA exposure was impaired development of mammary glands.

16. The most sensitive endpoint after gestational exposure to PFNA was increased liver weight in both maternal and offspring CD-1 mice, and a reduction in postnatal weight gain in F1. Other observed effects included delay in development, increase in neonatal mortality, decreased sperm production, decrease in cholesterol, steroidogenic enzymes and testosterone, as well as decreased number of pups in the next generation.

17. The most sensitive reproductive endpoint for PFHxS exposure was reduced litter size. Increased liver weight of dams was also observed. In general, gestational exposure to PFHxS produces effects in offspring animals at doses which are equal to or higher than those inducing responses in parental animals.

Neurotoxicity

18. In 2018, EFSA concluded that both PFOS and PFOA exert developmental neurotoxic effects in rodents. The behavioural analysis showed that the most frequent alterations observed are related to locomotor activity. PFOS exposure mostly decreased spontaneous activity, while PFOA increased it. In several neurodevelopmental exposure studies, a sex-related difference has been observed with males being more sensitive than females. No new relevant neurotoxicity studies in experimental animals were identified.

19. One study evaluated by EFSA shows that PFHxS can also decrease locomotor activity in rodents.

Immunotoxicity

20. The majority of studies for immunotoxicity of PFOS had already been assessed in the 2018 Opinion and are reviewed again in the current Opinion. The studies have different study design, duration, use different strains of mice or rats, applied different doses of PFOS and investigated different parameters that may highlight effects on the immune system. Two immunotoxicity studies had been published since the 2018 Opinion and are reviewed in this Opinion.

21. This literature supports the view that PFOS exposure, possibly more than PFOA, causes immunosuppression, as evidenced by decreased antibody responses to sensitisation to an antigen, and that suppressed immune functionality may lead to reduced resistance to infection.

22. Immunotoxicity studies for PFOA were reviewed in the previous Opinion and nothing additional has been published since then. The effects of PFOA in mice are similar to those of PFOS, with both structural and functional parameters influenced. However, the effects were observed at higher doses than with PFOS.

23. Data on PFAS other than PFOS and PFOA are rather limited with studies only available for PFNA and PFDA.

Genotoxicity

24. The CONTAM Panel reviewed the studies for genotoxicity for PFOS and PFOA in the 2018 Opinion and concluded that the available data were inconclusive. There was no evidence for a direct genotoxic mode of action for PFOS or PFOA. There has been some evidence for oxidative stress induction by both compounds. Three new studies and two NTP reports have been

published since the 2018 Opinion but these do not change the conclusion of reached in that Opinion.

25. For PFASs other than PFOS and PFOA the CONTAM Panel concluded that the study and data availability are limited. Due to structural similarity between PFOA and PFNA and between PFOS and PFHxS and some evidence for oxidative stress induction by PFNA and PFHxS it is unlikely that there is a direct genotoxic mode of action for PFNA and PFHxS.

Long-term toxicity and carcinogenicity

26. Long-term and carcinogenicity studies of PFOS and PFOA reviewed by EFSA previously (EFSA, 2008; EFSA CONTAM Panel, 2018) showed that both compounds are tumour promoters in rodent liver and PFOA may also induce Leydig cell tumours in rats. No new carcinogenicity studies were identified.

27. A few studies were available for long-term and carcinogenic assessment of other PFASs. A long-term study for PFHxA only provided no evidence for any carcinogenicity. PFNA and PFDA showed a liver promoting capacity in a trout two-stage model of hepatocarcinogenesis, while 8:2FTOH failed to do so. For the remaining PFASs considered in this Opinion there is no information on their carcinogenic potential.

Observations in humans

Fertility and pregnancy outcomes

Birth weight

28. In the 2018 Opinion on PFOS and PFOA, the CONTAM Panel reviewed 13 prospective studies and four cross-sectional studies that had examined associations between PFOS and/or PFOA and birth weight. A relatively modest inverse but consistent inverse associations with birth weight were observed for both compounds. This association may be partly confounded by physiological changes in pregnancy. The CONTAM Panel concluded that there may still be an association between PFOS and PFOA exposure and birth weight.

29. Since the 2018 EFSA Opinion, six new studies have been published on PFOS and PFOA. Several, but not all studies observed an association and none contradicted the conclusion from the 2018 Opinion.

30. For PFASs other than PFOS and PFOA, concentrations in studies were generally much lower compared to PFOS and PFOA and inconsistent associations with birth weight were observed.

