Minutes of the expert meeting on perfluorooctane sulfonic acid and perfluorooctanoic acid in food assessment

Article 30 of Regulation 178/2002

EFSA – ECHA – BfR - Danish EPA - RIVM

(Agreed on 10 December 2018)

Background

On 22 March 2018 the EFSA Panel on Contaminants in Food (CONTAM Panel) adopted a scientific opinion on the risks to public health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. Due to the fact that the CONTAM Panel, at the end, agreed to use endpoints from human epidemiological studies to derive the health-based guidance values, potential divergences between the CONTAM Panel scientific opinion and previous risk assessments of ECHA, Danish EPA and RIVM were identified at this stage. Following the presentation of the outcome of the opinion and the identified divergences to the EFSA Advisory Forum, potential contentious issues were raised also by BfR. Some of these issues were addressed by EFSA in correspondence with RIVM and BfR in preparation of the expert meeting.

An expert meeting was organised by EFSA to cooperate with the four interested parties, either to resolve the divergence or to prepare a joint document clarifying the contentious issues and identifying the relevant uncertainties, as indicated in Article 30 of Regulation 178/2002[1].

The minutes of the meeting were agreed by all parties on 10 December 2018.

1. Welcome and introduction to the meeting

The participants were welcomed by the Chair of the meeting, Juliane Kleiner.

2. Introduction of participants

The participants introduced themselves during a tour de table. The list of participants is enclosed (see Annex A).

3. Adoption of the agenda

The agenda (see Annex B) was adopted without changes.

4. Presentation of critical points from the EFSA assessment on PFOS & PFOA in food and summary of the potential divergences

Although experimental animal data were reviewed as part of the assessment in the EFSA CONTAM Panel opinion, due to differences in toxicokinetics and the relevance of observed effects in animals and underlying mode of action between experimental animals and humans, endpoints from human epidemiology studies were used to derive the Tolerable Weekly Intakes (TWIs).

The potential critical human endpoints were:

- increased serum cholesterol (indicating an increased risk of future cardiovascular disease).

[1] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, 1-24.

- increased prevalence of abnormal serum levels of alanine aminotransferase (ALT) (indicating an effect on hepatocytes).
- decreased antibody response after vaccination (indicating impaired immune function).
- decreased birth weight (which may increase risk of low birth weight (below 2500 g) and risk of future disease).

From these endpoints identified, the increase of serum cholesterol was considered to be the critical key adverse outcome for both PFOS and PFOA. For PFOS, three studies on serum cholesterol showed very similar $BMDL_5$ levels expressed as serum PFOS (21 – 25 ng/mL), corresponding to an estimated chronic daily intake of 1.7-2.0 (median 1.8) ng/kg bw per day. For PFOA, two studies on serum cholesterol showed very similar $BMDL_5$ levels expressed as serum PFOA (9.2 – 9.4 ng/mL), corresponding to an estimated chronic daily intake of 0.8 ng/kg bw per day. Considering the long half-life of PFOS and PFOA, the CONTAM Panel established TWIs of 13 and 6 ng/kg bw per week, respectively. If applied for all age groups, the TWI for PFOS is protective for adverse effects on vaccination response and reduced birth weight; maternal PFOS levels will be the major predictor of children's levels. For PFOA, the TWI is protective also for increased risk of liver damage (indicated by high serum ALT) and reduced birth weight.

EFSA identified the preference for human epidemiological studies over rodent studies for deriving health based guidance values for PFOS and PFOA as the major divergence with RIVM, ECHA and Danish EPA.

5. Presentation of the ECHA Position

In 2015, the committee for risk assessment (RAC), established a 'Derived No Effect Level' (DNEL) of 800 ng/mL serum for PFOA for the general population (ECHA, 2015). This was based on a mouse study by Lau et al, (2006) where a decreased pup growth rate in the order of 25-30% during post-natal days 13-23 was observed at doses of 3 mg/kg/day and higher, with a no-observed-adverse-effect-level (NOAEL) of 1 mg/kg/day. The corresponding serum concentration (estimated from the publication), gave a NOAEL of approximately 20,000 ng/mL. RAC used a total assessment factor of 12.5 (2.5 x 5), resulting in a worker DNEL of 1600 ng/mL serum. The corresponding DNEL for the general population was 800 ng/mL serum, using an intraspecies assessment factor of 10 (total assessment factor 2.5 x 10).

PFOA and its salts, and related substances, were restricted on the basis of the persistent bioaccumulating and toxic (PBT) identification and so this perceived divergence in the human health evaluation does not question the validity of the restriction or of EFSA's opinion. In the case of the human health evaluation, its only aim was to support the restriction more broadly and not to provide a definitive reference value or safe level. The divergence in the human health assessment comes from the different expert judgments on the robustness of the chosen point of departure, either based on animal or human information. This is noted by the ECHA secretariat and will be communicated for information to the former rapporteurs. ECHA and EFSA may consider how best to communicate the nature of this perceived divergence.

Human evidence was considered as part of the review, including developmental toxicity, cholesterolemia and immunotoxicity. However, ECHA considered these data not robust enough, or the adversity was unclear or there were uncertainties in the dose response.

6. Presentation of the Danish EPA position

The Danish EPA referred to the 2014 assessments by the US EPA (US EPA 2014a,b) to establish TDIs for PFOS and PFOA. The endpoint of liver toxicity in rats, from the studies by Thomford et al. (2002) and Palazzolo et al. (1993), was used to derive TDIs of 0.03 µg/kg bw per day and 0.1 µg/kg bw per day for PFOS and PFOA, respectively. Human studies were considered in the Danish EPA 2015 assessment (Larsen and Giovalle, 2015), however they were not considered to be adequate.

The divergence in the choice of the point of departure and TDIs between the EFSA opinion and Danish EPA assessment (2015) comes from the different expert judgments on the robustness of

human data. However, the Danish EPA is currently conducting a scientific review of the EFSA Scientific opinion in order to clarify if this divergence still exists.

7. Presentation of the BfR position

The BfR requested clarification on the following three main issues:

1. The relevance of the observed changes in biomarkers in epidemiological studies in the context of the derivation of TWI values for PFOS and PFOA.
2. The safety of a long breastfeeding period for young children regarding possible effects on reduced antibody formation after vaccination.
3. Exposure assessment: possible overestimation of estimated intake of PFOS/PFOA if a substantial proportion of samples originated from "hotspot regions".

Further details on each of these issues are provided below:

1) The relevance of the observed changes in biomarkers in epidemiological studies in the context of the derivation of TWI values for PFOS and PFOA.

Increase in total cholesterol

1. *Selection of total serum cholesterol (TC) as compared to differentiated cholesterol fractions (like LDL-C or TC/HDL-C) as point of departure for the derivation of the TWI-values.*

BfR agrees that the use of a less indicative factor such as total cholesterol is justified in the case that study data are limited, in this case data missing on LDL cholesterol. However, as this possibly limits data interpretability the BfR proposes that the resulting limitation should be discussed in the uncertainty analysis (Indicative power of total serum cholesterol as toxicological endpoint, chapter 3.6.2.2.1 serum cholesterol).

2. *Assessment of the study by Steenland et al (2009) from a clinical point of view*
3. *Selection of the threshold for a clinically relevant increase in total cholesterol in the light of the nature of cardiovascular diseases (CVD) as multifactorial processes/relationship between an increase in total serum cholesterol and an increase of cardiovascular diseases.*
4. *Assessment of the proportion of the population that would be above the reference range.*

BfR considers additional information provided by a letter from EFSA explaining how EFSA derived the value of 240 mg/dL serum cholesterol from the study by Steenland et al, (2009) as very helpful and proposes the inclusion of the following paragraph, which is based on the information from EFSA, in section 3.4.1.1 of the EFSA opinion:

> *"In the study by Steenland et al. (2009) the mean TC was 199 mg/dL and the SD was 42. For an ideal normal distribution, a shift of the whole distribution to the right due to an increase of serum cholesterol by 5%, will increase the prevalence of "high levels" (in this case serum cholesterol above 240 mg/dL, defined as "hypercholesterolemia" by Steenland et al., prevalence 15%) considerably (by about 9%). An unpublished evaluation of the raw data of Steenland et al. (2009) (Data provided (Fletcher, 2017) showed an approximately normal distribution of serum cholesterol levels. An increase of serum cholesterol levels by 5% would result in an increased prevalence of cholesterol levels above 240 mg/dL by more than 5%".*

In the view of BfR it could be concluded that a 5% shift to higher total cholesterol levels on the population level represents an undesirable change. However, the health risk that is associated with an increase of total cholesterol of 5% for an individual cannot be indicated without referring to other risk factors such as age or blood pressure. BfR would appreciate if the EFSA opinion or a related document on frequently answered questions (FAQs) could clearly state which health outcomes would result from an exceedance of the TWI for which groups of the population.

In the view of BfR one of the (crucial) limitations of the EFSA Opinion is that established drivers of CVD other than PFOS/PFOA are not discussed in detail. Given that the opinion relies heavily on epidemiological data to define cardiovascular risks as the most sensitive endpoint, established drivers for CVD other than PFOS/PFOA should be discussed in a separate chapter (at least age, gender, blood pressure).

