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It does not reflect the final views of the Committee and should not be cited.

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

First draft statement on the EFSA Opinion on "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food" – RESERVED Business

Background

1. EFSA are due to publish an Opinion "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food". New health-based guidance values have been established for both perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA).

2. A brief overview of the EFSA Opinion has been provided in the draft statement (Annex A). UK exposures have been provided in order to compare to the HBGV for an updated risk assessment.

3. A discussion paper was reviewed by the Committee at the September meeting. The Committee considered the use of epidemiology data for the derivation of an health-based guidance value and the bench mark dose (BMD) and physiologically-based pharmacokinetic modelling. In order to aid with their discussion additional experts were invited for PBPK modelling and epidemiology, especially relating to PFOS and PFOA. This draft statement reflects the discussions of the COT.

Questions on which the views of the Committee are sought

4. Members are asked to comment on the structure and content of the draft statement.

i). Do Members think that there is a need for further PBPK modelling?

ii) Do Members agree with the conclusions?

Secretariat

October 2018

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First draft statement on the EFSA Opinion on "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food" – RESERVED Business

Introduction

1. EFSA are due to publish an Opinion "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food". New health-based guidance values have been established for both perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). However, these are significantly different to the values established by EFSA in 2008.

2. Animal toxicity data have been considered. However, a large number of epidemiological studies have become available since the 2008 Opinion and it is these that EFSA have used to determine health-based guidance values.

3. In order to use the epidemiological data and establish HBGVs for PFOS and PFOA, EFSA used Benchmark dose (BMD) modelling to calculate $BMDL_5$ (the lower one-sided confidence limit of the BMD for a 5% response) values for each of the critical effects for PFOS and PFOA.

4. EFSA (2018) used physiologically based pharmacokinetic (PBPK) modelling to estimate the relationships between serum concentrations of PFOS and PFOA and dietary intakes. The $BMDL_5$ values calculated using the BMD modelling, expressed as PFOS and PFOA levels in plasma, were converted into dietary exposure values, corresponding to life-time continuous exposure.

5. The results from the PBPK modelling are used to derive tolerable weekly intakes. Members are asked to comment on the derivation of a TWI as the HBGV.

Previous EFSA Opinion

6. Prior to this EFSA had published an Opinion on these chemicals in 2008. In this the tolerable daily intake (TDI) for PFOS was established as 150 ng/kg bw per day. It was based on a NOAEL of 0.03 mg/kg bw per day identified in a subchronic study in cynomolgus monkeys. To this an overall uncertainty factor of 200 was applied. For PFOA a range of values from 0.3 – 0.7 mg/kg bw per day were identified for the 95% lower confidence limit of the benchmark dose for a 10% increase in effects on the liver ($BMDL_{10}$). EFSA selected the lowest value in the range and applied an uncertainty factor of 200 to establish a TDI of 1.5 µg/kg bw per day.

7. For the 2018 Opinion a literature search was undertaken by EFSA for the oral toxicity of PFASs their precursors and potential replacements in experimental

animals and humans covering the period 2008 to 2013. Further literature searches were carried out to cover the period between 2013 and 2016.

Brief summary of the 2018 EFSA Opinion

Toxicokinetics

PFOS

8. PFOS is extensively absorbed in humans and readily distributed in plasma, liver, kidney and lung. Both urine and bile are PFOS routes of excretion, with a biliary resorption rate of 97%, which could contribute to the long half-life in humans (5.4 years). In women, breast milk and menstruation fluids are additional elimination routes of PFOS. Urinary excretion of PFOS is dependent on the isomeric composition of the mixture present in blood and the gender/age/kidney function of the individuals. PFOS has been detected in umbilical cord blood, breast milk and plasma samples of breastfed toddlers indicating that maternal transfer occurs pre- and postnatally. (EFSA, 2018).

PFOA

9. Once absorbed PFOA distributes in plasma, liver, kidney, lung and bone and does not undergo metabolism. In plasma, PFOA is mainly bound to albumin. PFOA is eliminated primarily in the urine, with lesser amounts eliminated in the faeces. Biliary excretion of PFOA was significantly higher than serum clearance via the urine, but does not substantially contribute to overall elimination, due to high biliary reabsorption. Humans have a high estimated percentage of PFOA renal tubular reabsorption (99.94%). Several studies estimated the half-lives of PFOA in humans, most of them suggesting values between 2 and 4 years. In women, breast milk and menstruation fluids contribute to the elimination of PFOA. PFOA has been detected in umbilical cord blood, breast milk and plasma samples of breastfed toddlers indicating that maternal transfer occurs pre- and postnatally. (EFSA, 2018).

Toxicity in experimental animals

10. EFSA have evaluated and tabulated all of the animal toxicity studies for PFOS and PFOA. Studies on acute toxicity, repeated dose toxicity, developmental and reproductive toxicity, neurotoxicity, immunotoxicity, genotoxicity, and long-term toxicity and carcinogenicity had been published since the 2008 Opinion. Summaries have also been provided for each area of toxicity.

11. After consideration of the studies for acute toxicity and in agreement with the 2008 Opinion EFSA concluded that PFOS and PFOA have moderate acute toxicity after oral administration. Repeated dose toxicity studies have shown increased liver weight, hypertrophy of hepatocytes, and induction of peroxisomal β-oxidation an indication that the rodent liver is the major target organ for PFOS. Increased relative liver weights in studies since the EFSA Opinion of 2008, in rats and mice, confirmed that the liver is also the main target organ for PFOA induced toxicity. Another indication for liver toxicity of PFOA was enhanced lipid peroxidation. Alterations of

kidney and serum thyroid hormone levels have also been observed, but at higher concentrations of PFOA. (EFSA, 2018).