Preterm delivery, time to pregnancy, miscarriage and hypertension in pregnancy - preeclampsia

31. Studies for the above four endpoints were reviewed by the CONTAM Panel in 2018 and for each there was insufficient evidence to suggest that PFOS and/or PFOA exposures were associated with the effect. There was one study which had been published which looked at preterm delivery, but the data were in line with the conclusions of the 2018 Opinion.

Developmental effects

32. The CONTAM Panel reviewed studies on developmental effects and PFOS and PFOA in the 2018 Opinion. Studies for PFASs other than PFOS and PFOA were reviewed for the current Opinion. For all PFASs the CONTAM Panel concluded that there was insufficient evidence to suggest that PFASs may affect neurobehavioural development or overweight.

Neurotoxic outcomes

33. Studies for PFOS and PFOA were reviewed for the 2018 Opinion and other PFASs were reviewed for the current Opinion. The CONTAM Panel concluded that there is insufficient evidence to suggest that exposures to PFASs may adversely affect neurobehavioural, neuropsychiatric and cognitive outcomes.

Immune outcomes

Asthma and allergies in children in adults

34. In the 2018 Opinion the available studies were reviewed for PFOS and PFOA and the Panel concluded “that there is not much evidence to suggest that PFOS or PFOA are associated with asthma and allergies in children and adults”. Since then five new prospective studies have been published and reviewed by the CONTAM Panel for PFOS, PFOA and all other PFASs. These new studies did not change the conclusion from the previous 2018 Opinion.

35. The CONTAM Panel also reviewed any studies for PFASs other than PFOS and PFOA. The CONTAM Panel concluded that the available evidence was insufficient to suggest that exposures with PFASs are associated with allergy and asthma in children and adults.

Vaccination response

36. In the previous Opinion on PFOS and PFOA six studies were reviewed. Since then three more studies have been published. A summary of al the studies is provided in paragraph 44. The 2 studies (Grandjean et al., 2012; Abraham et al., 2020) used in the process of the derivation of the HBGV are described in more detail. (Annex B).

37. Grandjean et al. (2012) examined associations between both pre- (gestation week 32) and postnatal (5 years) serum concentrations of PFASs and offspring antibody concentrations against tetanus and diphtheria following booster vaccination at age 5 years (cohort 3, n=456-587, 1997-2000). Post-

natally, serum PFASs and pre-booster antibody concentrations were measured at a mean age (SD) of 5.0 (0.1) years. Serum antibody response was then measured about 4 weeks after booster vaccination and at offspring age 7.5 (0.1) years. The median concentrations for antibody titres to tetanus were 0.22 IU/mL at 5 years pre-booster, 35 IU/mL at 5 years post booster and 1.6 IU/mL at 7.5 years. For diphtheria the corresponding numbers were 0.12, 13.0 and 0.68 IU/m, respectively. Associations between offspring PFAS concentrations at age 5 pre-booster with antibody titres at age5- post-booster and 7.5 years post-booster can be interpreted as a short- and long-term influence on the efficacy of the booster vaccination, respectively. This study is interventional as well as observational. The large increase in antibody concentration is initiated through vaccination and this increase is examined in relation to baseline PFASs concentrations. The interpretation of associations reported between maternal PFAS concentrations and offspring antibody concentrations during childhood are, however, more challenging, as several vaccinations are administered from birth at various timepoints. Furthermore, among breastfed infants, maternal PFAS concentrations are, due to exposure through breastfeeding, strong determinants of offspring concentrations during the first few years of life. Several associations were explored in this study and the results are summarised below:

38. Association between maternal PFAS concentrations and antibody concentrations at ages 5 (pre- and post-booster) and 7.5:

PFOS: Mean concentration in maternal serum was 27.3 ng/mL. Each 2-fold increase in maternal PFOS concentrations was associated with -39 % (95 % CI: -55, -17) and -21 % (95 % CI: -38, 1) decrease in diphtheria antibody concentrations at 5 years pre- and post-booster, respectively. Non-significant but inverse direction associations were observed for tetanus antibody concentrations.

PFHxS: Maternal concentrations of PFHxS (mean: 4.4 ng/mL) were not associated with antibody concentrations to tetanus or diphtheria at age 5 years pre- and post-booster.

PFOA: Maternal concentrations of PFOA (mean: 3.2 ng/mL) showed a non-significant inverse association with antibody concentrations to diphtheria at age 5 years pre- and post-booster while the associations for tetanus were in opposite directions at pre- and post-booster, neither of them being significant.

PFNA: Similar to PFOA, maternal concentrations of PFNA (mean: 0.6 ng/mL) showed a non-significant inverse association with antibody concentrations to diphtheria at age 5 years pre- and post-booster, while the associations for tetanus were centred around the NULL.

