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)

1. Professor Neil Pearce from the London School of Tropical Medicine and Hygiene, an epidemiologist from COC and Dr Tony Fletcher, an epidemiologist from Public Health England (PHE) who participated as an "hearing expert" (meeting with the PFAS Working Group under the CONTAM Panel which prepared the 2018 PFOA /PFOS Opinion), were in attendance to assist the Committee. Dr George Loizou was available by teleconference to advise on physiologically based pharmacokinetic (PBPK) modelling.

2. Prof John Foster declared that he had read the pathology slides for some of the investigative studies conducted at CXR Biosciences Ltd, Dundee and was an author on some papers published prior to 2012. This was noted, and Prof Foster was allowed to join in discussions as the interest period had expired.

3. The Chair welcomed the invited experts to the meeting and thanked them for agreeing to participate in the discussions.

4. The Chair asked Professor Neil Pearce and Dr Tony Fletcher to comment on the robustness of the epidemiological data for the clinical endpoints in the EFSA opinion.

5. In general, positive associations have been reported between serum cholesterol levels and exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (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.

6. There were also occupational studies available which, generally, are not subject to as much, or the same confounding as cross-sectional studies in the general population. In these, associations were observed with serum cholesterol concentrations but not with cardiovascular disease (CVD). There was however an increase in low density lipoprotein and in serum triglyceride levels in association with PFOA exposure. In general, there was no change in high density lipoprotein. It is not clear what the mechanism is, but Members queried as to whether it could be PPARα, activation of which generally results in a reduction in serum cholesterol. 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.

7. 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[1]). On the other hand, dietary administration of PFOA at a 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[2]). 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.

8. Some cross-sectional studies and a cohort study showed a positive association between serum alanine aminotransferase (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.

9. No association was found between birth weight and maternal exposure to PFOA/PFOS. However, a paper In Press[3] (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.

10. 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.

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

[2] 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

[3] Steenland K, Barry V and Savitz D. (2018). Serum perfluorooctanoic acid (PFOA) and birthweight: an updated meta-analysis with bias analysis. Epidemiology. 2018 Jul 30. doi: 10.1097/EDE.0000000000000903. [Epub ahead of print]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30063543

11. 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.

12. 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.

13. 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.

14. 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. Otherwise, the Committee agreed with the BMD modelling approach undertaken.

15. The Committee also 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 were 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.

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

17. Many population groups with mean exposures are at or below the TWI for PFOS. For PFOA all mean and high exposure groups exceed the TWI. The levels of

these chemicals in breast milk may also be an issue, however the benefits of breastfeeding should be taken into account. These were likely to outweigh the risks. There were restriction orders on PFOS and PFOA in the EU, but there were concerns over their precursors.

18. The level of risk that was 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.

19. A draft statement would be brought back to the Committee at the October meeting, when it can be determined whether more modelling is required.