Furthermore, all epidemiological studies on the association of blood cholesterol and increased risk for CVD included in the EFSA Opinion are inherently limited with regard to the age of the study population. In the key study mentioned in the EFSA Opinion, the meta-analysis by Lewington et al. (2007) on the association between the relative risk for CVD and TC, the youngest age group is 40-49 years old. There is no information on the effect of cholesterol on CVD for younger subjects. In the meta-analysis by Mihaylova et al. (2012) a reduction of LDL-C was associated with a decrease of CVD only for the age groups studied (59±8 to 66±9 years). If there is no information on the effect of cholesterol on CVD for younger subjects (<40 years) then BfR suggests that the lack of data for people <40 years is indicated in the EFSA Opinion.

In the meta-analysis by Lewington et al. (2007) there is a *"negative association of cholesterol with stroke mortality at older ages or at higher blood pressures."* BfR proposes that this issue should be addressed in more detail including the discussion of results that at first might be contradictory.

5. Possible coincidence of increased serum levels of PFOS and PFOA with higher total cholesterol serum levels resulting from a possible common reabsorption (of bile salts, PFOS and PFOA) from the gut and the uptake into the liver via shared membrane transport pathways.

PFOS and PFOA as well as bile salts undergo enterohepatic circulation (EHC). The re-uptake of bile salts from the gut generates a negative feedback loop, effectively reducing the de novo synthesis of bile acids from cholesterol in the liver. The EHC requires the transporter-mediated uptake of bile salts into enterocytes and hepatocytes. Several transporters such as NTCP (Na^+/taurocholate co-transporting polypeptide), ASBT (apical sodium-dependent bile salt transporter) and OATPs (organic anion transporting peptide) are involved in the uptake of bile salts (Pellicoro and Faber, 2007). NTCP and ASBT are also involved in the transport of PFOS (PFOA was not tested) (Zhao et al., 2015). In addition, several OATPs (OATP1B1, OATP1B3, OATP2B1) can transport PFOA and PFOS (Zhao et al., 2017). A polymorphism in the OATP1B1-coding gene was found to be associated with the plasma concentrations of certain bile acids and a bile acid synthesis marker (Xiang et al., 2009). A sequence variation in a key EHC uptake transporter is therefore able to modulate the serum levels of EHC substances.

Against this background, BfR suggests the following mechanism for a possible coincidence of increased serum levels of PFOS and PFOA with higher total cholesterol serum levels:

1. A population-level variability in the enterohepatic circulation (EHC) of bile salts exists which is driven by minor variability of intestinal reabsorption.
2. The variability in EHC translates, via negative feedback regulation, into variability of TC serum levels.
3. The variability in EHC affects intestinal reabsorption of PFOS/PFOA and, thereby, the serum levels of PFOS/PFOA.

In a scenario with a constant population exposure to PFOS/PFOA, such a mechanism would generate a positive association between the TC serum level and the PFOS/PFOA serum levels. In a scenario with a variable population exposure (with constant exposure at the individual level), low PFOS/PFOA serum levels would occur in individuals with lower PFOS/PFOA exposure and reduced EHC. These individuals would also show lower TC serum levels. Applying then, for example, a quantile analysis to

the PFOS/PFOA serum level data would show the lowest average TC serum levels for the lowest PFOS/PFOA quintile. Such a mechanism would also be able to generate the saturating doses-response curves (serum TC vs PFOA/PFOS deciles) which were described by Steenland et al. (2009).

It should be noted that the proposed mechanism does not downplay the role of exposure as the primary driver for the PFOS/PFOA serum levels. Instead, the hypothesis is raised as an additional mechanism that could be able to modulate PFOS/PFOA serum levels. The results of the retrospect analysis by Winquist and Steenland (2014) do not invalidate the proposed hypothesis, and the longitudinal study of Fitz-Simon et al. (2013) found a tendency for study participants with larger decreases in PFOA/PFOS serum levels to have a larger decrease in TC and LDL-C serum levels. This finding would argue against the aforementioned mechanism, that is, if confounders such as age-dependent changes in EHC can be excluded.

In conclusion, given the evidence that such a mechanism could potentially be operating, BfR recommends to include a detailed account on this topic into the opinion. Concerning TWI derivation, the risk should be considered of basing a TWI on a relationship that is likely to be coincidental rather than causal.

2) The safety of a long breastfeeding period for young children regarding possible effects on reduced antibody formation after vaccination.

The observations of a partially reduced formation of vaccine antibodies in association with internal exposure to PFOS and PFOA are currently based on few studies. The strongest associations were observed in the study in the Faroe Islands (Grandjean et al., 2012), whose inhabitants have a relatively high exposure to a large number of persistent contaminants as a result of the high consumption of fish and whale meat/blubber (e.g. Oulhote et al., 2017), which accumulate in the food chain. Therefore, in particular other environmental contaminants with high persistence have to be considered as possible confounders. In Faroe Island study, however, only the PCBs were measured in the children and were taken into account in the evaluation, but it was not possible to consider the co-exposure to other contaminants (e.g. heavy metals) or the mixed exposure as such. Furthermore, it is not clarified why in the same participants, a significant proportion of the children did not show the expected further drop in antibody titers at the follow-up at the age of 13 years, and why at this age the trends for tetanus antibodies and PFAS were mostly positive (Grandjean et al., 2017; not considered by EFSA[2]).

The clinical significance of the findings observed with regard to a possibly reduced efficacy of vaccinations is unclear. The measurement of vaccine antibodies in serum is a simple and well-established method, but the result is only a surrogate marker for vaccine efficacy. For most vaccines, the titers provide no indication of the protective potency of the vaccine and the actual functioning of the immune system in the event of infection. Studies in humans on the PFAS effect on cellular components of the immune system or with functional examinations using *ex vivo* lymphocytes are not available. In addition, basic questions such as the underlying mechanisms of action or possibility of a sensitive time window during childhood (the studies available to date have looked at children 3 years and older) are unanswered. In addition, it cannot be inferred from the few available studies whether – if the effect is causally caused – the decreased antibody production for different vaccinations varies.

To date, there are only limited indications from studies with children whose prenatal exposure to PFAS has been recorded with regard to the question of a possibly existing general immunotoxic effect of PFAS compounds leading to an increased susceptibility to infections. Studies on the susceptibility to postnatal PFAS exposure in breastfed children are not available. Even if this only allows a rough statement, it can still be said that the large US cohort in the vicinity of a former PFOA-producing factory in Ohio/USA ("C8 study") with tens of thousands of participants despite comparatively high PFOA exposure (mean 69.2 µg/L in a group of 12,476 children and adolescents, Frisbee et al., 2010), there are yet no reports of increased incidence of infections or vaccine breakthrough infections.

[2] Note from EFSA: published after the literature inclusion deadline.

In conclusion, BfR rates the evidence for a reduced antibody formation after vaccination caused by PFOS/PFOA exposure as limited to moderate, and more preferably prospective studies are needed with high statistical power. These studies should include, in terms of the window of sensitivity, the end of a long lactation period (age 0.5 to 1.5 years) when the highest levels of PFAS in breastfed children are expected, and antibody response can be investigated for the many vaccinations carried out during the first year of life. In addition to titers of vaccine antibodies, also functional parameters of the immune system and metabolic parameters should be included. Furthermore, other research approaches should be used, e.g. the clarification of possible mechanisms of action.

Considering the current evidence available, BfR would not have used the study results to derive HBGVs.

Furthermore, BfR is not convinced by the modelling approach of the EFSA CONTAM Panel to derive an HBGV in case of antibody data and exposure to PFOS:

In principle, BfR agrees with the set-up of the modelling approach used by the EFSA CONTAM Panel. However, the way the model was used ("if a child would be breastfed exclusively for six months and partly … for some additional months, the serum levels will likely not reach the $BMDL_5$ at age 5 years") is not convincing for the BfR: the age of five years was used because in the key study (Grandjean et al., 2012), children were vaccinated at the age of five years and PFAS were analysed in blood. As shown by the modelling, breastfed children have distinctly higher PFOS levels at the age of six months (35 µg/L, compared to 9.6 µg/L at five years, scenario 2, Figure C4). If PFOS has indeed an immunotoxic effect, this will not be present at the age of five years only, and the first year of age would be expected to be more critical due to the much higher exposure in case of a long breastfeeding period as well as the due to the importance of this period regarding the vaccination regimen. In the BfR's view, the modelling approach used by the EFSA CONTAM Panel is not convincing to conclude on the safety of breastfeeding.

3) Exposure assessment: possible overestimation of estimated intake of PFOS/PFOA if a substantial proportion of samples originated from "hotspot regions".