12. EFSA summarised the developmental and reproductive studies and concluded that PFOS affected developmental processes with the most sensitive endpoints being impact on maternal liver weight, placental physiology and aspects of glucose homeostasis. No NOAEL was identified for these effects. For PFOA there was clearly an impact on developmental processes and metabolic processes at doses as low as 0.01 mg/kg bw per day. The most sensitive pathological change was noted for increased liver weight in pups at 0.1 mg/kg bw per day. (EFSA, 2018).

13. For neurotoxicity as an endpoint, both PFOS and PFOA appear to exert effects at doses in the range of 0.1-0.3 mg/kg bw per day or higher. The most frequent alterations were related to locomotor activity. PFOS exposure generally decreases spontaneous activity, whereas PFOA increases it. Sex-related differences have been observed in several studies with males being the most sensitive. (EFSA, 2018).

14. After assessing a number of studies with immunotoxicity as an endpoint EFSA concluded that PFOS disturbs homeostasis of the immune system and is immunotoxic at doses as low as 1.66 µg/kg bw per day. When assessing the available literature on PFOA, EFSA noted that the available evidence suggests that exposure has effects on the immune system *in vivo*. These data suggest a dysregulation of the immune system with different influences on innate versus acquired immunity. Effects were usually seen at doses that also induce general toxic effects such as on food intake and body weights. (EFSA, 2018).

15. When assessing the genotoxicity studies, EFSA concluded that the data for PFSO and PFOA are inconclusive. There is some evidence that observed effects are related to oxidative stress, but no evidence for a direct genotoxic mode of action *in vivo* or *in vitro*. (EFSA, 2018).

16. No new long-term or carcinogenicity studies for PFOS or PFOA had been published since the 2008 Opinion. However, a re-evaluation of a long-term carcinogenicity study had been published for PFOS and confirmed that the liver is the main target organ for chronic toxicity and carcinogenicity. Re-evaluations of former studies were also carried out for PFOA. EFSA concluded that there is a lack of consistent data and knowledge on the mode of action and it therefore cannot be excluded that PFOA is carcinogenic to humans. This is in agreement with the classification of PFOA by IARC as a group 2B carcinogen. (EFSA, 2018).

Human observations

17. A number of epidemiological studies were assessed by EFSA. There were no studies on acute effects of either PFOS or PFOA. Other toxicological endpoints that were assessed include: fertility and pregnancy outcomes, developmental outcomes, neurotoxic outcomes, immune outcomes, endocrine outcomes, metabolic outcomes, kidney and uric acid, carcinogenicity outcomes, cardiovascular outcomes, and other studies/various outcomes.

18. A number of studies looking at birth weight were assessed by EFSA. Although not all studies reported significant inverse association with birth weight there appears to be an overall tendency towards an inverse correlation between concentrations of PFOS/PFOA and birth weight. Overall, despite relatively consistent inverse associations being observed there remains some uncertainty about the causality of the findings. EFSA considered a number of other fertility and pregnancy outcomes but concluded that there was insufficient or limited evidence to associate PFOS or PFOA with increased risk of preterm delivery, birth defects or still births, increased risk of pregnancy loss, pregnancy induced hypertension or preeclampsia, or that PFOS or PFOA may adversely affect fecundity. (EFSA, 2018).

19. EFSA evaluated 30 longitudinal studies looking at developmental outcomes and overall concluded that there was insufficient support for an association between prenatal exposure to PFOS or PFOA and early life neurobehavioral development or overweight. (EFSA, 2018).

20. EFSA assessed 8 cross-sectional studies, 5 in children and 3 in adults, with various neurotoxicity outcomes. No consistent adverse associations were found with serum levels of PFOS or PFOA. Several studies found inverse (protective) associations. (EFSA, 2018).

21. EFSA assessed studies with immune outcomes. Based on a number of studies EFSA concluded that there is not much evidence to suggest that PFOS or PFOA are associated with asthma and allergies in children and adults and there is little evidence to suggest that early life exposures to PFOs or PFOA are causally related to allergies or asthma in children. There is, however, relatively strong evidence that serum concentration of PFOS or PFOA are adversely associated with antibody response. Although confounding cannot be fully excluded, EFSA concluded that the association between PFOS and PFOA, with serum antibody concentrations is likely to be causal. (EFSA, 2018).

22. EFSA assessed the studies for endocrine outcomes. Based on 4 studies there was little evidence suggesting that PFOS or PFOA are related to the development of puberty, menopause or menstrual cycle length. Based on 2 cross-sectional studies there was insufficient evidence that PFOS and PFOA are associated with endometriosis. There was insufficient support for associations between PFOS or PFOA and thyroid disease or changes in thyroid hormones. In studies with adult males, the evidence in these cross-sectional studies did not support the hypothesis that serum PFOS and PFOA concentrations are predictors of semen quality or adverse changes in reproductive hormones. (EFSA, 2018).

23. Studies looking at metabolic effects were assessed. Twenty-six studies on associations between PFOS and/or PFOA and serum lipids were assessed by EFSA. Of these 16 were published after the 2008 Opinion and most of these showed significant positive associations between PFOS and/or PFOA and total cholesterol. Results for LDL cholesterol were similar but associations for HDL were usually null. Based on these studies EFSA concluded that it is likely that associations between serum PFOS and PFOA levels and serum cholesterol are causal. EFSA assessed a number of studies and concluded that it was likely that there was a causal positive association between PFAO and ALT, but that this adversity had not been shown

within the reference range. However, in one very large cohort an association between PFOA and ALT was found above the reference range. The data for PFOS are inconsistent. Fifteen studies were assessed on the associations between PFOS and or PFOA and glucose homeostasis or diagnosis of diabetes. Overall the results do not indicate adverse effects on glucose homeostasis or increased risk of diabetes, overweight or obesity due to exposure to PFOS or PFOA. EFSA therefore concluded that there was no evidence that PFOS or PFOA increase the risk of metabolic syndrome. (EFSA, 2018).

