Toxicity - Statement on the EFSA Opinion on the risks to human health related to the presence of perfluoroalkyl substances in food

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Observations in experimental animals

32. Studies on effects following repeated exposures to PFOS and PFOA published prior to 2017 have been reviewed in previous EFSA Opinions. This statement 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 is covered in the EFSA Opinion and in more detail in Appendices D to I of the opinion.

Effects following acute exposure

33. Considering the limited number of published data on acute exposure effects, studies on both oral and non-oral exposure were considered.

34. For the group of PFCAs, studies on PFHxA and PFDA were identified. The LD50s for PFHxA ranged between 1,750 and 5,000 mg/kg bw in female rats (route not stated but probably oral) and for PFDA between 120 and 129 mg/kg bw in female mice (oral gavage). In male mice, PFDA reduced the expression of major transporters for bile acids in the liver; as a result, 80 mg/kg bw increased serum bile acid concentrations. The same dose elevated the hepatic expression of the hepatic transporters Mrp3 and Mrp4 interfering with the hepatic efflux of bilirubin and bile acids to serum. Hepatocellular injury and inflammation at 50–80 mg of PFDA/kg bw were also reported .

35. With regard to other PFASs, EtFOSE did not alter peroxisomal ß-oxidation or relative liver weights, when administered i.p. to male rats at 100 mg/kg bw.

36. Cynomolgus monkeys, treated with a single dose of 9 mg PFOS/kg bw by gavage, showed no significant effects. A single gavage dose of 8:2 FTOH at 500 and 2,000 mg/kg bw exerted no effects in male and female rats.

Effects following repeated exposure

37. The most consistent and sensitive endpoint was increased relative liver weight, especially in male rodents, seen for all PFCAs studied.

38. Disturbances in lipid metabolism, hepatotoxic effects and signs of cholestasis were evident, mostly at higher dose levels. For some PFCAs, increased relative kidney weight, alterations of the mucosa in the nasal cavity and olfactory epithelium and disturbed thyroid hormone levels were among the most sensitive endpoints.

39. An elevated absolute and relative liver weight was the most sensitive endpoint for PFBS, PFHxS and PFOS. No repeated dose toxicity studies were available for PFHpS and PFDS. Disturbed lipid metabolism, necrosis and inflammation in the liver were mostly seen at higher dose levels. Also disturbed thyroid hormones and alterations in the kidney (PFBS only) were documented.

40. Studies were available for 8:2 FTOH and EtFOSE, while for FOSA and EtFOSA, no studies were identified. 8:2 FTOH treatment increased dose-dependently the relative liver weight and hepatic beta-oxidation. Liver toxicity was evident by histological changes, comprising vacuolation, cell swelling, immune cell infiltration, karyopyknosis and nuclear swelling. Several EtFOSE metabolites were present in liver and serum, with PFOS and FOSA being predominant. EtFOSE treatment lowered the body growth rate and increased the relative liver weight. Peroxisomal ß-oxidation activity was elevated non-significantly.

Developmental and reproductive toxicity

41. 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 (Tables 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).

42. PFOA exposure was shown to impair normal development of the mammary gland in mice exposed late in gestation or via lactation, in studies in two mouse strains, which was the most sensitive developmental outcome. The pup LOAEC was around 20 ng/mL on PND 22 corresponding to a maternal LOAEC of around 66 ng/mL. No NOAEC was identified.

43. The most sensitive endpoint after gestational exposure to PFNA was increased liver weight in both maternal and offspring mice, and a reduction in postnatal weight gain in F1, with an LOAEL of 1 mg/kg bw per day, and a corresponding concentration in serum from the dam at term of 20 µg/mL. Delay in development was seen at 3 mg/kg bw per day, and at 5 mg/kg bw per day, there was an increase in neonatal mortality. A 90-day male reproductive study reported decreased sperm production, decrease in cholesterol, steroidogenic enzymes and testosterone, as well as decreased number of pups in the next generation, with an NOAEL and LOAEL of 0.2 and 0.5 mg/kg bw per day, respectively. Effects on male reproduction parameters were also reported by NTP in rats at higher exposure levels (it was noted by EFSA that 28 days is shorter than one spermatogenic cycle and too short to fully assess male reproductive parameters).

44. Exposure of rats to PFDoDA prior to and during gestation induced maternal and reproductive effects (continuous dioestrus and fetal loss) with an NOAEL of 0.5 mg/kg bw per day. Male reproductive effects (decreased spermatid and spermatozoa counts) were seen at a similar NOAEL of 0.5 mg/kg bw per day, which is higher than the NOAEL of 0.1 mg/kg per day observed for repeated dose toxicity in the same experiment.