The BfR considers that the opinion does not fully reflect the importance of the hotspot issue and the subsequent uncertainties associated with the exposure assessment. Two examples are described:

Example 1: PFOA in eggs
Occurrence data from Germany:

- ***27%** of the analytical results (45/164) traced to districts containing "hotspots"*
- *Analytical results **> LOD**: **14/15** originated from districts containing "hotspots"*

Example 2: PFOA in cow milk
*LB mean in the EFSA Draft Opinion: **0.067 µg/kg***
Only few samples above LOD/LOQ (97% left censored)
*Estimated quantifiable concentration **3.2 µg/kg***
***Translation into concentrations in feed** with transfer factors feed/milk:*
***2700 µg PFOA/kg DM in feed** or 670 µg PFOA/kg in water*

- *Values could be clearly attributed to a "**hotspot region**"*

The BfR propose that the EFSA opinion should include a more critical appraisal of this problem and suggest the expansion of the following paragraph from section 3.6.1 (indicated below in underlined text), as follows:

- "*The information on occurrence in food comes from monitoring programs, and also from routine measurements within the frame of official food controls, so they originated from both random and targeted sampling. Targeted sampling is usually focused on known or suspected contamination sites.* Given that contamination of the environment with PFOS/PFOA is spatially

very variable and substantially elevated in "hotspot" regions, inclusion of such data may result in significant *overestimation of exposure* for the general population not affected by the food and drinking water originated from hotspot areas."

Breast feeding risk-benefit analysis

In addition to the three main issues, BfR raised the issue of breastfeeding and whether EFSA intends to carry out a risk-benefit analysis of breastfeeding.

8. Presentation of the RIVM position

With regards to the chronic exposure to PFOA in the EFSA CONTAM Panel Scientific opinion, RIVM identified three main issues:

1. The suitability of the information in the epidemiological studies available for deriving a Point of Departure (PoD);
2. The assumptions made in the derivation of the PoD;
3. The inconsistency of the applied BMD analysis with the existing EFSA guidance.

These three issues are discussed below:

1) Suitability of the reported information of the epidemiological data for deriving a PoD.

The epidemiological data used by EFSA are insufficiently reported in the underlying publications to allow using them as a basis for quantitatively deriving a PoD. Typically, dose-response analysis (of continuous data) requires individual measurements or summary statistics (mean, SD/SEM and group size). Figures 2 and 3 in Steenland et al. (2009) provide modelled geometric mean TC and their confidence intervals (CIs) but the underlying group sizes and SDs are not reported. Neither does the EFSA opinion report the group sizes that were used from this study in the BMD analysis. In addition, it is not described how the SDs of ~60 used in the opinion were derived. Furthermore, Figures 2 and 3 in Steenland represent only a small subpopulation (one age group) and it is unclear from the Steenland study how this subpopulation relates to other subpopulations in the study and if the derived BMDs would be similar in those other subpopulations.
Specific issues addressed here are illustrated with the Steenland et al (2009) study but similar issues can be raised for the other studies analysed by EFSA in the opinion (Eriksen et al. 2013, Nelson et al. 2010, Grandjean et al. 2012, Whitworth et al., 2012, Gallo et al. 2012 and Fei et al. 2007).

2) Assumptions made in the derivation of the PoD.

2a. Validity of the dose-response curve

The dose-response for the effect by PFOA on TC as reported in Steenland et al. is a curve that levels off only 5% above the lowest decile (TC around 210 mg/dL versus around 200 mg/dL). However, it is known that the maximum response is a property of the endpoint (Slob and Setzer, 2014) and it tends to be much larger than 5% (Slob, 2017). For cholesterol, the response was estimated to level off at around 150% (in rodents) by Slob (2017). Compared to that estimate, a change of 5% is a minimal change and it can be questioned if this can be considered a correct maximum response in a dose-response relationship for cholesterol and thus usable for derivation of a PoD.

2b. Contribution of individual PFAS to the critical effect

Based on the data reported by Steenland et al. it is impossible to determine the contribution of each individual PFAS (PFOA, PFOS, PFNA, PFHxS) to the increased level of cholesterol. This was already mentioned by Steenland et al. who stated that the PFAS blood concentrations are correlated, 'making it difficult to sort out the role of each specific perfluorinated compound'. In the draft EFSA opinion, the increase in cholesterol is attributed to PFOA and PFOS individually for the derivation of the PoD. However, if one of the components would be completely responsible for the effect on cholesterol (which is the assumption in an individual BMD derivation), then the others could not have any impact at all.

3) Applied BMD analysis

3a. Applicability of EFSA BMD guidance

RIVM does not agree with the statement in Section 2.2.3, page 24 that 'the EFSA (2017) guidance does not apply to human data because of (1) the greater scattering of doses, i.e. there is no group with uniform dose in epidemiological studies compared to animal experiments, and (2) there is no control group without exposure due to the ubiquitous nature of contaminants like PFASs'. RIVM would like to refer to the EFSA BMD guidance where it is explicitly stated that (section 2.5.8): 'In principle, the BMD approach would also be applicable to human data.' Indeed, the scattering of doses leads to an increased uncertainty in the responses when doses are pooled into quantiles. In the case of continuous responses (as with cholesterol) the shape of the dose-response is not affected by variation within dose groups. Regarding the missing control group, in EFSA (2009) (section 5.7) and EFSA 2017 (example 3) it is explicitly stated that with epidemiology data the approach described in the guidance '…still applies, since fitting a dose-response curve does not necessarily require observations at zero exposure'. RIVM would like to emphasize that:

i. The EFSA guidance on BMD modelling applies to all study types, regardless which subjects and test methods are used: drosophila, nematodes, fish, in vitro cell systems, mice, rats, humans, etc. I.e. basic principles of BMD modelling apply equally to clinical trials, epi studies and other types of human studies.
ii. EFSA has been discussing appropriate methods and assumptions to perform BMD analysis in a working group existing of a large number of experts for years. It seems inappropriate to disregard the resulting BMD guidance and to decide to take an ad hoc approach.

3b. Definition of BMR

RIVM does not agree with the definition of the BMR in the opinion. According to EFSA BMD guidance (2009 and 2017) the BMD is a dose level, estimated from the fitted dose–response curve, associated with a specified change in response, the benchmark response (BMR). For continuous data (as applies here) the BMR is defined as a percent change in the mean response as compared to the background response. However, in the opinion (section 2.2.3, page 24) the BMR is redefined as 'an increase relative to the lowest quantile'. By using the lowest quantile as the proxy of the background response, the BMD heavily depends on the choice of the number of quantiles. For example, when the number of quantiles from the Steenland et al. study (Opinion, Appendix B, analysis 1) would have been five instead of ten, then the total cholesterol at the lowest quantile would have been higher. Consequently, the estimated BMD would have been higher too. In this case, RIVM is of the opinion that this approach for the BMR is not valid. In the PFOA analysis for TC the approach was taken of model-deriving the response at an extrapolated background serum level of 1 ng/mL. The main issue with most of the currently assessed datasets (as reported in appendix B to the opinion on PFOS and PFOA) is indeed the lack of information about the background (at dose zero) response. However, as an exception, the Steenland et al. data on PFOS do seem to allow estimating the background response (i.e. 196.6 mg/dL). In principle RIVM is of the opinion that it would be a better approach to use this PFOS-derived background value in the PFOA data as well, since the same response data are considered for both PFAS.

3c. Choice of software

For RIVM it remains unclear why the BMD analyses were performed with software other than the PROAST or BMDS software. The PROAST or BMDS softwares are widely validated and recommended in the EFSA BMD guidance, and the technical limitations for use of PROAST and BMDS in the current analysis are not specified. Furthermore, the specifications, assumptions and settings of the alternative software used in the opinion are lacking.

3d. Selection of applicable models

For RIVM is it not clear which 100 models (as reported) were applied in the dose-response modelling. In earlier correspondence, EFSA explained that 'All data were analysed using numerous models as described in Budtz-Jorgensen et al. (2001) because of the supposed high sensitivity of the BMDL to the model'. However, in the paper of Budtz-Jorgensen et al. only four models are described: K-power, linear, square root- and log-linear. It remains unclear which other 96 models were used and therefore it cannot be judged whether some of these other models would be applicable, neither can they be

reproduced. Furthermore, it is unclear which criteria were used to obtain the best fitting model. In previous correspondence EFSA stated that: 'The best choice was calculated using three statistical parameters together in order to have a more global point of view on this evaluation as described in Haber et al. (2018). The best fitting evaluation (sic) in the lowest deciles were visually evaluated'. In fact, Haber et al. proposed a 'holistic approach' of model selection. In this approach they stress that 'it is important to be transparent about the rationale for the choice […]'. The current PFOS/PFOA opinion lacks such a transparent rationale. It is unclear which (100) models were fitted and it is unclear what the values of the 'different statistical parameters' are. In addition, it is unclear how these parameters were judged and weighted to arrive at a final best model.

The results of the NULL and FULL models are missing and model uncertainty cannot be evaluated. These results should be reported in a sound BMD analysis (see e.g. EFSA BMD guidance 2017, page 25, 'The AIC criterion') to arrive at a valid final BMDL or BMD confidence interval. Note that the NULL and FULL models are standard output in the PROAST software and the US-EPA BMDS software.