24. Studies looking at kidney and uric acid were assessed by EFSA. After consideration, EFSA concluded that the evidence that PFOS/PFOA exposure causes reduced glomerular filtration rate (GFR) or kidney disease was insufficient. In assessing association with PFOS/PFOA and uric acid, 4 studies found a positive association between serum PFOS and serum uric acid and 6 studies found an association for serum PFOA. The associations may be causal, but they may also be confounded by GFR. Overall EFSA concluded that there was insufficient evidence to conclude that exposure to PFOS and PFOA cause increased levels of uric acid in the serum. (EFSA, 2018).

25. Studies looking at carcinogenicity outcomes were either in an exposed population or 3 studies looked at background exposure. Based on these studies EFSA concluded that studies in the occupationally exposed population and individuals with background exposure to PFOS and PFOA provide limited evidence to suggest that there is an association with increased cancer risk. This conclusion is in agreement with the conclusion from the recent IARC report on PFOA, that there was limited evidence for carcinogenicity. (EFSA, 2018).

26. EFSA evaluated the available 5 cross-sectional and 4 longitudinal studies for associations between PFOS/PFOA and cardiovascular outcomes. Overall, these studies do not show any clear causal association. However, if there is only a small increase of relative risk, these studies would not be able to demonstrate it. (EFSA, 2018).

27. There were also studies available for a few other outcomes. Some results from a very large cohort study suggest an association between serum PFOA (but not PFOS) and risk of ulcerative colitis. However, more studies are needed to assess this hypothesis. Three cross-sectional studies were available for arthritis and provided only limited support for an association between PFOA and risk of osteoarthritis, and for PFOS the results are inconsistent. EFSA evaluated 2 cross-sectional studies which showed some inverse associations between PFOS/PFOA and bone mineral density, but only in some subgroups and for some sites, with limited consistency between the studies. There was also a single paper using multi-level regression analysis based on a very large cohort which presented slight but statistically significant associations between serum PFOA and C-reactive protein, within water and between water districts. (EFSA, 2018).

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

Critical effects

28. EFSA considered associations between serum levels of PFOS/PFOA and several health outcomes to be causal and adverse. Because most of the human studies were not available for the 2008 EFSA Opinion and the toxicokinetics of PFOS/PFOA are different in animals and humans, EFSA decided to use human observations to establish critical effects and an HBGV

29. From a number of endpoints, EFSA selected 4 critical effects for which they deemed there was sufficient evidence of causality with exposure to PFOS and/or PFOA: increased serum cholesterol (indicating an increased risk of future cardiovascular disease) (paragraphs 23 and 26), increased prevalence of abnormal serum ALT levels (indicating an effect on hepatocytes) (paragraph 23), decreased antibody response after vaccination (indicating impaired immune function) (paragraph 21), and decreased birth weight (which may increase risk of low birth weight (below 2500 g) and risk of future disease) (paragraph 18). (EFSA, 2018).

COT comments on suitability of studies and causality

30. A full review of the discussion can be found in the Minutes from the September meeting[1].

Cholesterol

31. In general, positive associations have been reported between serum cholesterol levels and exposure to PFOS and PFOA in cross-sectional studies, most of which measured serum concentrations of these chemicals. There was no direct interaction between cholesterol and PFOS or PFOA. Whilst there appears to be an association, there may also be unidentified confounders. The cross-sectional studies were insufficient on their own for the association to be deemed causal, but there was also a longitudinal study which showed a positive association. When all the studies are taken together the association was considered likely to be causal. There were also occupational studies in which associations were observed with serum cholesterol concentrations but not with cardiovascular disease (CVD). There was a clear association up to about 40 ng/mL PFOA, but no association at concentrations greater than this suggesting that the mechanism may become saturated above this concentration.

32. Members discussed the observation that animal data show PFOA and PFOS generally cause a decrease in cholesterol levels, compared to the increase observed in humans. A recent study in human cancer patients, where PFOA was administered as a potential anti-cancer treatment, showed a decrease in serum cholesterol levels (Convertino *et al*., 2018[2]). On the other hand, dietary administration of PFOA at a

[1] Item 7: Discussion paper on the EFSA Opinion on "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. (Reserved Business) (TOX/2018/33). Once these Minutes are published a link will be added.
[2] Convertino M, Church TR, Olsen GW, Liu Y, Doyle E, Elcombe CR, Barnett AL, Samuel LM, MacPherson IR and Evans TRJ. (2018). Stochastic Pharmacokinetic-Pharmacodynamic Modeling for

dose of 0.5 mg/kg bw to mice on a high-fat, high-cholesterol diet resulted in 30-70% increase in serum cholesterol levels (Rebholz *et al*., 2016[3]). On balance, there was significant uncertainty as to whether the association between PFOA and PFOS and cholesterol levels in humans was causal. However, the Committee concluded that in general, the epidemiology data were consistent and it was difficult to dismiss this as not being causal.

ALT

33. Some cross-sectional studies and a cohort study showed a positive association between serum ALT levels and intakes of PFOA. However, the increase in ALT was modest, no adverse effects on the liver having been reported, and could be subject to confounding. The overall conclusion for ALT and PFOA is that whilst there was likely to be some confounding, some of the association could be causal. The Committee concluded that the data for a causal effect of PFOA on ALT levels were less convincing than for serum cholesterol.

Birth weight

34. No association was found between birth weight and maternal exposure to PFOA/PFOS. However, a paper In Press[4] (not reviewed by EFSA), in which birth weight was stratified according to when, during pregnancy, serum levels were taken, reported a positive association in late pregnancy, but not in early pregnancy. This was consistent with confounding affecting the overall association. A larger baby would have a larger volume of distribution and therefore a lower PFOS/PFOA concentration. The Committee concluded that the data for an effect of PFOS or PFOA on birth weight were not very robust.

Immune effects

35. The studies which looked at immune effects studied different endpoints, different PFOA/PFOS concentrations and showed different associations. There was no consistent measure across studies. These studies were considered to be more hypothesis generating in nature.

Overall

36. The evidence for cholesterol and ALT shows that the association could well be causal, however for birth weight and immune effects it was much more questionable as to whether the associations were causal.