PFDA: Maternal concentrations of PFDA (mean: 0.3 ng/mL) were significantly and inversely associated with antibody concentrations to diphtheria (around 20 % decrease per 2-fold increase) at age 5 years pre- and post-booster. No association was observed for tetanus.

Combined exposures: Structural equations were used to evaluate the associations for combined exposure to PFOS, PFHxS and PFOA during pregnancy and in relation to offspring antibody response to diphtheria and tetanus at age 5.0 years pre-booster and at age 7.5 years pre-booster. A 2-fold increase in maternal concentrations during pregnancy was significantly associated with -48 % (95 % CI: -68, -16) and -42 % (95 % CI: -66, -1) decrease in serum antibody response to diphtheria at age 5 pre-booster and age 7.5 post-booster, respectively. No associations were observed for tetanus.

39. Offspring PFAS concentrations at age 5 and offspring antibody concentrations at ages 5 and 7.5 years:

PFOS: Each 2-fold increase in offspring PFOS concentrations at 5 years pre-booster (mean 16.7 ng/mL) was associated with -29 % (95 % CI: -46, -6) and -24 % (95 % CI: -44, 4) change in post-booster antibody response to tetanus at ages 5-year and 7.5 years, respectively. The corresponding estimates for diphtheria were -16 % (95 % CI: -32, 4) and -28 % (-46, -3), respectively.

PFHxS: At age 5 years pre-booster, 2-fold offspring concentrations of PFHxS (0.6 ng/mL) were significantly associated with -19 % (95 % CI: -30, -7) lower tetanus antibody concentration at 5 years post-booster and -20 % (95 % CI: -32, -6) lower concentration was observed for diptheria for these two timepoints.

PFOA: At 5 years of age, pre-booster offspring concentrations of PFOA (4.1 ng/mL) showed a weak but inverse association with antibody response to tetanus and diphtheria post-booster at age 5 years (6-13 % decrease). At age 7.5 years the association for both antibody titres to diphtheria and tetanus was, however, strongly significant, corresponding to around ~25 % decrease per 2-fold increase in PFOA.

PFNA: At 5 years pre-booster, each 2-fold increase in offspring PFNA concentrations (mean: 1.0 ng/mL) was associated with around 15-20 % decrease in antibody response to diphtheria and tetanus at age 5- and 7.5-years, although formal significance was not always reached.

PFDA: At 5-years pre-booster, each 2-fold increase in PFDA (mean: 1.0 ng/mL) concentrations was associated with around 10-20 % decrease in antibody response to diphtheria and tetanus at 5- and 7.5-years post-booster, although formal significance was reached only for tetanus.

Combined exposures: Structural equations were used to evaluate the associations for combined exposures to PFOS, PFHxS and PFOA at offspring age 5 years (pre-booster) in relation to offspring antibody response to diphtheria and tetanus at age 5 years pre-booster and at age 7.5 years post-booster. A 2-fold increase in offspring serum levels

at age 5 years pre-booster showed a non-significant inverse association with antibody concentrations age 5 years pre-booster. A 2-fold increase in combined exposures at age 5 .0 years pre-booster was, however, significantly associated with a -44 $ (95 % CI: -66, -11) and -55 % (95 % CI: -73, -25) decrease in serum antibody response to diphtheria and tetanus at age 7.5, respectively.

Low antibody levels: At age 5 years pre-booster, a 2-fold increase in PFOS concentrations was associated with 1.6 (95 % CI: 1.1, 2.3) higher odds of being below a protective level (0.1 IU/mL) against diphtheria. The corresponding estimates for PFOA was OR 1.2, 95 % CI: 0.8-1.7. Slightly elevated but non-significant OR were observed for tetanus. At age 7.5 years concentrations of PFOS and PFOA at age 5 years were associated with 2.4 (95 % CI: 0.9, 6.4) and 3.3 (95 % CI: 1.4, 7.5) higher odds of being below protective levels against diptheria. Similar elevated odds were reported for tetanus at age 7.5.

40. Co-exposures: Concerning possible confounding by other co-exposures, PCBs in maternal samples and offspring samples at age 5 years showed a weak correlation with individual PFASs. Adjustment for these co-exposures had no impact on the effect estimates. With respect to individual PFASs, the correlation between the five substances at offspring age 5 years ranged between 0.2 and 0.8. The strongest correlation was observed between PFNA and PFDA, while for PFOS and PFOA the correlation was ~0.5. Other pair-wise correlations were weaker. The authors performed benchmark dose (BMD) analyses for each of the five PFASs in serum of the 5-year old children in relation to antibody response at 5 and 7.5 years. The results were reported with and without mutual adjustment for PFOS and PFOA (Budtz-Jorgensen and Grandjean, 2018). In short, the modelling showed that both PFOS and PFOA, in statistical terms, were associated with antibody concentrations independent of each other (not confounded).