3e. BMD confidence interval

RIVM cannot agree with the derivation of the confidence interval (CI). The EFSA guidance states that 'the BMD confidence interval needs to be based on the results from various models, instead of just a single ('best') model '(section 2.5.3 of EFSA 2017). In the opinion a BMD confidence interval was based on the best fitting curve. However, the EFSA guidance states that the BMD CI should take model uncertainty into account and hence be based on the results of all applied models, preferably using model averaging (section 2.5.6 of EFSA, 2017). The EFSA guidance also provides a method for determining the BMD CI for the case that model averaging software is not available.

RIVM notes that the information on the width of the CI is missing. To gain insight into the uncertainty of the data and consequently of the derived BMD, the entire BMD (90%) confidence interval should be reported, i.e. the BMDL and BMDU. The BMD/BMDL ratio does not suffice to determine the uncertainty (EFSA, 2009 and 2017).

Conclusion: RIVM supports optimal use of epidemiological data in risk assessment. RIVM considers the currently presented (PFOA and PFOS) information from the epidemiological studies not a suitable basis for deriving a PoD. In addition, RIVM does not agree with the assumptions made in the derivation of a PoD. Even if the available epidemiological data were considered to be a reliable basis for deriving a PoD, in RIVM's view the BMD approach is not applied and reported correctly in the opinion. Furthermore, the analysis is not in line with the EFSA BMD guidance, and RIVM cannot agree with the (lack of) reported reasons for deviation from the EFSA BMD guidance. For example, RIVM does not support the way the missing background response was dealt with, and to RIVM's view the model uncertainty needs to be taken into account. These issues are considered as general requirements of a sound BMD analysis, which are not related to the fact that the analysed data originate from an epidemiological study.
In the case of PFOA and PFOS, RIVM concludes that the available epidemiological information cannot be used for deriving a HBGV as has been done in the adopted opinion.

9. Discussion and responses of EFSA to the positions of ECHA, Danish EPA, BfR and RIVM

In general, clarifications to the points raised will be included in the meeting minutes or in a frequently asked questions (FAQs) document. It would not be possible to include new points in the adopted opinion however clarifications to existing points could be included.

9.1 ECHA

EFSA agrees that the divergence is not substantive due to the different scopes of the assessments by EFSA and ECHA.

9.2 Danish EPA

EFSA agrees that the current divergence with the Danish EPA 2015 assessment (Larsen and Giovalle, 2015) stands due to the different approach used in deriving the HBGV.

9.3 BfR

With regards to the points raised by BfR:

Issue 1
The relevance of the observed changes in biomarkers in epidemiological studies in the context of the derivation of TWI values for PFOS and PFOA.

Increase in total cholesterol

1. *Selection of total serum cholesterol (TC) as compared to differentiated cholesterol fractions (like LDL-C or TC/HDL-C) as point of departure for the derivation of the TWI-values.*

EFSA agrees that the selection of total cholesterol over differentiated cholesterol fractions, such as LDL cholesterol which is considered a stronger risk factor for cardiovascular disease, may introduce some uncertainty into the assessment. There are, however fewer studies reporting associations between PFOS/PFOA and LDL cholesterol (see Table 23 in the opinion). EFSA chose to perform BMD modelling in three studies with >500 participants. LDL cholesterol is usually calculated from TC, HDL and triglycerides and could not be calculated in some study participants in the study by Steenland et al. (2009). The study by Nelson et al. (2010) reported LDL cholesterol for only half of the participants, and the study by Eriksen et al. (2013) reported only results for TC.

It should be noted that LDL is the major part of TC, and that, also for TC, the association with cardiovascular risk is well established. A key reference used in the PFOS/PFOA opinion is the meta-analysis by Lewington et al. (2007) in the Lancet. It reviews 61 prospective studies with 900,000 adults and 55,000 cardio vascular deaths. Within each age stratum there is an approximately linear association between the relative risk (hazard ratio) and total cholesterol (TC). Lewington et al. also present similar associations between total cholesterol and stroke. In addition, Lewington et al. showed similar associations between cardiovascular mortality and non-HDL cholesterol, which is mostly LDL cholesterol. But, as could be expected, the change in cardiovascular risk per mmol/L of non-HDL cholesterol is stronger.

2. *Assessment of the study by Steenland et al. (2009) from a clinical point of view*
3. *Selection of the threshold for a clinically relevant increase in total cholesterol in the light of the nature of cardiovascular diseases (CVD) as multifactorial processes/relationship between an increase in total serum cholesterol and an increase of cardiovascular diseases.*
4. *Assessment of the proportion of the population that would be above the reference range.*

With regards to the following paragraph proposed by BfR:

> *"In the study by Steenland et al. (2009) the mean TC was 199 mg/dL and the SD was 42. For an ideal normal distribution, a shift of the whole distribution to the right due to an increase of serum cholesterol by 5%, will increase the prevalence of "high levels" (in this case serum cholesterol above 240 mg/dL, defined as "hypercholesterolemia" by Steenland et al., prevalence 15%) considerably (by about 9%). An unpublished evaluation of the raw data of Steenland et al. (2009) (Data provided by Tony Fletcher (2017) showed as approximately normal distribution of serum cholesterol levels. An increase of serum cholesterol levels by 5% would result in an increase prevalence of cholesterol levels above 240 mg/dL by more than 5%".*

EFSA agrees with this paragraph, although inclusion in the opinion is not considered necessary.

EFSA agrees to develop a FAQs document which would include information on which health outcomes would result from an exceedance of the TWI for different groups of the population, and the established drivers for CVD other than PFOS/PFOA such as age, gender, blood pressure. This

document will also mention that in young people (<40 years of age) the cardiovascular risk is low, and there is insufficient information on the association between total cholesterol and cardiovascular risk in young people <40 years of age.

With regards to the negative association of cholesterol with stroke mortality at older ages or at higher blood pressures, in the meta-analysis by Lewington et al. (2007), EFSA agrees that in the meta-analysis by Lewington et al. (2007) the association between cholesterol and cardiovascular disease is stronger for ischemic heart disease than for stroke. For stroke, the association is, however, statistically significant in the age group 40 – 69 years. It is true that the association for those with high blood pressure has an opposite direction compared with those having a normal blood pressure.

5. *Possible coincidence of increased serum levels of PFOS and PFOA with higher total cholesterol serum levels resulting from a possible common reabsorption (of bile salts, PFOS and PFOA) from the gut and the uptake into the liver via shared membrane transport pathways.*

With regards to the possible coincidence of increased serum levels of PFOS and PFOA with higher total cholesterol serum levels resulting from a possible common reabsorption (of bile salts, PFOS and PFOA) from the gut and the uptake into the liver via shared membrane transport pathways, EFSA agrees that it is an interesting hypothesis. The issue seems to be whether changes in reabsorption could lead to a positive association between serum levels of PFOS/PFOA and cholesterol, the latter being affected by reabsorption of bile acids. Increased re-uptake of bile acids would generate negative feed-back loops via farnesyl-X-receptor and reduce the de-novo synthesis of bile acids by inhibiting 7-alpha-hydroxylase (CYP7A1), the first and rate-limiting step in the formation of bile acids from cholesterol. So indirectly - perhaps - there could be an increase in cholesterol, since the heavily recycling bile acids block the metabolism of cholesterol. There is one report that in human hepatocytes, CYP7A1 may be down-regulated by PFASs (Beggs et al., 2016). However, there are multiple counter-regulations in the body to keep the homeostasis in cholesterol.

Nevertheless, this possible confounding was further investigated. As described in the Opinion, it is evident that both PFOS and PFOA are eliminated not only by renal clearance but also via the bile. It is well-known that bile acids that are excreted into the intestine are extensively reabsorbed, and similar has been suggested for PFASs. Harada et al. (2007) and Fujii et al. (2015) estimated that respectively 89 and 97% of PFOA excreted via bile has to be reabsorbed, in order to explain the long half-live of this compound in humans. For PFOS, Harada at al. (2007) estimated this figure to be 97%. There are papers from Zhao et al. (2015, 2017) demonstrating that PFASs are transported by NTCP, ASBT and OATPs, contributing to the enterohepatic circulation of these contaminants. These transporters also mediate the uptake of bile acids. Studies in both rats and humans with cholestyramine, a bile acid resin used for lowering serum cholesterol, demonstrate the importance of enterohepatic cycling of PFASs and of this excretion route (Johnson et al., 1984; Genuis et al., 2010, 2013). This implies that also other drugs and food components that are lowering cholesterol by increasing the excretion of bile acids, and could have a similar effect on PFASs, might somehow contribute to the observed association between serum cholesterol and serum PFAS levels. It is evident that this could explain the observed association in cross-sectional and longitudinal studies, including those that were included in the risk assessment. However, except from the results obtained with cholestyramine, there have been no studies to confirm this. Furthermore, based on those studies that have taken dietary factors into considerations, confounding by diet in general (that could be mediated through this mechanism) does not seem to be important (Skuladottir 2015, Nelson 2012), although these studies did not focus on specific factors in the diet like cholesterol lowering dietary products.