Assessing the Systemic Health Risk of Perfluorooctanoate (PFOA). Toxicological Sciences. 163(1): 293-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29462473

[3] Rebholz SL, Jones T, Herrick RL, Xie C, Calafat AM, Pinney SM, Woollett LA. (2016). Hypercholesterolemia with consumption of PFOA-laced Western diets is dependent on strain and sex of mice. *Toxicology Reports*. 3: 46-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26942110

37. There was also some suggestion of a carcinogenic effect in some occupational studies. A positive association was seen for both testicular and kidney cancers. However, the number of individuals was relatively small and the exposure range was wide. It was also noted that IARC have listed PFOA as class 2B highlighting that the evidence in humans for carcinogenicity is limited. It was unlikely that EFSA were convinced that there was a causal relationship because they did not use cancer as a critical endpoint.

38. Members noted that a range of studies had been considered in the EFSA opinion, but there was not much evidence synthesis. Instead, much of the report was summary and description of the studies. Members would have liked to have seen more evidence synthesis, weight of evidence in use, scoring to rank the studies and a commentary on the use of epidemiological rather than animal data. The Committee agreed that the epidemiological data was coherent and consistent and cannot be dismissed.

BMD modelling

39. BMD modelling was performed for each of these 4 critical effects for PFOS and/or PFOA using TableCurve2D software as EFSA had concluded that BMD software packages such as PROAST and BMDS were not applicable. According to EFSA with epidemiological data there is greater scattering of concentrations compared with animal experiments, no group with uniform concentration and no control group without exposure. It is also difficult to obtain individual data points and the data are analysed grouped as quantiles. (EFSA, 2018).

40. Using the TableCurve2D software BMD modelling was performed for each of the critical endpoints. Tables 1 and 2 provide an overview of the BMD modelling carried out by EFSA for PFOS and PFOA, respectively.

41. For most of the critical endpoints the BMD modelling was performed for a 5% increase (BMD_5) and a $BMDL_5$ calculated. However, for ALT and PFOA an absolute increase of 5% in serum ALT did not occur, but a 3% increase could be modelled therefore a $BMDL_3$ was calculated. This still enabled a comparison with other critical endpoints. For PFOS, $BMDL_5$ values were 21, 22 and 26 ng/mL for total cholesterol, 10.5 ng/mL for the vaccination response for children, and 21 ng/mL for birth weight (Table 1). For PFOA $BMDL_5$ values were 9.2 and 9.4 ng/mL for total cholesterol; 21 ng/mL for ALT ($BMDL_3$), and 4.0 and 10.6 ng/mL for birth weight (Table 2). (EFSA, 2018).

Table 1. Overview of the BMD analysis performed by EFSA for PFOS

Human response variable	BMD_5	$BMDL_5$	Number of people (cohort)	Data type	Model used	Reference
Total cholesterol	29	26	46,294 (C8 health project)	Decile	Lognormal cumulative	Steenland *et al.*, 2009[a]

	31	22	753 (Danish cohort 1996-2002)	Octile	Sqrt	Eriksen *et al.*, 2013[a]
	31	21	860 (NHANES)	Quartile	Exponential	Nelson *et al.*, 2010
Vaccination response for children	11.6	10.5	431 (Faroese birth cohort 1997-2002)	Decile	Logarithmic	Grandjean *et al.*, 2012[a]
Birth weight	36	21	901 (Norwegian mother and child cohort-MoBa)	Quartile	Logarithmic	Whitworth *et al.*, 2012[a]

Taken from EFSA (2018)
BMD: Benchmark dose; BMDL5: benchmark dose for a 5% increase; PFOS: Perfluorooctane sulfonic acid
[a] additional documentation provided to EFSA for the BMD modelling

Table 2. Overview of the BMD analysis performed by EFSA for PFOA

Human response variable	BMD_5	$BMDL_5$	Number of people (cohort)	Data type	Model used	Reference
Total cholesterol	12[c]	9.4[c]	46,294 (C8 health project)	Decile	Lognormal cumulative	Steenland *et al.*, 2009[b]
	12.4	9.2	753 (Danish cohort 1996-2002)	Octile	Lognormal cumulative	Eriksen *et al.*,2013[b]
Alanine transferase[a]	80	21	47092 (C8 health project)	Decile	Logistic	Gallo *et al.*, 2012[b]
Birth weight	14.5	10.6	1400 (Danish national birth cohort 1996-2002)	Decile	Linear	Fei *et al.*, 2007[b]
	4.4	4.0	901 (Norwegian mother and child cohort)	Quartile	Exponential	Whitworth *et al.*, 2012[b]

Taken from EFSA (2018)
BMD: Benchmark dose; $BMDL_5$: benchmark dose for a 5% increase; PFOA: Perfluorooctanoic acid
[a] BMD_3 and $BMDL_3$ for alanine transferase
[b] additional documentation provided to EFSA for the BMD modelling
[c] This was modelled extrapolating to a reference value of 1 ng/mL PFOA in serum (half the median of the median PFOA in Table 8 of EFSA (2018). A 5% increase in the lowest quantile could not be modelled.

42. The Committee discussed the benchmark dose (BMD) modelling carried out by EFSA. There was uncertainty as to why PROAST (EFSA's BMD software package) could not be used to perform the modelling. It would have been preferential to see more discussion from EFSA as to how they reached their conclusion as to the unsuitability of PROAST and BMDS. Otherwise, the Committee agreed with the BMD modelling approach undertaken by EFSA.

PBPK modelling

43. EFSA used a PBPK model developed by Loccisano *et al.* (2011) to estimate the daily dietary intake associated with the $BMDL_5$ serum/plasma concentrations for the potential critical effects. There are several PBPK models available for PFOS and PFOA in humans, but these are all based on the Loccisano (2011) model. The model simulations were consistent with the observed serum data with PFOS and PFOA at different exposure levels. This PBPK model for monkeys contains compartments for gut, plasma, liver, kidney, renal filtrate, fat, skin and rest of the body. Only the free fraction of the chemicals was assumed to partition into tissues.