41. In a cohort of 101 infants from Germany, Abraham *et al.* (2020) examined the association between plasma concentrations of PFHxS, PFOS, PFOA and PFNA and antibodies to diphtheria, tetanus and haemophilus influenzae type b (Hib). Mothers and their children were recruited in 1997-1999 when the infants were between 341 and 369 days old. Of these 21 were formula fed (≤2 weeks of breastfeeding) and 80 were breast fed for >4 months. When combining exclusive and partial breastfeeding into “equivalent to exclusive breastfeeding” the median duration was 7.4 months. Mean levels of PFASs in plasma from, respectively, non-breastfed and breastfed infants were for PFOA 3.8 and 16.8 ng/mL, for PFOS 6.8 and 15.2 ng/mL, for PFHxS 1.7 and 2.1 ng/mL and for PFNA 0.2 and 0.6 ng/mL. For the mothers, the mean concentrations in plasma among those who did not breastfeed (n=21) and those who breastfed (n=80) were for PFOA 4.9 and 3.2 ng/mL, for PFOS 17.2 and 14.1 ng/mL, for PFHxS 1.8 and 1.0 ng/mL and for PFNA 0.4 and 0.3 ng/mL. Higher concentrations in plasma among breastfed infants and lower

concentrations among mothers who breastfed is explained by lactational transfer of PFASs from the mother to the baby. This transfer into breast milk is more effective for PFOA compared to PFOS, which also explains the differences in PFOS/PFOA ratio between mothers and infants.

42. Concentrations of PFOA in infant plasma were significantly and inversely correlated with antibody concentrations to diphtheria (r=-0.23, p=0.02), tetanus (r=-0.25, p=0.01) and Hib (r=-0.32, p=0.001). Analyses were adjusted for time since last vaccination and for tetanus also the number of vaccinations. Adjustment for other co-contaminants quantified in infant blood, including PCBs, dioxins (I-TEQ), organochlorine pesticides, mercury, cadmium and lead did not influence these associations. Adjustment for duration of exclusive breastfeeding had no relevant influence. The NOAECs for PFOA, estimated by dividing exposure into quintiles, ranged between 18.9 and 19.4 ng/mL, depending on the type of antibody titers. In terms of effect size the mean reduction in antibody response when comparing the highest to lowest quintile of PFOA exposure was -57 %, -53 % and -78 % for diptheria, tetanus and Hib, respectively. Associations for PFOS, PFHxS and PFNA were not significant. Upon request from EFSA, the authors provided analyses of the associations with the sum of PFOA, PFNA, PFHxS and PFOS (EFSA Opinion, Appendix K). Similar to PFOA, the sum of the four PFASs was significantly and inversely correlated with tetanus and Hib, while the correlation for diphtheria was borderline significant.

43. The different PFASs show significant findings across different studies. This is not unexpected as there are differences in the concentrations and mixture compositions. It is therefore difficult to know whether one of the PFASs is more potent. A more detailed analyses of the Grandjean *et al.* (2012) study carried out by Budtz-Jorgensen and Grandjean (2018) suggests that both PFOS and PFOA may affect antibody response independently.

44. The studies published since the 2018 Opinion strengthen the conclusion that both PFOS and PFOA are associated with reduced antibody response to vaccination. The evidence for other PFASs is weaker as concentrations are lower.

Clinical Infections

45. There is some evidence to suggest that exposures to PFASs are associated with increased propensity of infections, but more studies with objective measures of infections (not self-reporting) are needed.

Endocrine effects

46. The CONTAM Panel reviewed studies which looked at PFOS, PFOA and other PFASs in thyroid function and disease, male fertility and puberty

and female fertility, menstrual cycle and puberty and concluded that there was insufficient evidence available to suggest that the PFAS exposures are associated with these effects.

Metabolic outcomes

Blood lipids

47. In the 2018 Opinion the CONTAM Panel concluded that "it is likely that associations between serum PFOS and PFOA levels and serum cholesterol are causal and that an increase in cholesterol was considered adverse".

48. Associations between PFOS/PFOA and cholesterol have been reviewed by the CONTAM Panel again after external comments to the previous Opinion. This review included some studies published since the 2018 Opinion. The current consideration is that the uncertainty regarding causality is larger than that stated in the previous Opinion.

49. The CONTAM Panel reviewed 12 studies on associations between cholesterol and PFASs other than PFOS and PFOA. The results were mostly inconsistent. However, in almost all studies significant associations were found with PFNA and total cholesterol. The data suggest that PFNA has an association with serum cholesterol which is independent from PFOS/PFOA.