The hypothesis also implies that increased serum levels of PFOS/PFOA are caused by increased reabsorption in the GI-tract rather than only increased exposure. However, Shin et al. (2011) estimated PFOA exposure of participants from the C8 cohort and showed a Spearman's rank correlation coefficient of 0.67 with measured serum levels. Also at much lower exposure, Haug et al. (2010) showed a relation between increased exposure (primarily from fish and other seafood) and serum levels of PFOS and PFOA.

"Additional analyses from the C8 cohort showed that mean cholesterol levels increased significantly (p-values for trend 0.02 for PFOA, and 0.004 for log PFOA) across water districts with geometric mean serum PFOA ranging from 13 to 209 ng/mL due to varying drinking water contamination" (Tony Fletcher – personal communication, 2018). These results are not in line with the hypothesis that the association between serum PFOA and cholesterol is fully explained by a shared determinant of excretion. However, as these are unpublished results the importance of these findings as support for causality can only be properly evaluated once these results along with relevant background information have been published. Furthermore, in a subgroup of the C8 cohort, there was a reduction in serum levels of PFOS and PFOA over a 4 to 5 years period and the change of PFOS/PFOA was statistically significantly associated with the change in serum cholesterol (Fitz-Simon et al., 2013). In this study people served as their own controls. Provided that their diet and physiology were more or less unchanged, these findings seem to rule out individual differences in reabsorption of bile acids and PFASs as cause of the association.

In summary some of the information available suggests that the concomitant reabsorption of bile acids and PFASs in the intestine could play a role in the observed association between serum PFAS levels and serum cholesterol, implying confounding by such varying reabsorption. At present there is, however limited empirical data demonstrating such confounding. EFSA therefore decided to include the association between serum cholesterol and PFOS/PFOA in the derivation of the TWIs for PFOS and PFOA. The hypothesis of confounding by concomitant reabsorption will need exploration in future research projects.

Issue 2

The safety of a long breastfeeding period for young children regarding possible effects on reduced antibody formation after vaccination.

BfR notes that observations on reduced antibody response are based on few studies and that in the study with the strongest associations (in the Faroe Islands; Grandjean et al., 2012), there was co-exposure to other contaminants. EFSA, in the evaluation considered co-exposure to PCBs but not other contaminants (e.g. heavy metals) or the mixed exposure as such. Methyl mercury exposure comes in this population from whale meat and/or fish consumption. Studies looking at immunologic effects of mercury have been inconsistent (Karagas et al., 2012; Monastero et al., 2017).

The main reason that EFSA considered only co-exposure to PCBs was that an association had been shown between reduced antibody response and PCBs by Heilman et al. (2010). The co-exposure with PCBs was measured and adjusted for in the Grandjean study (supplemental material). The relatively high concentrations of PCBs in the Faroese study is largely explained by consumption of whale blubber and this would also be the main source of organochlorine pesticides and dioxins and other lipophilic seafood borne contaminants. The adjustment made for PCBs would therefore in statistical terms, to some extent, account for these co-exposures as well. In addition, it is worth pointing out that the association between PFOS and PFOA with serum antibodies is not only observed in populations where consumption of seafood is high. Similar findings have been reported in US (Stein et al., 2016) and in Denmark (Kielsen et al 2016) where consumption of seafood and exposure to seafood born contaminants is likely to differ substantially. Regarding the fact that no studies in children have been published from the C8 study on antibody response, there can be various reasons for that but any attempt to address that from our side would be speculative.

Regarding mixed exposure to PFOS and PFOA, EFSA took this into account, abstaining from using the association between PFOA and reduced antibody response (Grandjean et al., 2012) as a critical effect when deriving a HBGV for PFOA. The reason for this was that serum levels of PFOS were much higher than levels of PFOA.

Regarding the clinical significance of the findings of reduced antibody response to vaccines, EFSA agrees that it is not quite clear. Certain individuals that are at the lower end of the magnitude of the vaccination response may however, because of exposure, end up having insufficient titers. More important – an immunotoxic effect of PFASs (as supported by experimental animal data) could cause increased propensity for common infections, and there is indeed some empirical support for this.

Human studies designed to detect protection from vaccination in relation to PFOS/PFOA exposure would be near impossible to perform. However, evidence from observational setting suggests that exposure to PFOS/PFOA is associated with increased propensity for common infections which further strengthens the argument on adversity above. For further clarifications on the adversity of a reduced antibody response, please see Section 3.4.1.3 of the opinion.

On the issue of lack of an association with serum antibodies at 13 years of age (raised by BfR), it does on its own not invalidate the findings at earlier age. During that follow-up environmental concentrations had been decreasing and the immune system is more developed at age 13 compared to early childhood. EFSA agrees with BfR that the most sensitive period for effects on the developing immune system could have been earlier than at the age of 5 years, when also the serum concentration of PFOS was higher according to the models. However, the modelling of serum levels at age 5 also include higher serum levels at lower age, and future studies will have to address the question whether adverse effects on the immune system can be observed at lower age and if so at lower maternal exposure.

Issue 3

Exposure assessment: possible overestimation of estimated intake of PFOS/PFOA if a substantial proportion of samples originated from "hotspot regions".

EFSA does take steps to avoid the inclusion of data from hotspot areas where possible. Data providers are asked to report to EFSA if specific samples are collected as "targeted samples".

And as described in section 3.1.1 Current occurrence data in food *"A close attention was paid to data reported for suspect samples. As inclusion of these samples may lead to an overestimation of the contamination levels, the CONTAM Panel decided to exclude them (n=480 (total); n=240 for both PFOS and PFOA) from further analysis."*

Further it is stated in the same section that *"However, it should be kept in mind that some of the remaining samples may also have been collected in a more targeted way."* This has been acknowledged in section 3.6.1.Uncertainty in exposure estimates, *"The information on occurrence in food comes from monitoring programs, and also from routine measurements within the frame of official food controls, so they originated from both random and targeted sampling. Targeted sampling is usually focused on known or suspected contamination sites and inclusion of such data may therefore result in an overestimate of exposure."*

EFSA is of the view that this issue is covered comprehensively in the opinion, and further elaboration is not considered necessary.

Breast feeding risk-benefit analysis

In relation to BfR's comment on the risk-benefit analysis for breastfeeding, as this is not in the remit of the mandate it was agreed to include this subject in the FAQs document which will be published at the same time as the opinion.

9.4 RIVM

1) Suitability of the reported information of the epidemiological data for deriving a PoD.

EFSA responded that the epidemiological data were often extracted from graphs in the paper or supplied by the authors. Unfortunately, not all information was supplied in the papers, more specifically the numbers and SDs per quantile. For the numbers per quantile, it was assumed that the total number of subjects was distributed equally over the quantiles.

As an example, in the case of the Steenland et al. (2009) study, this number was subsequently used to translate the CI in the figures into an SD. This is justifiable considering that for studies with several hundred participants, where exposures is divided into quantiles, small differences in the numbers per quantile are not expected to have a substantial effect on the calculation of the BMD and BMDL.

For the study by Steenland et al. (2009), the issue of subpopulations in the predicted model was explained in detail at the expert meeting. In short the same BMD/BMDL would be observed, independent of which part of the study population is selected to be predicted by the model. That is, the characteristics of the study population chosen in the Steenland study determines the mean cholesterol level in the lowest decile but the relative shape and response of the curve is the same regardless of what characteristics are chosen (same BMD/BMDLs will always be observed).

EFSA indicated that further clarifications to the points raised by RIVM will be added to the BMD methodology section of the opinion and to the appendix containing the BMD modelling analyses.

2) Assumptions made in the derivation of the PoD.

2a. Validity of the dose-response curve

In EFSA's response, the point raised by RIVM was briefly addressed. In regard to changes in TC, the BMR selection is discussed in detail in the opinion and justified by the relevance of the change in relation to the health implications at population level, as reiterated in these minutes (Section 9.3).

2b. Contribution of individual PFASs to the critical effect

EFSA responded that concerning the issue on the mixture effects, this is a valid point and was discussed in the uncertainty section of the opinion. Since in the C8 cohort (Steenland and Gallo studies), levels of PFOA were as high and, in a part of the population, higher than levels of PFOS, it was decided to perform BMD modelling on PFOA in these studies, and in a number of other studies as supportive evidence. Future research should focus on mixture effects and relative potencies of PFASs, and consider a group HBGV for at least some of the PFASs. Such approach was indicated by the last of the recommendations in the EFSA opinion, and would be in line with the guidance on mixtures that has been for public consultation and that will be finalised by the EFSA Scientific Committee in 2019.

3) Applied BMD analysis

3a. Applicability of EFSA BMD guidance

Concerning the BMD modelling of the epidemiological data, EFSA responded that the 2017 EFSA BMD guidance document (EFSA, 2017) considers the possible application of the BMD approach to data from epidemiological studies. However, the guidance concludes that it is not addressed in the document and instead a specific EFSA guidance on the use of the BMD approach to analyse human data was recommended. It has to be acknowledged that the application of BMD in human epidemiology is much less advanced and harmonised than in the field of intervention studies in experimental systems. The CONTAM Panel considers it essential that a thorough analysis of application of BMD to epidemiological data is performed with the aim to have a harmonised approach in the future.