44. The monkey PBPK model was extrapolated to humans (Loccisano *et al.*, 2011). The parameters used for PFOS and PFOA for humans were those previously described for the monkey and in addition, the physiological parameters were human data. The PBPK model means that measured serum/plasma concentrations can be used to reconstruct past intakes. This model was modified further by integrating an equation describing the increase in weight according to age and by correcting some other parameters. The daily dietary intakes of PFOA and PFOS associated with the $BMDL_5$ concentrations for the potential critical effects in the BMD analysis can thus be calculated (Tables 3 and 4).

45. For PFOS the calculated dietary intakes were 1.7, 1.8 and 2.1 ng/kg bw per day for total cholesterol as the critical effect and 1.9 ng/kg bw per day for birth weight. For PFOA the estimated dietary intakes were 0.8 ng/kg bw per day for total cholesterol, 2.0 ng/kg bw per day for ALT and for birth weight as the critical end point were 1.0 and 0.4 ng/kg bw per day. These estimates correspond to the life-time continuous dietary exposure estimates which should not be exceeded in order to reach the target concentration (BMDLs) at adult age. (EFSA, 2018).

Table 3. Summary of dietary intake estimates, calculated by EFSA, that by PBPK modelling predict PFOS serum concentration at the $BMDL_5$ for potential critical effects

Human response variable	$BMDL_5$ (ng/mL)	Reference	Estimated dietary intakes (ng/kg bw/day) corresponding to the $BMDL_5$ using the PBPK model
Total cholesterol	26	Steenland *et al.*, 2009	2.1
	22	Eriksen *et al.*, 2013	1.8
	21	Nelson *et al.*, 2010	1.7
Birth weight	21	Whitworth *et al.*, 2012	1.9

Taken from EFSA (2018).
BMDL5: Benchmark does for a 5% increase; PBPK: physiologically-based pharmacokinetic (model).
[a] At 50 years
[b] At 35 years, relevant age for pregnant women

Table 4. Summary of dietary intake estimates, calculated by EFSA, that by PBPK modelling predict PFOA serum concentration at the BMDLs for potential critical effects

Human response variable	$BMDL_5$ (ng/mL)	Reference	Estimated dietary intakes (ng/kg bw/day) corresponding to the $BMDL_5$ using the PBPK model
Total cholesterol	9.4	Steenland *et al.*, 2009	0.8
	9.2	Eriksen *et al.*, 2013	0.8
Alanine transferase	21	Gallo *et al.*, 2012	2.0
Birth weight	10.6	Fei *et al.*, 2007	1.0
	4	Whitworth *et al.*, 2012	0.4

Taken from EFSA (2018)
BMDL5: Benchmark does for a 5% increase; PBPK: physiologically-based pharmacokinetic (model).
[a] BMD_3 and $BMDL_3$ for alanine transferase
[b] At 50 years
[c] At 35 years, relevant age for pregnant women

46. The Committee discussed the PBPK modelling carried out by EFSA. There were a few concerns regarding the model used. A key factor in the modelling was the long half-lives assumed for PFOS and PFOA. The robustness of the estimates used was questioned. Also, there may be limitations in extrapolating to children less than 5 years of age because the model will give different values due to the growth rates and organ masses etc at this age. When used to predict plasma levels in pregnant women, this model was rather simplistic and other models would be more realistic. The model used by EFSA was originally built as a model for cynomolgus monkeys, but the physiological and anatomical factors used were human. Assumptions were made within the modelling, the partition coefficients seemed low, but may not have been wrong. The code appears to be acceptable. This was a quite simple deterministic model and not much can be said about the variability. In order to determine how sensitive model output was to the parameters, a local sensitivity analysis was used. Global sensitivity analysis should also have been undertaken.

Health-based guidance values

47. Individual HBGVs were established for PFOS and PFOA. EFSA considered that the toxicity and underlying modes of action were not sufficiently understood and might differ or overlap and could not therefore establish a group HBGV.

48. Three potential critical endpoints (serum cholesterol, antibody response after vaccination and birth weight) were considered for PFOS. EFSA weighed the overall evidence from the human observational studies. For these endpoints the daily calculated intakes resulting in the critical serum concentrations were 1.7 – 2.1 ng/kg bw per day. For the increase in serum cholesterol, the critical effect in adults, it was a median value of 1.8 ng/kg bw per day. The dietary intake for reduced birth weight was 1.9 ng/kg bw per day and was in the same range as increased cholesterol. In addition, when the maternal serum PFOS is in the range of the $BMDL_5$ values for increase of serum cholesterol, the child's serum PFOS can be expected not to exceed the $BMDL_5$ of 10.5 ng/mL. (EFSA, 2018).

49. EFSA considered the value of 1.8 ng/kg bw per day to be an appropriate reference point for PFOS without the need for any additional uncertainty factor, because the BMD modelling was based on large epidemiological studies. In order to take into account the long half-life of this contaminant EFSA established a tolerable weekly intake (TWI) of 13 ng/kg bw per week for PFOS. (EFSA, 2018).

50. In the case of PFAO, EFSA considers the increase of serum cholesterol to be the critical effect and the intake value of 0.8 ng/kg bw per day to be an appropriate reference point. As with PFOS due to the long half-life of PFOA, EFSA established a TWI of 6 ng/kg bw per week for PFOA. This TWI is also protective for increased liver damage, indicated by high serum ALT and against reduced birth weight. No additional uncertainty factor was used because the BMD modelling was based on large epidemiological studies. (EFSA, 2018).

UK exposures

51. Exposures to PFOS and PFOA by UK populations have been calculated for breast milk and the diet and are presented below. In the time available it has not been possible to gather data and calculate exposures for water, air, soil and dust. These exposures can be presented in a follow-up paper.