Diabetes, Obesity and Metabolic Syndrome

50. In the 2018 Opinion the studies reviewed led the CONTAM Panel to conclude that there was no evidence that PFOS or PFOA increases the risk of metabolic disease. Studies reviewed for the current Opinion for PFASs other than PFOS and PFOA are inconsistent.

Liver

51. In the previous Opinion the CONTAM Panel considered that the association between PFOA and elevated ALT was causal, but the adversity of the increase in the normal range was considered uncertain since the increase in ALT per unit PFOS/PFOA was small and no association with liver disease was shown. The data for PFOS was inconsistent. Studies published since the previous Opinion have been reviewed by the CONTAM Panel and are in agreement with the conclusion in the 2018 Opinion.

52. The CONTAM Panel reviewed studies on PFASs other than PFOS and PFOA and the results indicate positive associations between PFHxS/PFNA and serum ALT. However, the association was modest in most of the studies.

53. The available evidence on associations between ALT and PFASs is insufficient for use as the basis for an HBGV.

Kidney function and uric acid

54. When reviewed in the 2018 Opinion studies showed that there were relatively strong associations between serum PFOS/PFOA and estimated GFR as well as serum uric acid. However, taking into account that some reverse causality is plausible, that there may be confounding and no significant associations were shown between PFOS/PFOA and chronic kidney disease, the CONTAM Panel considered the evidence that PFOS/PFOA exposures causes reduced GFR insufficient. For studies with other PFAS there was insufficient evidence to conclude that exposures to PFASs decrease GFR or increase uric acid in serum.

Carcinogenicity outcomes

55. When the CONTAM Panel (2018) reviewed studies on cancer incidence or cancer mortality, they provided limited evidence that exposure to PFOS or PFOA are related to cancer risk. Studies with PFOS, PFOA and other PFASs published since the 2018 Opinion have been reviewed and provide no evidence for a link between exposure to PFASs and cancer risk.

Cardiovascular disease and mortality

56. In the previous Opinion (2018) studies examining associations of PFOS/PFOA exposure and cardiovascular outcomes were reviewed. The studies did not show any clear association between PFOS/PFOA exposure and cardiovascular disease.

57. When studies which looked at other PFASs exposure and cardiovascular disease were reviewed by the CONTAM Panel it was noted that some recent studies suggest an association between exposure to PFAS and cardiovascular disease, but insufficient for use as an HBGV.

Bone mineral density

58. Two studies that examined associations between PFOS/PFOA and bone mineral density were reviewed (2018) and some inverse associations were noted (with caveats). The magnitude of the associations were small and may be due to reverse causation or residual confounding. Only one study was available to review for other PFASs. The findings from this single study are insufficient as evidence that PFNA or PFHxS has an impact on bone mineral density.

Exposure

59. The EFSA Opinion included UK data both on occurrence and consumption. The UK specific data and exposures (Annex C, Tables 1a and 1b) are within, and towards the lower end of the range of data from the EU (Table 22 (P.159) of the 2020 EFSA Opinion).

Critical effects, dose-response assessment and derivation of an health-based guidance value

60. The CONTAM Panel decided to base its assessment on epidemiological studies.

61. Various associations between serum levels and a number of outcomes have been reported in human studies. In 2018 the CONTAM Panel considered four effects as potentially critical for PFOS and/or PFOA. These were:

- Increased serum total and LDL cholesterol (risk factor for cardiovascular disease,
- Increased ALT levels (indicating effects on liver cells),
- Reduced birth weight and
- Effects on the immune system as shown by decreased antibody response to vaccines.

62. In their 2018 Opinion, the CONTAM Panel used the effects on serum cholesterol levels to derive TWIs for PFSO and PFOA. These were also protective for the other potential critical endpoints. Although the association with increased cholesterol was observed in a large number of studies, the CONTAM Panel now considers the uncertainty regarding causality larger. This is primarily due to a postulated process around the enterohepatic cycling of both PFASs and bile acids, the latter affecting serum cholesterol levels.

63. The association with reduced birth weight could in part be explained by physiological changes during pregnancy. There is currently little evidence for an increase in the proportion of children with low birth weight.

64. There is a consistent increase in ALT levels in general population studies, which appear to be supported by observations in animal studies but were not observed in occupational studies. In the critical study (Gallo *et al.*, 2012) the increase in subjects with high ALT levelled off at relatively low serum concentrations (about 30 ng/mL of PFOS and PFOA) and above that it did not increase further. In contrast, rodent studies only show an increase in ALT at the high-end of the dose-response curve. This inconsistency creates some uncertainty and for these reasons, this endpoint was not considered as the critical effect.