3b. Definition of BMR

A particular issue with epidemiological data on widespread environmental contaminants is that there is no group with no exposure (control group). Ideally, it would be possible to estimate the response of a low-exposed population from the dose-response curve and use this to calculate the dose associated with a 5% increase in the response. EFSA responded that the approach suggested by

RIVM to use the background response from a low(er)-exposed group of the population to improve the curve-fit at the lower end of the curve is interesting but has some limitations. Although an estimation of the response in a low(er)-exposed group would make the modelling independent from the number of quantiles, it would have to rely on a series of additional assumptions. One obstacle is that there are always differences between study populations that are difficult to account for. Therefore it was decided to estimate the response for the lowest quantile from the fitted curve and use this as a starting point for calculating the BMR. An exception were the cholesterol data for PFOA from the Steenland et al. (2009) study. It is acknowledged that the approach taken by the CONTAM Panel to derive the $BMDL_5$ was based on the assumption that a linearly decreasing trend continues below the lowest quantile of the dataset. The uncertainties related to this approach are discussed in detail in the opinion.

3c. Choice of software

EFSA responded that preliminary attempts to model the data with PROAST or BMDS led to the conclusion that these software programs were not suitable for the modelling.

Recent work with BMDS showed that BMDs and BMDLs close to the ones in the Opinion could be obtained when data were scaled. This was done by defining the lowest quantile as zero dose and then adding the median concentration for the lowest quantile to the derived BMD/BMDL.

3d. Selection of applicable models

EFSA responded that the statistical parameters used are described in the opinion: for goodness of fit, r^2, DOF r^2, standard error and F statistic. For curve fitting, Lorentzian minimization, least square minimization and Pearson minimization can be used. Visual analysis (expert judgment) was also part of the model selection.

NULL and FULL models are necessary in PROAST, because it used the procedure described in the guidance for BMD in animal toxicology. In our case the estimation of goodness of fit does not use these models. For the studies used to derive health based guidance values the fitted model was in all cases significantly different from the NULL.

Regarding the comment on model selection and the use of AIC, this approach was not used by the working group. Instead the selection was based on the "best fit model" by statistical approaches (described in the opinion), expert judgment and by visual inspection. The AIC include likelihood and a penalty for the number of parameters. However, the AIC mainly provides a qualitative model comparison: a model with a lower AIC value is better, but how much better is difficult to discern. Many different equations may fit a data set equally well and there are no fixed rules for choosing between them for epidemiological studies.

3e. BMD confidence interval

EFSA acknowledge that the applied approach relies only on the outcome of the selected model and does not allow a full analysis of the model uncertainty under the principles of the EFSA guidance on BMD. BMDUs were not calculated.

The BMD confidence intervals were computed using an approach similar to the Wald limits method. The confidence limits provided by the software (TableCurve2d) and the confidence interval from the asymptotic distribution of the likelihood could be different. Nevertheless, when fitting a model to a large data set, Wald limits and likelihood-ratio limits will be quite similar.

RIVM announced a written post-meeting reaction on the orally presented EFSA response.

10. Overall Conclusion

The divergence between ECHA and the EFSA CONTAM Panel Scientific Opinion was considered to be not substantive due to the different scopes of the CONTAM Panel risk assessment and the ECHA RAC restriction procedure.

The divergence between the 2015 Danish EPA assessment and the 2018 EFSA CONTAM Panel Scientific Opinion is confirmed due to different expert judgments on the robustness of the human data. The Danish EPA indicated that a review of the available data will be undertaken to see whether the divergence can be solved.

EFSA agreed with the BfR that in young people (<40 years of age) the cardiovascular risk is low, and there is insufficient information on the association between total cholesterol and cardiovascular risk in young people <40 years of age. A FAQs document will be published, including the information on health outcomes of an exceedance of the TWI for different groups of the population and the relation to established drivers for CVD such as age, gender, blood pressure. In general BfR was satisfied with the clarifications provided to their potentially contentious issues. There are arguments for and against the suggested confounding by concomitant intestinal reabsorption of bile acids and PFOS/PFOA raised by BfR, and EFSA agrees that this aspect, implying higher uncertainty in this critical endpoint, needs to be addressed in future studies. BfR rates the evidence for a reduced antibody formation after vaccination caused by PFOS/PFOA exposure from the epidemiological studies available, as limited to moderate. Considering the current evidence available, BfR would not have used these study results to derive HBGVs. EFSA agrees that the clinical significance of the findings of reduced antibody response to vaccines is not quite clear. Furthermore, BfR is not convinced by the modelling approach of the EFSA opinion to derive an HBGV, as it does not consider the relatively high exposure resulting from a long breastfeeding period.

EFSA diverges with RIVM. For deriving a HBGV, RIVM did consider (RIVM, 2016) the available epidemiological information and the opinions of institutes like ATSDR, US-EPA, ECHA/RAC about the quality of the available epidemiological information. No analysis of individual epidemiological studies was performed. However, in agreement with the mentioned institutes, RIVM also considered the epidemiological data not sufficiently informative for (quantitatively) deriving a health-based guidance value (e.g. TDI, TWI). RIVM did not consider the dose response modelling approach applied by EFSA as sufficiently transparent and scientifically robust. Overall, the different approaches for benchmark dose modelling of human epidemiological data illustrate the need for guidance from the Scientific Committee on this issue.

RIVM expressed its availability for further discussions on the sources of divergence in the current risk assessment of PFOA and PFOS.

Following the meeting, RIVM reacted in writing to the responses from EFSA in Section 9.4 of this report. RIVM concluded that the additional clarifications provided during the meeting were not sufficient to clarify all the points raised and provided additional comments which are attached as Annex C to this meeting report. The EFSA experts have not evaluated nor agreed to these post-meeting comments received from RIVM.

11. Final Remarks

Further clarifications on the scientific approach taken will be provided in the EFSA CONTAM Panel Scientific Opinion and/or are considered covered in the meeting minutes.

FAQs will be prepared in conjunction with EFSA Communications Unit and these will be published together with the EFSA CONTAM Panel Scientific Opinion and the meeting minutes.[3] A clear reference to the meeting minutes will be included in the opinion.

In view of the uncertainties identified, the participants agreed that further discussion is needed on these substances and that collaboration on future assessments would be needed.

The participants were informed that the possibility to issue public consultations will be considered as a default for all the future opinions of the CONTAM Panel.

[3]The development of a FAQs document, as proposed by the BfR, was agreed during the meeting by EFSA. However, this document will not be prepared at this current stage, as the conclusions of the assessment will be reviewed in parallel with the finalisation of the EFSA scientific opinion on *The risks to human health related to the presence in food of perfluoroalkylated substances other than PFOS and PFOA* (EFSA-Q-2017-00549), and with the possible application of the forthcoming Scientific Committee guidance on combined exposure to multiple chemicals.

References

Beggs KM, McGreal SR, McCarthy A, Gunewardena S, Lampe JN, Lau C and Apte U, 2016. The role of hepatocyte nuclear factor 4-alpha in perfluorooctanoic acid- and perfluorooctanesulfonic acid-induced hepatocellular dysfunction. Toxicology and Applied Pharmacology, 304, 18-29.

Budtz-Jorgensen E, Keiding N and Grandjean P, 2001. Benchmark dose calculation from epidemiological data. Biometrics 57, 698-706.

ECHA (European Chemicals Agency), 2015. Committee for Risk Assessment (RAC) Opinion on an Annex XV dossier proposing restrictions on Perfluorooctanoic acid (PFOA), its salts and PFOA-related substances ECHA/RAC/RES-O-0000006229-70-02/F

EFSA (European Food Safety Authority), 2009. Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. EFSA Journal 2009;7(6):1150, 72 pp. https://doi.org/10.2903/j.efsa.2009.1150

EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Aerts M, Bodin L, Davis A, Edler L, Gundert-Remy U, Sand S, Slob W, Bottex B, Abrahantes JC, Marques DC, Kass G and Schlatter JR, 2017. Update: guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658, 41 pp. https://doi.org/10.2903/j.efsa.2017.4658.

Eriksen KT, Raaschou-Nielsen O, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K and Sørensen M, 2013. Association between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population. PLoS One, 8, e56969. doi:10.1371/journal.pone.0056969

Fei C, McLaughlin JK, Tarone RE and Olsen J, 2007. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. Environmental Health Perspectives, 115, 1677-82.

Fitz-Simon N, Fletcher T, Luster MI, Steenland K, Calafat AM, Kato K and Armstrong B, 2013. Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid. Epidemiology, 24, 569–576.

Frisbee SJ, Shankar A, Knox SS, Steenland K, Savitz DA, Fletcher T and Ducatman AM, 2010. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: results from the C8 Health Project. Archives of Pediatrics and Adolescent Medicine, 164, 860–869. https://doi.org/10.1001/archpediatrics.2010.163

Fujii Y, Niisoe T, Harada KH, Uemoto S, Ogura Y, Takenaka K and Koizumi A, 2015. Toxicokinetics of perfluoroalkyl carboxylic acids with different carbon chain lengths in mice and humans. Journal of Occupational Health, 57, 1–12.