Breast milk

52. A literature search was carried out for concentrations of PFOS and PFOA in human breast milk. There were no UK data. Only data from countries in the EU with breast milk samples taken after 2008 were considered. Only those that had median and/or maximum values were included in the exposure calculations. Tables 5 and 6 show the studies and breast milk concentrations for PFOS and PFOA, respectively

Table 5. Concentrations of PFOS in breast milk in EU studies where breast milk samples were taken after 2008.

Region, country	Year of sampling	No. of samples	Mean LB-UB (SEM) (ng/L)	Median (ng/L)	Range (ng/L)	Reference
Barcelona, Spain	2009	20	116-117[#]	84[#]	< LOQ-865	Llorca *et al.*, 2010
France	2010	30	78	74	24-171	Kadar *et al.*, 2011
Belgium	2009-2010	40 (P & M)	130	100	NR	Croes *et al.*, 2012
Bologna, Italy	2010	21 (P)	57 (13)	NR	<15-288	Barbarossa *et al.*, 2013
		16 (M)	36 (7)	NR	<15-116	
France	2010-2013	61	40	<LOQ	<LOD-376	Cariou *et al.*, 2015
Czech Republic	2010	50	33	30	7-114	Lankova *et al.*, 2013

P – primiparous; M – multiparous; SEM – standard error of the mean; NR – not reported; *identified by year; [#]calculated from individual data in the published paper

Table 6. Concentrations of PFOA in breast milk in recent EU studies where breast milk samples were taken after 2008

Region, country	Year of sampling	No. of samples	Mean LB-UB (SEM[a] or SD[b]) (ng/L)	Median LB-UB (ng/L)	Range (ng/L)	Reference
Barcelona, Spain	2009	20	150-158[#]	0-15[#]	< LOQ-907	Llorca *et al.*, 2010
France	2010	30	59	57	18-102	Kadar *et al.*, 2011
Belgium	2009- 2010	40 (P & M)	80	70	NR	Croes *et al.*, 2012
Bologna, Italy	2010	21 (P)	76 (14)[a]	NR	24-241	Barbarossa *et al.*, 2013
		16 (M)	43 (6)[a]	NR	24-100	
France	2010-2013	61	41	<LOQ	<LOD-308	Cariou *et al.*, 2015
Czech Republic	2010	50	50	44	12-128	Lankova *et al.*, 2013
Murcia, Spain	2014	40/67 (P & M)	54 (54)[b]	26	<LOQ-211	Motas-Guzman *et al.*, 2016

P – primiparous; M – multiparous; SEM – standard error of the mean; NR – not reported; *Eleven additional samples were above the detection limit (0.01 ng/mL) but the blank level was > 50% of the detected concentrations (blank level 0.209 ng/mL); [$]identified by year; [#]calculated from individual data in the published paper; [a]SEM; [b]standard deviation (SD)

53. In the absence of a suitable UK study of PFOS and PFOA in breast milk, data from EU studies for which all samples were taken after 2008 have been used in this paper. The exposure estimates are based on: (i) a PFOS concentration of 72 ng/L (derived as a mean of the median values reported by Llorca *et al*., 2010, Kadar *et al*., 2011, Croes *et al*., 2012 and Lankova *et al*., 2013); (ii) a PFOS concentration of 322 ng/L (derived as a mean of the highest values reported by; Llorca *et al*., 2010, Kadar *et al*., 2011, Barbarossa *et al*., 2013, Cariou *et al*., 2015 and Lankova *et al*., 2013) (iii) a PFOA concentration of 42 ng/L (derived as a mean of the median values reported by Llorca *et al*., 2010, Kadar *et al*., 2011, Croes *et al*., 2012, Lankova *et al*., 2013 and Motas-Guzman *et al*., 2016); (iv) a PFOA concentration of 285 ng/L (derived as a mean of the highest values reported by Llorca *et al*., 2010, Kadar *et al*., 2011, Barbarossa *et al*., 2013, Cariou *et al*., 2015, Lankova *et al*., 2013 and Motas-Guzman *et al*., 2016).

54. No consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months. Therefore, the default consumption values used by the COT in other evaluations of the infant diet of average (800 mL) and high-level (1200 mL) consumption have been used to estimate exposures to PFOS and PFOA from breast milk. The ranges of mean and high-level exposure to PFOS in exclusively breastfed 0 to 6-month-old infants were 52 – 310 ng/kg bw/week and 78 – 460 ng/kg bw/week respectively (Table 7). The ranges of mean and high-level exposure to PFOA in exclusively breastfed 0 to 6 month-old infants were 30 – 270 ng/kg bw/week and 45 – 410 ng/kg bw/week respectively (Table 7).

55. Data on breast milk consumption for infants and young children aged 4 to 18 months were available from the DNSIYC and the NDNS and have been used to estimate exposures at these ages (Table 7).

56. There were too few records of breast milk consumption for children older than 18 months in the NDNS to allow a reliable exposure assessment, and breast milk is expected to contribute minimally in this age group.

57. Mean exposures to PFOS for 4 to 18 month olds were estimated to be between 13 to 210 ng/kg bw/week, and 97.5th percentile exposures were between 26 to 360 ng/kg bw/week (Table 7). Mean exposures to PFOA for 4 to 18 month olds were 7.4 to 180 ng/kg bw/week and 97.5th percentile exposures were 15 to 320 ng/kg bw/week (Table 7).