65. Reduction in thyroid hormone levels is often observed in animal studies. Epidemiological studies provide insufficient support of the associations between exposure to PFASs and changes in thyroid hormone levels or thyroid functions.

66. The effects on the immune system were observed at the lowest serum levels in both humans and animals. The CONTAM Panel considered these findings robust since they were consistently observed for several PFASs and for several species. In the present Opinion, the CONTAM Panel decided to base their PFASs assessment on effects on the immune system.

67. A decrease in vaccination response is considered adverse as summarised by WHO/IPCS (2012) in the Guidance for immunotoxicity risk assessment for chemicals. This may apply to vulnerable population groups such as infants and the elderly, considering their higher infection risk.

68. For compounds that accumulate in the body the CONTAM Panel prefer to identify serum or tissue levels associated with adverse effects. The Panel decided to combine its assessment on the serum levels for the sum of four PFASs (PFOS, PFOA, PFNA and PFHxS). These are currently the PFASs which contribute most to the levels observed in human serum. Although some other PFASs like PFBA and PFHxA also contribute significantly to the exposure, these compounds have much shorter half-lives in humans. The available data are insufficient to derive potency factors for the PFASs.

69. A study on children in the Faroe Islands (Grandjean *et al.*, 2012) showed several inverse associations between serum levels of PFOA, PFNA, PFHxS and PFOS, as well as the sum of PFOA, PFHxS and PFOS at five years of age, before booster vaccination, and antibody titres against diptheria and tetanus, at both the age of 5, shortly after booster vaccination and at 7.5 years. Additional data on the sum of PFOA, PFNA, PFHxS and PFOS were obtained for this study (EFSA Opinion appendix L). The CONTAM Panel identified a no observed adverse effect concentration (NOAEC) serum levels at the age of 5 years for the sum of PFOA, PFNA, PFHxS and PFOS of 27.0 ng/mL, based on decreased antibody titres for diphtheria at the age of 7 years.

70. A more recent study from Germany supported this (Abraham *et al.*, 2020). An inverse association was observed between serum levels of PFOA, but also the sum of PFOA, PFNA, PFHxS and PFOS (EFSA Opinion appendix K), and antibody titres against haemophilus influenzae type b (Hib), diphtheria and tetanus in serum sampled from 1-year-old children predominantly breastfed for a median duration of 7.4 months. A NOAEC of 31.9 ng/mL at the age of 1 year was derived for the sum of PFOA, PFNA, PFOS and PFHxS based on association with reduction in antibody titres against Hib. For PFOS, PFHxS and PFNA alone, no significant associations

were observed in this study. The association with reduced tetanus antibody titres was also significant, whereas the association between the sum of the 4 PFASs and diphtheria was only borderline significant.

Mixture Approach

71. In 2018, the CONTAM Panel derived separate TWIs for PFOS and PFOA. Since that Opinion, EFSA published a guidance document on how to evaluate the effects of mixtures (EFSA Scientific Committee, 2019) and it was considered that similarities in chemical properties and effects warranted a mixture approach for PFASs. Therefore, in this Opinion the CONTAM Panel decided to focus on the four PFASs (PFOA, PFNA, PFOS and PFHxS). In humans these four show the highest concentrations in blood plasma and serum. In general, they also show the same effects when studied in animals.

72. The studies by Abraham *et al.*, (2020) and Grandjean *et al.*, (2012) showed significant associations for the sum of the four PFASs and antibody titres. A later study by Grandjean *et al.* (2017) showed PFOA had stronger associations than PFOS. Since PFOA and PFOS concentrations are higher compared to serum concentrations of PFNA and PFHxS, and PFOA highly correlates with the serum levels of the other PFASs, it is uncertain whether PFOA has a higher potency for this critical endpoint than the other PFASs and therefore drives the association. The CONTAM Panel assumed equal potency by default for these four PFASs on immune outcomes. This was done on a weight base rather than a molar base, to allow easier comparison with the exposure assessment.

Dose-response assessment

73. The modelling approach used in the 2018 EFSA Opinion was criticised during the expert meeting (EFSA/CONTAM/3503). The lowest decile of antibody titre was used as the reference value rather than extrapolate and evaluate the BMR for a serum PFOS concentration of zero. In the present Opinion the data from both the Faroe Islands and Germany were modelled with PROAST and BMDS which resulted in wide BMDL-BMDU intervals, as a consequence of extrapolating to zero exposure (well below the lowest observed serum levels). Therefore, NOAECs were derived based on the distribution of participants into quintiles.