Gallo V, Leonardi G, Genser B, Lopez-Espinosa MJ, Frisbee SJ, Karlsson L, Ducatman AM and Fletcher T, 2012. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. Environmental Health Perspectives, 120, 655-660.

Genuis SJ, Birkholz D, Ralitsch M and Thibault N, 2010. Human detoxification of perfluorinated compounds. Public Health, 124, 367-375.

Genuis SJ, Curtis L and Birkholz D, 2013. Gastrointestinal Elimination of Perfluorinated Compounds Using Cholestyramine and *Chlorella pyrenoidosa*. ISRN Toxicology Volume 2013, Article ID 657849, 8 pages http://dx.doi.org/10.1155/2013/657849

Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P and Heilmann C, 2012. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 307, 391-397.

Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB and Budtz-Jorgensen E, 2017. Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. Environmental Health Perspectives, 125, 077018.

Haber LT, Dourson ML, Allen BC, Hertzberg RC, Parker A, Vincent MJ, Maier A and Boobis AR, 2018. Benchmark dose (BMD) modeling: current practice, issues, and challenges. Critical Reviews in Toxicology, 48, 387-415. https://doi.org/10.1080/10408444.2018.1430121

Haug LS, Thomsen C, Brantsaeter AL, Kvalem HE, Haugen M, Becher G, Alexander J, Meltzer HM and Knutsen HK, 2010. Diet and particularly seafood are major sources of perfluorinated compounds in humans. Environment International, 36, 772–778.

Heilmann C, Budtz-Jørgensen E, Nielsen F, Heinzow B, Weihe P and Grandjean P, 2010. Serum concentrations ofantibodies against vaccine toxoids in children exposed perinatally to immunotoxicants. Environmental Health Perspectives, 118, 1434–1438.

Johnson JD, Gibson AJ and Ober RE, 1984. Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium perfluorooctanoate or potassium perflurooctanesulfonate. Fundamental and Applied Toxicology, 4, 972–976.

Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, Cowell W, Grandjean P and Korrick S, 2012. Evidence on the human health effects of low-level methylmercury exposure. Environmental Health Perspectives, 120, 799-806. doi:10.1289/ehp.1104494.

Kielsen K, Shamim Z, Ryder LP, Nielsen F, Grandjean P, Budtz-Jørgensen E and Heilmann C, 2016. Antibody response to booster vaccination with tetanus and diphtheria in adults exposed to perfluorinated alkylates. Journal of Immunotoxicology, 13, 270–273. https://doi.org/10.3109/1547691X.2015.1067259.

Larsen PB and Giovalle E, 2015 Perfluoroalkylated substances: PFOA, PFOS and PFOSA. Evaluation of health hazards and proposal of a health based quality criterion for drinking water, soil and ground water. Environmental project No 1665, 2015. 90 pp.

Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB and Strynar MJ, 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicological Sciences, 90, 510-518.

Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R and Collins R and Prospective Studies Collaboration, 2007. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet, 370, 1829–1839.

Loccisano AE, Campbell JL Jr, Andersen ME and Clewell HJ, 2011. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. Regulatory Toxicology and Pharmacology, 59, 157–175.

Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R and Baigent C and Cholesterol Treatment Trialists' (CTT) Collaborators, 2012. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet, 380, 581–590.

Monastero RN, Karimi R, Nyland JF, Harrington J, Levine K and Meliker JR, 2017. Mercury exposure, serum antinuclear antibodies, and serum cytokine levels in the Long Island Study of Seafood Consumption: A cross-sectional study in NY, USA. Environmental Research, 156, 334-340. doi:10.1016/j.envres.2017.03.037

Nelson JW, Hatch EE and Webster TF, 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. Environmental Health Perspectives, 118, 197-202. doi:10.1289/ehp.0901165

Oulhote Y, Shamim Z, Kielsen K, Weihe P, Grandjean P, Ryder LP and Heilman C, 2017. Children's white blood cell counts in relation to developmental exposures to methylmercury and persistent organic pollutants. Reproductive Toxicology, 68, 207-214.

Palazzolo MJ, 1993. Thirteen-week dietary toxicity study with T-5180, ammonium perfluorooctanoate (CAS No. 3825-26-1) in male rats. Final Report. Laboratory Project Identification HWI 6329-100. Hazleton Wisconsin, Inc. U.S. Environmental Protection Agency Administrative Record 226-0449

Pellicoro A and Faber KN, 2007. Review article: The function and regulation of proteins involved in bile salt biosynthesis and transport. Alimentary Pharmacology and Therapeutics, 26 Suppl 2, 149–160.

Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S and ESC Scientific Document Group, 2016. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal, 37, 2315-2381. doi: 10.1093/eurheartj/ehw106.

RIVM (National Institute for Public Health and the Environment), 2016. Risk assessment of the emission of PFOA: Location: Dupont/Chemours, Dordrecht, the Netherlands. RIVM, 2016-0049; 68 pp.

Shin HM, Vieira VM, Ryan PB, Steenland K and Bartell SM, 2011. Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health project. Environmental Health Perspectives, 119, 1760–1765.

Skuladottir M, Ramel A, Rytter D, Haug LS, Sabaredzovic Bech BH, Henriksen TB, Olsen SF and Halldorsson TI, 2015. Examining confounding by diet in the association between perfluoroalkyl acids and serum cholesterol in pregnancy. Environmental Research, 143, 33–38.

Slob W, 2017. A general theory of effect size, and its consequences for defining the benchmark response (BMR) for continuous endpoints. Critical Reviews in Toxicology, 47, 342-351.

Slob W and Setzer RW, 2014. Shape and steepness of toxicological dose-response relationships of continuous endpoints. Critical Reviews in Toxicology, 44, 270-297.

Steenland K, Tinker S, Frisbee S, Ducatman A and Vaccarino V, 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. American Journal of Epidemiology, 170, 1268-1278. doi:10.1093/aje/kwp279

Stein CR, McGovern KJ, Pajak AM, Maglione PJ and Wolff M, 2016a. Perfluoroalkyl and polyfluoroalkyl substances and indicators of immune function in children aged 12–19 y: national health and nutrition examination survey. Pediatric Research, 79, 348–357.

Thomford PJ, 2002. 104-week dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in rats. 6329-183. Covance Laboratories Inc.

Thomsen C, Haug LS, Stigum H, Frøhaug M, Broadwell SL and Becher G, 2010. Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation. Environmental Science and Technology, 44, 9550-9556.

Winquist A and Steenland K, 2014. Modeled PFOA exposure and coronary artery disease, hypertension and high cholesterol in community and worker cohorts. Environmental Health Perspectives, 122, 1299–1305.

Whitworth KW, Haug LS, Baird DD, Becher G, Hoppin JA, Skjaerven R, Thomsen C, Eggesbo M, Travlos G, Wilson R, Cupul-Uicab LA, Brantsaeter AL and Longnecker MP, 2012. Perfluorinated compounds in relation to birth weight in the Norwegian Mother and Child Cohort Study. American Journal of Epidemiology, 175, 1209-1216.

US EPA (US Environmental Protection Agency), 2014a. Health Effects Document for Perfluorooctanoic Acid (PFOA). U.S. Environmental Protection Agency. EPA Document Number: 822R14001 Date: February 2014

US EPA (US Environmental Protection Agency), 2014b. Health Effects Document for Perfluorooctane Sulfonate (PFOS). U.S. Environmental Protection Agency. EPA Document Number: 822R14002 Date: February 2014

Xiang X, Han Y, Neuvonen M, Pasanen MK, Kalliokoski A, Backman JT, Laitila J, Neuvonen PJ and Niemi M, 2009. Effect of SLCO1B1 polymorphism on the plasma concentrations of bile acids and bile acid synthesis marker in humans. Pharmacogenetics and Genomics, 19, 447–457.

Zhao W, Zitzow JD, Ehresman DJ, Chang SC, Butenhoff JL, Forster J and Hagenbuch B, 2015. Na+/Taurocholate Cotransporting Polypeptide and Apical Sodium-Dependent Bile Acid Transporter Are Involved in the Disposition of Perfluoroalkyl Sulfonates in Humans and Rats. Toxicological Sciences, 146, 363-373.

Zhao W, Zitzow JD, Weaver Y, Ehresman DJ, Chang SC, Butenhoff JL and Hagenbuch B, 2017. Organic Anion Transporting Polypeptides Contribute to the Disposition of Perfluoroalkyl Acids in Humans and Rats. Toxicological Sciences, 156, 84-95.