Table 7. Estimated PFOS and PFOA exposure in 0 to 18-month-old infants and young children from breast milk

Exposure (ng/kg bw/week)	Age group (months)					
	0 to <4	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18
Average consumer (PFOS concentration 72 ng/L)	68[a]	52[a] 46[b]	34[b]	16[b]	15[b]	13[b]
High-level consumer (PFOS concentration 72 ng/L)	100[a]	78[a] 78[b]	80[b]	58[b]	38[b]	26[b]
Average consumer (PFOS concentration 322 ng/L)	310[a]	230[a] 210[b]	150[b]	86[b]	66[b]	57[b]
High-level consumer (PFOS concentration 322 ng/L)	460[a]	350[a] 350[b]	360[b]	260[b]	170[b]	120[b]
Average consumer (PFOA concentration 42 ng/L)	40[a]	30[a] 27[b]	20[b]	11[b]	8.6[b]	7.4[b]
High-level consumer (PFOS concentration 42 ng/L)	60[a]	45[a] 46[b]	47[b]	34[b]	22[b]	15[b]
Average consumer (PFOA concentration 285 ng/L)	270[a]	200[a] 180[b]	130[b]	76[b]	59[b]	50[b]
High-level consumer (PFOA concentration 285 ng/L)	410[a]	310[a] 310[b]	320[b]	230[b]	150[b]	100[b]

[a] Based on default consumption values of 800 and 1200 mL for average and high level exclusive consumption of breast milk and expressed on a bodyweight (5.9 kg for infants aged 0-4 months and 7.8 kg for infants aged 4 to < 6 months) basis.
[b] Based on mean and 97.5th percentile consumption of breast milk from DNSIYC (DH,2013)
Values rounded to 2 SF

Overall exposures from the diet

58. Concentrations of PFOS and PFOA in foods sampled in the UK were for the 19 composite food groups of the 2012 Total Diet Study (TDS) (Fernandes *et al.,* 2012).

59. PFOS was detected in all food groups at concentrations ranging from 0.02 µg/kg to 2.7 µg/kg. The highest concentrations were in offal and fish samples. PFOA was detected in all group except fats and oils at a range of <0.05 (fats and oils group) to 1.5 µg/kg (in the fish group).

60. Data from the TDS were used to calculate Upper-bound (UB) mean and high-level exposures to PFOS and PFOA in different population groups (Table 8). In the case of toddlers, adults, including the elderly, and young people (all age brackets) the exposure data reported were based on consumption data from the NDNS rolling survey (Bates *et al.*, 2014; Bates *et al.*, 2016; and Roberts *et al.*, 2018). Data on consumption from the Diet and Nutrition Survey in Infants and Young Children (DNSIYC) (Department of Health, 2013) together with those on occurrence of PFOS and PFOA from the UK TDS were used to estimate dietary exposures of infants from complementary foods (Table 8).

PFOA

61. The overall UB mean and 97.5th percentile PFOA exposures from consumption of all foods for infants and young children aged 4 – 18 months, were 53 and 120 ng/kg bw per week, respectively.

62. Mean and high-level exposure in toddlers and young people (aged 4-6 years) was similar to infants. Mean and high-level exposures were lower in young people aged 7 – 10 years. Young people aged 11-14 and 15 – 18 years had mean and 97.5th percentile exposures similar to those of adults aged 19+ years (22 and 45 ng/kg bw/week, respectively). The consumption of offal and fish made the main contribution to total PFOS exposure.

PFOS

63. The overall UB mean and 97.5th percentile PFOS exposures from consumption of all foods for infants and young children aged 4 – 18 months were 27 and 65 ng/kg bw/week, respectively.

64. The corresponding exposures calculated for toddlers were similar. Mean and high-level exposures in young people aged 4 -6 and 7 – 10 years were slightly lower. Mean and 97.5th percentile exposures in young people aged 11 – 14 and 15 – 18 years were approximately the same as those of adults (11 and 22 ng/kg bw per week, respectively). The consumption of offal and fish made the main contribution to total PFOS exposure.

Table 8. PFOS and PFOA exposures (ng/kg bw per week) for UK population groups calculated from the 2012 Total Diet Study.

Age Group	Exposure to Perfluorinated Compounds (ng/kg bw/wk)			
	PFOA		PFOS	
	Mean Exposure UB	P97.5 Exposure UB	Mean Exposure	P97.5 Exposure

4 to 18-month Olds	53	120	27	65
Toddlers (1.5 - 3 years old)	69	120	32	60
Young People (4-6 years old)	62	110	26	48
Young People (7-10 years old)	46	88	19	37
Young People (11-14 years old)	29	54	12	24
Young People (15-18 years old)	22	45	9.8	22
Adults (19+ year olds)	22	45	11	22

65. In addition, as PFOS and PFOA were due to be reviewed by the COT as part of the infant (0-12 moths) and young child (1-5 years) work requested by the Scientific Advisory Committee on Nutrition[5], a second table (Table 9) shows PFOS and PFOA exposures for age groups consistent with those used in the statements for other chemicals.

PFOA

66. Mean UB PFOA exposures ranged from 26 to 72 ng/kg bw/week for infants and young children. The corresponding high-level exposures ranged from 83 to 130 ng/kg bw/week.

PFOS

67. Mean PFOS exposures ranged from 17 to 36 ng/kg bw/week for infants and young children. Corresponding high-level exposures ranged from 52 to 69 ng/kg bw/week for infants and young children.

Table 9. PFOS and PFOA exposures for UK infants aged 4 to 12 months and young children aged >12 to 60 months (ng/kg bw per week) calculated from the 2012 Total Diet Study.

Age Group	**Exposure to Perfluorinated Compounds (ng/kg bw/wk)**	
	PFOA	**PFOS**

[5] A Scoping paper in 2015 outlined chemicals which could be reviewed as part of the infant and young children aged 1-5 years feeding work. Available at: https://cot.food.gov.uk/sites/default/files/TOX2015-32%20Feeding%20Review%20Scoping%20Paper.pdf
The Minutes reflecting the views of the COT are available at:
https://cot.food.gov.uk/sites/default/files/cotfinalminutes-27oct15.pdf

	Mean Exposure UB	P97.5 Exposure UB	Mean Exposure	P97.5 Exposure
4 to 5.9 month Olds	26	83	17	62
6 to 8.9 month Olds	36	100	19	63
9 to 11.9 month Olds	48	110	24	64
12 to 14.9 month Olds	64	130	34	69
15 to 18 month Olds	69	130	36	66
18 to 24 month Olds	72	130	36	65
24 to 60 month Olds	67	110	30	52

Provisional risk characterisation

68. A provisional risk characterisation has been carried out.

Breast milk

69. Average PFOS exposures from breast milk (with a concentration of 72 ng/L) for infants and young children aged 0 – 18 months range from 13 – 68 ng/kg bw/week. High-level exposures at the same concentration range from 26 – 100 ng/kg bw/week. Average exposures are 100 – 520 % of the TWI of 13 ng/kg bw/week. High-level exposures are 200 – 770 % of the TWI.