74. For the Faroe Island study a NOAEC of 27.0 ng/mL was derived for the sum of the four PFASs in serum of 5-year-old children (serum level in 4th quintile, Appendix L of the EFSA Opinion). A NOAEC of 31.9 ng/mL was obtained for 1-year-old children in the study from Germany (3rd quintile, EFSA Opinion Appendix K). Since PFAS serum levels in breastfed children are in general higher at 1 years of age than at 5 years of age, this NOAEC corresponds to a lower intake by the child and thus the mother in her life up to

pregnancy. Therefore, this NOAEC was used to estimate the daily intake by mothers that would result in this critical serum concentration at 1 year of age in breastfed children. This daily intake was subsequently used to derive a maternal reference point for the sum of PFOA, PFNA, PFHxS and PFOS.

75. A physiologically-based pharmacokinetic (PBPK) model was used in the previous Opinion (EFSA, 2018) to translate the critical serum levels into a daily intake and was carried out for PFOS only. In the current Opinion PFOA is also modelled (EFSA Opinion Appendix M provides details of the PBPK modelling). It has been shown that during breastfeeding, a substantial part of the PFASs in the mother is transferred to the infant, and as a result, serum levels in the mother but also milk levels decrease over the lactation period. This decline was also included in the model. The data for PFNA and PFHxS were insufficient, but it was assumed that these compounds behave like PFOA and PFOS, respectively.

76. The serum level of 31.9 ng/mL was the sum of the levels of PFOA, PFNA, PFHxS and PFOS of 15.1, 0.5, 2.1 and 14.2 ng/mL, respectively. Alternatively this is 15.6 ng/mL for the PFCAs and 16.3 ng/mL for the PFSAs. Using the model, and assuming 12 months of breastfeeding, it was estimated that for PFOA/PFNA this corresponds to an intake by the mother of 0.33 ng/kg bw per day and for PFHxS/PFOS of 0.83 ng/kg bw per day, or 1.16 ng/kg bw per day for the sum of the four PFASs. These intakes would result in serum levels in the mother at 35 years of age of 3.5 ng/mL for PFOA/PFNA and 9.1 ng/mL for PFHxS/PFOS or a combined value of 12.6 ng/mL. This serum level would result in initial milk levels of 0.11 and 0.14 ng/mL for PFOA/PFNA and PFHxS/PFOS, respectively, based on the applied milk to serum ratios of 0.03 and 0.015.

77. The CONTAM Panel decided to use the daily intake of 1.16 ng/kg bw per day as the starting point for the derivation of an HBGV for the sum of the four PFASs.

78. The CONTAM Panel considered animal studies, but when compared to the results of human studies, suggested that the application of the various uncertainty factors is too conservative and supports the use of the human data to derive an HBGV.

79. The CONTAM Panel also considered the mammary gland effects, observed in animal studies, to be potentially adverse for humans. However, basing the assessment on the effects on mammary glands using animal data and uncertainty factors, would result in a much lower HBGV.

Derivation of a Health Based Guidance Value

80. The CONTAM Panel decided to derive an HBGV based on immune effects in humans. Two studies showed a dose-response and the NOAEC from the most sensitive study was used to derive a reference point, being 1.16 ng/kg bw per day for the sum of the four PFASs.

81. No additional uncertainty factors were applied because the NOAEC is based on infants which are expected to be a sensitive population. The CONTAM Panel also took into account that the NOAEC is based on risk factors for disease rather than disease.

82. The CONTAM Panel established a TWI of 7 x 1.16 = 8 ng/kg bw per week, to take into account the long half-lives of these PFASs.

83. This TWI is protective for the other potential critical endpoints (increase in serum cholesterol, reduced birth weight and high serum levels of ALT).

Risk Characterisation based on the new TWI

53. UK Lower bound mean exposures (Annex C, Table 1b) for adolescents, adults, the elderly and the very elderly are below the TWI of 8 ng/kg bw per week. These exposures for other children just exceed the TWI, with a value of 9.7 ng/kg bw per week. Toddler and infant exceedances range from approximately 2- to 8-fold the TWI.

54. The UK lower bound 95th percentile exposures for adolescents, adults, the elderly and the very elderly do exceed the TWI up to about 2-fold. For other children the exceedance is greater than 3-fold. Toddler and infant exceedances range from approximately 3- to 10-fold the TWI.

55. UK upper bound mean exposures range from 97 to 590 ng/kg bw per week across the population groups, with infants having the highest exposures. These are 12- to 74-fold the TWI.