45. Reproductive toxicity was not reported in rats exposed to PFBS up to 1,000 mg/kg bw per day. Delay in development and decrease in body weight gain were seen in mice exposed during gestation, with an NOAEL of 50 mg/kg bw per day (74 ng/mL serum in the dam at GD 20).

46. The most sensitive reproductive endpoint for PFHxS exposure was reduced litter size at 1 mg/kg bw per day in mice (51.5 µg/mL serum on GD 18 in dams) with an NOAEL of 0.3 mg/kg bw per day (16.8 µg/mL serum on GD 18 in dams). At 1 mg/kg bw per day, increased liver weight was seen in the dams. Gestational exposure to PFHxS produced effects in offspring animals at doses which were equal to or higher than those inducing responses in parental animals.

Neurotoxicity

47. 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.

48. One study indicates that PFDoDA, in contrast to PFDA and PFOA, can efficiently transfer into rat brain and causes cognitive behavioural changes.

Immunotoxicity

49. 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.

50. 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.

51. 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.

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

Genotoxicity

53. 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 reached in that Opinion.

54. 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

55. Long-term toxicity 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.

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

Observations in humans

57. Regarding the four outcomes (increased serum cholesterol, impaired antibody response after vaccination, increased serum ALT, and decreased birth weight) that were considered potential critical effects in the Opinion on PFOS and PFOA (EFSA CONTAM Panel, 2018), key studies published after the deadline of the literature review for the PFOS and PFOA Opinion (EFSA CONTAM Panel, 2018), were also considered.

Fertility and pregnancy outcomes

Birth weight

58. 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. Relatively modest 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.

59. Since the 2018 EFSA Opinion, eight new studies have been published on PFOS and PFOA. None of these studies contradicted the conclusion from the 2018 Opinion that “there may well be a causal association between PFOS and PFOA and birth weight”.

60. 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

61. 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 (Meng et al., 2018) which looked at preterm delivery and maternal serum PFAS, but the data were in line with the conclusions of the 2018 Opinion.

Developmental effects

62. 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

63. 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

64. 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.

65. 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

66. In the previous Opinion on PFOS and PFOA six studies were reviewed. Since then, three more studies have been published. 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 in this draft statement and appendices L and K of EFSA (2020) for the Grandjean et al and Abraham et al studies, respectively.

67. 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 age 5 years 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, in that vaccination was an deliberative procedure. 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:

68. 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.

69. Association between 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 diphtheria 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 antibody 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 antibody levels against diphtheria. Similar elevated odds were reported for tetanus at age 7.5.

70. **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. Hence, it is unclear whether the associations reported previously for PCBs were due to confounding by exposure to PFASs. 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).

71. 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.

72. 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 titres. 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 diphtheria, 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.

73. In summary, the different compounds appear to 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.

74. The studies published since the 2018 Opinion strengthen the conclusion that both PFOS and PFOA are associated with reduced antibody response to vaccination, although there are some inconsistencies. The evidence for other PFASs is weaker, possibly because the concentrations are lower.

Clinical Infections

75. 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

76. 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 effects on these endpoints.

Metabolic outcomes

Blood lipids

77. 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”.

78. 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 conclusion is that the uncertainty regarding causality is larger than that stated in the previous Opinion.

79. 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 shows an association with serum cholesterol which is independent from PFOS/PFOA.

Diabetes, Obesity and Metabolic Syndrome

80. 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

81. In the previous Opinion the CONTAM Panel considered that the association between PFOA and elevated ALT was causal, but the adversity of an increase that was within 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 EFSA Opinion.

82. 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.

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

Kidney function and uric acid

84. When reviewed in the 2018 Opinion studies showed that there were relatively strong associations between serum PFOS/PFOA and estimated glomerular filtration rate (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 were associated with a decrease GFR or increase uric acid in serum.

Carcinogenicity outcomes

85. When the CONTAM Panel (2018) reviewed studies on cancer incidence and 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

86. 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.

87. 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 the basis of an HBGV.

Bone mineral density

88. 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 was 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.

Mode of Action

89. In animals, the most commonly reported effects are those on the liver (increased weight, hypertrophy, increased fat content) and the levels of thyroid hormones, cholesterol and triglycerides, and liver transaminases in serum. In addition, some PFASs were shown to cause liver tumours.

90. Furthermore, effects on the immune system, as well as on the development of the mammary gland, were observed in various studies, often at lower levels than those causing effects on the liver and thyroid hormones.

91. The MoA behind the most sensitive PFOA effect, which is a decrease in mammary gland development in animals dosed during gestation and neonatally, is unknown. Normal mammary gland development does not require PPARα expression, but PPARα activation in pregnancy can reduce mammary gland development in the dam.