70. Average PFOS exposures from breast milk (with a concentration of 322 ng/L) for infants and young children aged 0 – 18 months range from 57 – 310 ng/kg bw/week. High-level exposures at the same concentration range from 120 – 460 ng/kg bw/week. Average exposures are 440 – 520 % of the TWI of 13 ng/kg bw/week. High-level exposures are 920 – 3500 % of the TWI.

71. Average PFOA exposures from breast milk (with a concentration of 42 ng/L) for infants and young children aged 0 – 18 months range from 7.4 – 40 ng/kg bw/week. High-level exposures at the same concentration range from 15 – 60 ng/kg bw/week. Average exposures are 120 – 670 % of the TWI of 6 ng/kg bw/week. High-level exposures are 250 – 1000 % of the TWI.

72. Average PFOA exposures from breast milk (with a concentration of 285 ng/L) for infants and young children aged 0 – 18 months range from 50 – 270 ng/kg bw/week. High-level exposures at the same concentration range from 100 – 410 ng/kg bw/week. Average exposures are 830 – 4500 % of the TWI of 6 ng/kg bw/week. High-level exposures are 1700 – 6800 % of the TWI.

UK dietary exposures

73. PFOS and PFOA exposures were calculated for the rest of the diet, excluding drinking water, for all of the population groups in Table 10. For mean PFOS exposures young people aged 11-18 years and adults aged 19+ years are below the TWI. Other age groups range from 150 – 250 % of the TWI. All age groups exceed the TWI at 97.5th percentile exposures and these range from 170 – 500 % of the TWI of 13 ng/kg bw/week. All age groups exceed the TWI for PFOA at mean and 97.5th percentile exposures. Mean exposures range from 370 – 1200 % of the TWI and 97.5th percentile exposures range from 750 – 2000 % of the TWI.

Table 10. Percent of the TWI calculated for PFOS and PFOA exposures from the diet for NDNS population groups

Age Group	Percent of the TWI (%)			
	PFOA (TWI of 6 ng/kg bw/week)		PFOS (TWI of 13 ng/kg bw/week	
	Mean Exposure UB	P97.5 Exposure UB	Mean Exposure UB	P97.5 Exposure UB
4 to 18 month Olds	880	2000	210	500
Toddlers (1.5 - 3 years old)	1200	2000	250	460
Young People (4-6 years old)	1000	1800	200	370
Young People (7-10 years old)	770	1500	150	280
Young People (11-14 years old)	480	900	90	180
Young People (15-18 years old)	370	750	80	170
Adults (19+ year olds)	370	750	90	170

74. PFOS and PFOA exposures were calculated for the rest of the diet, excluding drinking water, for all of the infant and young child population groups in Table 11. All age groups exceed the TWI for PFOS and PFOA at both mean and 97.5th percentile

exposures. PFOS mean exposures range from 130 – 280 % of the TWI and 97.5th percentile range from 400 – 530 % of the TWI of 13 ng/kg bw/week. Mean PFOA exposures range from 430 – 1200 % of the TWI of 6 ng/kg bw/week and 97.5th percentile exposures range from 1400 – 2200 % of the TWI.

Table 11. Percent of the TWI calculated for PFOS and PFOA exposures from the diet for infants aged 4 to 11.9 months and young children aged 12 to 60 months.

Age Group	Percent of the TWI (%)			
	PFOA (TWI of 6 ng/kg bw/week)		PFOS (TWI of 13 ng/kg bw/week)	
	Mean Exposure UB	P97.5 Exposure UB	Mean Exposure UB	P97.5 Exposure UB
4 to 5.9 month Olds	430	1400	130	480
6 to 8.9 month Olds	600	1700	150	480
9 to 11.9 month Olds	800	1800	180	490
12 to 14.9 month Olds	1100	2200	260	530
15 to 18 month Olds	1200	2200	280	510
18 to 24 month Olds	1200	2200	280	500
24 to 60 month Olds	1100	1800	230	400

Conclusions

75. Members agreed that the human data should be used to establish a health-based guidance value. They agreed with the critical endpoints selected by EFSA, with some caveats. However, there were some reservations about the PBPK modelling.

76. All PFOS breast milk exposures were at, or exceeded, the TWI of 13 ng/kg bw. All PFOA exposures exceeded the TWI of 6 ng/kg bw. The levels of these chemicals in breast milk may be an issue, however the benefits of breastfeeding should be taken into account. These are likely to outweigh the risks. There are restriction orders on PFOS and PFOA in the EU, but there were concerns over their precursors.

77. For mean dietary PFOS exposures, young people aged 11-18 years and adults aged 19+ years were below the TWI of 13 ng/kg bw. All other calculated dietary PFOS exposures (Tables 10 and 11) exceeded the TWI by up to 530% (in young children aged 12 to 14.9 months (Table 11)).

78. For mean and 97.5th percentile PFOA dietary exposures, all population groups exceeded the TWI of 6 ng/kg bw by up to 2200% (Tables 10 and 11).

79. There is some level of concern for the exceedances of the TWIs for both PFOS and PFOA.

80. The level of risk that is acceptable needs to be determined in providing advice to consumers based on the EFSA risk assessment. Levels need to be monitored over time to determine whether there is a downward trend in serum PFOS and PFOA concentrations.

Secretariat

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