Critical effects, dose-response assessment and derivation of a health-based guidance value- Statement on the EFSA Opinion on the risks of perfluoroalkyl substances

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Critical effects

127. The CONTAM Panel decided to base its assessment on epidemiological studies. The EFSA assessment is summarised in the following paragraphs.

128. 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:

i. Increased serum total and LDL cholesterol (risk factor for cardiovascular disease,

ii. Increased ALT levels (indicating effects on liver cells),

iii. Reduced birth weight and

iv. Effects on the immune system as shown by decreased antibody response to vaccines.

129. In their 2018 Opinion, the CONTAM Panel used the effects on serum cholesterol levels to derive TWIs for PFOS 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.

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

131. There is a consistent association with an 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 (EFSA, 2020).

132. 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 function.

133. The effects on the immune system were observed at the lowest PFASs 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.

134. 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.

135. 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.

136. 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 diphtheria 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). BMDL modelling was carried out for this study but did not provide a BMDL considered suitable for risk assessment. The CONTAM Panel identified a no observed adverse effect concentration (NOAEC) serum level 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.

137. 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.

138. 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 an association with a 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.

139. A lowest BMDL10 of 17.5 ng/mL at the age of 1 year was derived for the sum of PFOA, PFNA, PFHxS and PFOS, based on the inverse association between serum levels of the sum of these four PFASs and antibody titres against diphtheria.

Mixture Approach

140. 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 chemicals show the highest concentrations in blood plasma and serum. In general, they also show the same effects when studied in animals.

141. 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 basis rather than a molar basis, to allow easier comparison with the exposure assessment.

Dose-response assessment

142. 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.

143. For the Faroe Island study, BMD modelling was undertaken by EFSA but resulted in wide BMDL– BMDU intervals. This was as a consequence of extrapolating to zero exposures and well below the lowest observed serum levels. Therefore, 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 4^{th} quintile, Appendix L of the EFSA Opinion), based on the decreased antibody titres for diphtheria at the age of 7 years.

144. For the Abraham study, BMD modelling was undertaken, and an association between serum levels of the sum of the four PFASs and titres of diphtheria and tetanus antibodies was shown. From 4 individual models (Appendix K. EFSA 2020) BMDL- BMDU intervals of 17.5 – 46.6 and 18.8 – 56.3 ng/mL were calculated for antibodies against diphtheria and tetanus, respectively. The models provided similar results. A critical effect size of 10 % was used due to the large variation in the response. The lowest BMDL of 17.5, from the individual models was used as the reference point. EFSA Opinion Appendix K).

145. This BMDL10 of 17.5 ng/mL corresponds to a lower intake by the child and thus the mother in her life up to pregnancy, than the NOAEC of 27.0 ng/mL from the Faroe Islands study. The CONTAM Panel also considered that PFAS serum levels in breastfed children are in general higher at 1 year of age than at 5 years. Therefore, this BMDL10 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 an HBGV for the sum of PFOA, PFNA, PFHxS and PFOS.

146. 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). The model was originally developed for adults but had been adapted to estimate the serum levels in growing children and to include exposure via breastfeeding. Data from human biomonitoring studies had been used to estimate the levels in human milk corresponding to a certain serum level in the mother. The prenatal exposure and body burden of the new-born were also estimated.

147. Using a PBPK model, and assuming 12 months of breastfeeding, it was estimated that the BMDL10 in infants corresponds to an intake by the mother of 0.63 ng/kg bw per day for the sum of the four PFASs. Such intake would result in a serum level in the mother at 35 years of age of 6.9 ng/mL.

148. 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 the mother’s milk level decrease over the lactation period . This decline was also included in the model. The data for PFNA and PFHxS were insufficient, but due to structural and toxicokinetic similarities, it was assumed that these compounds behave like PFOA and PFOS, respectively.

149. The serum level of 17.5 ng/mL was the sum of the levels of PFOA, PFNA, PFHxS and PFOS with relative contributions (based on the mean levels of these PFASs in 1-year old breastfed infants) of 48.4, 1.7, 6.1 and 43.8 %, respectively. This equates to contributions of 8.47, 0.30, 1.06 and 7.67 ng/mL for PFOA, PFNA, PFHxS and PFOS, respectively. The PBPK model was used to calculate the critical milk and corresponding serum levels in the mother at 35 years that would result in these levels of PFAS in the one-year old infant. Subsequently an estimate was made of the daily intakes by the mothers that lead to this critical serum level at 35 years. Assuming 12 months of breastfeeding, it was estimated that the BMDL10 in infants corresponds to an intake by the mother

of 0.63 ng/kg bw per day for the sum of the four PFASs (12 months was used as the duration of breastfeeding in the model because of current breastfeeding practices in Europe and based on the WHO recommendations to breastfeed exclusively for 6 months with continued breastfeeding along with appropriate complementary foods up to two years of age or beyond (EFSA, 2020)).

150. The CONTAM Panel decided to use the daily intake of 0.63 ng/kg bw per day as the starting point for the derivation of an HBGV for the sum of the four PFASs.

151. 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.

152. 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. Based on the uncertainties on whether these effects on mammary gland development occur in humans and extrapolation between species, the CONTAM Panel decided to use the vaccination response in humans as the critical endpoint. Nevertheless, this potential developmental effect is of potential concern.

Derivation of a Health Based Guidance Value

153. The CONTAM Panel decided to derive an HBGV based on immune effects in humans. Two studies showed a dose-response, although only one these was considered suitable for determination of a BMDL for risk assessment. After BMD modelling of this study, the lowest BMDL10 of 17.5 ng/mL was selected as the reference point. This was lower than the NOAEC in the other study, and was therefore considered sufficiently protective. PBPK modelling was then used to calculate the daily intake of the mother.

154. The daily intake of 0.63 ng/kg bw per day was decided upon as the starting point.

155. The CONTAM Panel established a group tolerable weekly intake (TWI) of 7 x 0.63 = 4.4 ng/kg bw per week for the sum of PFOA, PFNA, PFHxS and PFOS, to take into account the long half-lives of these PFASs.

156. It was decided that no additional uncertainty factors need to be applied, because the BMDL10 is based on infants, who are expected to be a sensitive population group, as is true for many immunotoxic chemicals. In addition, a decreased vaccination response is considered a risk factor for disease rather than an adverse outcome per se.

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