56. UK upper bound 95th percentile exposures range from 200 to 870 ng/kg bw per week across the population groups, with infants having the highest exposures. These are 25- to 110-fold the TWI.

57. Serum level modelling of the four PFASs indicates that the lower bound exposure is a more accurate prediction of the exposure than the upper bound estimates which would lead to a much higher exceedance of the critical serum levels.

58. The exceedances of the TWI at lower bound exposure estimates indicate a health concern.

59. Members are invited to read the Opinion and Annex attached as Annexes on this paper and comment on the approach used by EFSA.

Questions for the Committee

i. Does the Committee agree with the selection of the critical study for the derivation of an HBGV?
ii. Do Members agree with the approach of using the sum of four PFASs?
iii. Do the Members agree on the model used by EFSA for the derivation of an HBGV?
iv. Do the Members agree on the TWI established?
v. Do the Members have any further comments?

Secretariat

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Abbreviations

Abbreviations for the perfluoroalkylated substances have not been included as they are in a table at the beginning of the document.

ALT	Alanine aminotransferase
ANSES	Agency for Food, Environmental and Occupational Health and Safety
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMDU	Benchmark dose upper confidence limit
BMR	Benchmark response
CI	Confidence interval
CONTAM	Contaminants in the Food Chain
EFSA	European Food Safety Authority
FSANZ	Food Safety Australia New Zealand
GFR	Glomerular filtration rate
GI	Gastrointestinal tract
HBGV	Health-based guidance value
HBM	German Human Biomonitoring
Hib	Haemophilus Influenzae type b
IPCS	International Programme on Chemical Safety
LDL	Low-density lipoprotein
NOAEC	No observed adverse effect concentration
OATs	Organic anion transporters
PBPK	Physiologically-based Pharmacokinetic
PFASs	Perfluoroalkylated substances
RIVM	Dutch National Institute for Public Health and the Environment
TEQ	Toxic equivalent
TWIs	Tolerable weekly intakes
WHO	World Health Organisation

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Discussion paper for the EFSA Public Consultation on the draft Opinion on the risk to human health related to the presence of perfluoroalkyl substances in food

The link below is to the EFSA Opinion "Risk to human health related to the presence of perfluoroalkyl substances in food" and its associated annexes

https://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-opinion-risks-human-health

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Discussion paper for the EFSA Public Consultation on the draft Opinion on the risks to human health related to the presence of perfluoroalkyl substances in food

The following are the references for the 2 epidemiological papers used in the process of the derivation of the HBGV:

Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P and Heilmann C. (2012). Serum Vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA*. **307:** 391-397. doi: 10.1001/jama.2011.2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22274686

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UK exposures

UK exposures from the EFSA Opinion have been tabulated for ease. The values were taken from Annex A, Table/Spreadsheet A5. Only data from UK surveys for the sum of all 4 PFASs were included. The data in the Opinion were on a bw/day basis (Table 1a). The values were multiplied by 7 (Table 1b) to gives values for bw/week.

Table 1a. Mean and 95th percentile(a) chronic exposures to the 4 PFASs (ng/kg b.w. per **day**) for total population

Survey	Age	Number of subjects	LB Mean exposure	UB Mean exposure	LB 95th Exposure	UB 95th Exposure
NDNS years 1-3	Toddlers	185	2.4	64	6.4	120
NDNS years 1-3	Other children	651	1.4	47	3.9	91
NDNS years 1-3	Adolescents	666	0.5	21	1.5	49
NDNS years 1-3	Adults	1266	0.6	14	1.8	29
NDNS years 1-3	Elderly	166	0.8	14	2.1	29
NDNS years 1-3	Very elderly	139	0.8	16	2.2	32
DNSIYC 2011	Infants	1369	8.8	85	15	120
DNSIYC 2011	Toddlers	1314	4.1	66	11	110

Exposures are to 2 significant figures

Table 1b. Mean and 95th percentile(a) chronic exposures to the 4 PFASs (ng/kg b.w. per **week**) for total population

Survey	Age	Number of subjects	LB Mean exposure	UB Mean exposure	LB 95th Exposure	UB 95th Exposure
NDNS years 1-3	Toddlers	185	17	450	45	850
NDNS years 1-3	Other children	651	9.7	330	27	640
NDNS years 1-3	Adolescents	666	3.2	150	10	350
NDNS years 1-3	Adults	1266	4.3	97	13	200
NDNS years 1-3	Elderly	166	5.5	100	14	210
NDNS years 1-3	Very elderly	139	5.6	110	15	220
DNSIYC 2011	Infants	1369	61	590	110	870
DNSIYC 2011	Toddlers	1314	29	460	74	770

Exposures are to 2 significant figures

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