Annex A: list of participants

Expert Meeting: Risk assessment of perfluorooctane sulfonic acid and perfluorooctanoic acid in food

Article 30 of Regulation 178/2002

24 September 2018

List of Participants

Klaus ABRAHAM	**BfR**	Department Food Safety, Head of Unit Risks for Subpopulations and Human Studies
Lars BARREGARD	**EFSA**	CONTAM WG on PFAS in food
Marco BINAGLIA	**EFSA**	BIOCONTAM Unit
Mark BLAINEY	**ECHA**	Risk Management Implementation Unit
Laurent BODIN	**EFSA**	CONTAM Panel / CONTAM WG on PFAS in food
Rik BOGERS	**RIVM**	Centre for Sustainability, Environment and Health
Bas BOKKERS	**RIVM**	Centre for Safety of Substances and Products. Department for Consumer and Product Safety
Tim BOWMER	**ECHA**	Chairman of the Committee for Risk Assessment (RAC)
Thorhallur HALLDORSSON	**EFSA**	CONTAM WG on PFAS in food
Joke HERREMANS	**RIVM**	Centre for Safety of Substances and Products. Head of department for Consumer and Product Safety
Ron HOOGENBOOM	**EFSA**	CONTAM Panel & CONTAM WG on PFAS in food
Juliane KLEINER	**EFSA**	RASA Department - Head of Department *(a.i.)*
Helle KNUTSEN	**EFSA**	CONTAM Panel Chair (2015-2018)
Ernesto LIEBANA CRIADO	**EFSA**	BIOCONTAM Unit - Head of Unit *(a.i.)*
Karen MACKAY	**EFSA**	BIOCONTAM Unit
Hans MIELKE	**BfR**	Department Exposure – Unit Epidemiology, Statistics and Mathematical Modelling
Ulrike PABEL	**BfR**	Department Safety in the Food Chain – Unit Feed and Feed Additives
Alain-Claude ROUDOT	**EFSA**	CONTAM WG on PFAS in food
Dieter SCHRENK[4]	**EFSA**	CONTAM Panel Chair (2018-2021)
Tanja SCHWERDTLE	**EFSA**	CONTAM Panel/CONTAM WG (Chair) on PFAS in food
Veerle VANHEUSDEN[4]	**EC-DG SANTE**	Unit E2. Food Processing and Novel Foods
Toke WINTHER	**Danish EPA**	Chemical unit
Marco ZEILMAKER	**RIVM**	Centre for Nutrition, Prevention and Health Services
Sebastian ZELLMER	**BfR**	Department Chemical and Product Safety – Unit Safety of Food Contact Materials

[4] observer

Annex B: Agenda

Parma, 21 September 2018
EFSA/CONTAM/3504

Expert Meeting: Risk assessment of perfluorooctane sulfonic acid and perfluorooctanoic acid in food

Article 30 of Regulation 178/2002

Draft Agenda

Meeting dates: **24 September 2018**
Venue: **EFSA, Via Carlo Magno 1/a, 43126 Parma**
Meeting Room: **Board room-Auditorium**
Starting Hour: **1330h(CET)**
Finishing Hour: **1630h (CET)**

Draft Agenda

#	Items	Document/Reference Comments
1.	Welcome and introduction to the meeting	Chair/EFSA
2.	Introduction of participants	All
3.	Adoption of agenda	All
4.	Presentation of critical points from the EFSA assessment on PFOS & PFOA in food and summary of the potential divergences	EFSA
5.	Presentation of the ECHA position	ECHA
6.	Presentation of the Danish EPA position	Danish EPA
7.	Presentation of the BfR position	BfR
8.	Presentation of the RIVM position	RIVM
9.	Discussion	All
10.	Overall conclusion	All
11.	Final Remarks	All
12.	Closure of meeting	All

Annex C: RIVM Post-meeting written response to EFSA clarifications (section 9.4)

The EFSA experts have not evaluated nor agreed to these post-meeting comments received from RIVM.

RIVM studied the clarifications by EFSA after the meeting. In general, RIVM is of the opinion that the responses by EFSA do not address or do not fully address the issues raised by RIVM.

Considering point 1. In RIVM's view it remains unclear how SDs are calculated from the data available in the underlying studies. In the specific case of Steenland, the data in the study represent a (small) fraction of the survey population. RIVM cannot accept the assumption that the number of individuals in the survey equals the number of the subpopulation of which data is analysed.
Despite EFSA's response RIVM is of the opinion that the study population subgroup in the Steenland et al. (2009) study cannot serve as a proxy for the risk of the entire population. This is because although the shape of the dose-response curve is independent of the subgroup chosen, however the fraction of the subgroup at risk is not. Subpopulations with curves below (or above) the presented curve may experience a lower (or higher) risk of exceeding some clinical cholesterol level (e.g. 240 mg/dL), hereby altering the (overall) population's risk. Hence, it can be questioned if the increase of 5% in cholesterol in the Steenland subpopulation truly relates to the increase in 5% cardiovascular disease in the entire population, as mentioned in the opinion.

Point 2a. The choice of the value (of 5%) used as BMR is not questioned here. The concern of RIVM is that the dose-response for the effect by PFOA on TC as reported in Steenland et al. is a curve that levels off only 5% above the lowest decile (TC around 210 mg/dL versus around 200 mg/dL). However, it is known that the maximum response is a property of the endpoint (Slob and Setzer, 2014) and it tends to be much larger than 5% (Slob, 2017). For cholesterol, the response was estimated to level off at around 150% (in rodents) by Slob (2017). Compared to that estimate, a change of 5% is a minimal change and it can be questioned if this can be considered a correct maximum response in a dose-response relationship for cholesterol and thus usable for derivation of a PoD.

Point 2b. RIVM supports the remark that future research should focus on mixture effects and relative potencies of PFASs, including the consideration of a group HBGV for some of the PFASs. However concerning the current risk assessment RIVM notes that also other studies (next to Steenland) suffer from an exposure to multiple substances (PFAS and other substances), and that no correction was applied to correct for this combined exposure.

Point 3a. RIVM acknowledges that extra effort is required to successful analysis of epidemiological data, which should result in guidance. However, the basic principles of BMD analysis apply also to epidemiological data, e.g. the definition of the BMR, transformation of (response) data, parameter constraints, model fitting procedure, methods to compare models, model averaging or otherwise deriving the BMD confidence interval, and reporting results. All these principles are included in the EFSA guidance on the BMD approach. Despite EFSA's response RIVM cannot support the BMD analyses applied as it deviates from this BMD guidance without a clear and scientifically sound explanation of the alternative approach followed.

Point 3b. RIVM acknowledges the fact that it may be difficult to derive information about the background (at dose zero) response. However, RIVM is of the opinion that redefining the BMR in terms of a change compared to the lowest quantile is not the appropriate method to solve this issue. When it turns out that the available data do not allow the derivation of the background response, it can be questioned whether the available data are sufficiently informative to derive a PoD.

Point 3c. is a direct consequence of point 3b. The available software cannot solve the lack of information addressed in point 3b. With regards to software selected by EFSA, more information on the specification, assumptions and settings of the used software would be helpful for the transparency of the opinion, including the possibilities to repeat the performed BMD analysis.

Scaling the exposure of the lowest quantile to a zero exposure as proposed in the EFSA reaction is in RIVM's view scientifically incorrect. Firstly, this implies that the response at the first quantile is equal to the background response (see issue under point 3b). Secondly, scaling by subtracting (exposure) is in RIVM's view incorrect. E.g. scaling from 10 to 5 dose units is not equivalent to scaling from 100 to 95, but rather from 100 to 50 dose units. Scaling (exposures and responses) is only justified by division. As a consequence, scaling from the first quantile to zero would imply dividing by infinitive, hampering scaling of subsequent quantiles.

Point 3d. As already stated under point 3a, it is still not clear why and how the alternative methods to compare models are used. What are the advantages compared to the AIC and which criteria were used, e.g. how much should the r^2s of two models differ to prefer one of the models above the other?

EFSA's assumptions about the purpose of the NULL and the FULL models in the EFSA BMD guidance are not complete. We agree with EFSA that these models are applied (in PROAST, but also in BMDS) because they are required in the procedure to derive a BMD confidence interval. However, the NULL and the FULL models also provide fundamental insight of the dose-response relationship and the quality of the available data, regardless whether epidemiological, animal or any other type of data is considered. The NULL model is needed to determine whether there is a dose-response relationship or not, and the FULL model should be applied to test for non-random errors in the data, or in specific cases, for misspecification of the distributional part of the model. See BMD guidance sections 2.5.5 and 2.5.7. for more details.

Point 3e. In their response to point 3d EFSA confirms that various models may describe the data. In accordance with the EFSA BMD guidance (section 2.5.3) RIVM prefers to derive a BMD confidence interval (including the BMDU) based on multiple models, instead of selection of the BMD confidence interval of a single ('best') model.
As the purpose of a BMD analysis is not to find the best estimate of the (true) BMD but rather to find all plausible values of the (true) BMD, given the data available, not only the best-fitting model but also the models resulting in a slightly poorer fit need to be taken into account. After all, it could well be that the second (or third, . . .) best-fitting model is closer to the true dose–response than the best-fitting model. This type of uncertainty is called 'model uncertainty', and implies that the BMD confidence interval needs to be based on the results from various models, instead of just a single ('best') model (EFSA BMD guidance section 2.5.3).
Assuming that the CONTAM panel has the results of all models readily available, it is advised to present the BMD confidence interval based on multiple models in the opinion.