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New health-based guidance values for the industrial chemicals PFOS and PFOA

BfR opinion No 032/2019 of 21 August 2019

Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are industrial chemicals. PFOS was used until 2006 e.g. as a starting material for the production of dirt, grease and water repellent surface treatments of carpets, upholstery and packaging made of cardboard and paper and in fire extinguishing agents. In 2006, the European Commission severely restricted the use of PFOS, so that the substance has only been allowed in a few special applications since then (e.g. in the space industry). PFOA, however, may still be used until 2020. It is used in industry to make non-stick coatings for frying pans as well as impregnating clothes to make them water, oil and dirt repellent. From 2020, PFOA, its salts and precursors may not be produced or marketed.

Both substances are chemically very stable, dissolve in both water and fat and are therefore easily distributed in the environment. From there, they enter the food chain. Humans take in PFOS and PFOA primarily via food (including drinking water). Both substances are secreted only slowly by humans and accumulate in tissue if small amounts are ingested daily.

The German Federal Institute for Risk Assessment (BfR) was asked to comment on the reassessment of both substances by the European Food Safety Authority (EFSA). For the reassessment, EFSA relied for the first time primarily on data from epidemiological studies that correlated PFOS/PFOA concentrations in the blood with changes in biological parameters that may eventually increase the occurrence of certain diseases in the population in the long-term. A particularly well-documented relationship exists for changes in the lipid metabolism (increase in the total cholesterol level). Cholesterol is one of the known risk factors for cardiovascular diseases. However, there are other factors that have a significant impact on the risk of these diseases. So far, there is no reliable epidemiological evidence for a relationship between PFOS/PFOA concentrations in the blood and a higher risk of these diseases in particularly exposed population groups.

EFSA has derived new, significantly lower tolerable weekly intakes (TWI). For PFOS, these are now thirteen nanograms (ng) per kilogram (kg) of body weight per week, for PFOA six ng per kg of body weight per week. The values indicate the weekly doses that can be consumed over the course of a lifetime without causing any appreciable health effects in humans.

The BfR recommends using these TWI values to assess the health risk of PFOS and PFOA intake with food. However, the BfR observes scientific uncertainties and further research needs within the current derivation. EFSA also describes scientific uncertainties. As part of an ongoing assessment of further compounds in this substance group, EFSA will therefore re-examine PFOS and PFOA.

The new TWI values are exceeded through intake of PFOS and PFOA via food among parts of the population. However, both the occurrence data used by EFSA for exposure assessment and the occurrence data available to the BfR from Germany are subject to large uncertainties. In addition, short-term increased intakes of PFOS and PFOA, which are in the range of TWI values for a certain time, do not necessarily mean that their concentration in the blood is hazardous to health.

An assessment based on PFOS/PFOA concentrations in the blood is probably more meaningful. These indicate a decreasing trend in Germany since 2009. Studies in 2016 within an urban region in Germany show that those blood concentrations that form the basis for the newly derived TWI values for PFOS and PFOA are not exceeded in the investigated group.

The BfR recommends measures to further minimise the exposure of consumers to PFOS and PFOA via food. In principle, it is recommended to include drinking water as a source of exposure.

It is the view of the BfR that there is a need for research, in particular with regard to the evidence of causality and clinical relevance of the results from epidemiological studies used for the TWI derivation. There is also a need to improve the data base for estimating external and internal exposure to PFOS and PFOA for consumers in Germany. In light of these findings regarding exposure through food, the BfR cannot fully uphold its 2008 statement that a health risk to consumers is unlikely due to current exposure to PFOS and PFOA through food.

1 Subject of the opinion

By order of 08 June 2018 (Ref. no.: IG II 2 - 63000/10), the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) asks the German Federal Institute for Risk Assessment for an opinion on the draft EFSA Opinion “Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food”. In particular, taking into account the draft EFSA Opinion, a review of BfR's statement in its 2008 Opinion is requested, that a health risk to consumers from exposure to PFOA and PFOS via food is unlikely (BfR 2008).[1] Furthermore, the BfR is invited to outline the conclusions drawn from EFSA's opinion on environmental food safety.

For information: Publication of the EFSA opinion occurred on 13 December 2018 (EFSA 2018a). The publication is accompanied by a statement from EFSA that the opinion on PFOS and PFOA will be revised as part of the finalisation of EFSA's opinion on additional PFAS. The reasons for this are the uncertainties associated with the opinion on PFOS and PFOA and the possible application of an EFSA scientific guidance on the assessment of mixed exposures which will be available soon.
With the aim to enter into a scientific discourse with EFSA on their assessment, the BfR requested by letter of 21 June 2018 the inclusion of a potential divergence procedure under Article 30 (2) of Regulation (EC) No 178/2002. At the invitation of EFSA, an expert discussion took place on 24 September 2018, together with other member states and bodies, which also sought a potential divergence procedure.

[1] "*Based on the TDI utilisation, which results based on the data provided by the BVL, it is currently unlikely that exposure to PFOS via food poses a risk to consumer health."*

"Based on data provided by the BVL, estimated intake of PFOA via food in the range of 0.71-0.95 ng/kg bw/day (mean consumption of foods that have mean PFOA concentrations) and 13.03-13.11 ng/kg bw/day (high consumption of foods high in PFOA) only utilises a very low percentage of the TDI derived by EFSA (2008) of 1.5 µg/kg bw/day. EFSA also comes to the conclusion that the TDI for PFOA via food is under-utilised on the basis of its exposure assessment (EFSA 2008)." (BfR 2008)

Together with EFSA's opinion, the minutes of this expert discussion between EFSA, ECHA, the BfR, the Danish EPA and the RIVM were published to discuss the issues related to the potential divergence procedure (EFSA 2018b).

2 Result

- *TWI derivation from EFSA (2018)*

The EFSA opinion (2018) derives tolerable weekly intakes (TWIs) of 6 ng/kg bw per week for PFOA and 13 ng/kg bw per week for PFOS. The values are significantly lower than the health-based guidance values derived previously by EFSA and other international bodies.

The current derivations by EFSA are based on observations of correlations between the concentrations of PFOS and PFOA and an increase in total cholesterol levels in the blood in epidemiological studies. In addition, exposure to PFOS is considered to be critically related to decreased antibody formation following certain childhood vaccinations. Exposure to PFOA was also associated with interference with a liver enzyme.

After examining EFSA's opinion, the BfR believes there is a need for further research on, inter alia, the question of an actual causal relationship between the intake of PFOS and PFOA and the increase in total serum cholesterol and the relevance to health of this effect. From the point of view of the BfR, there are considerable uncertainties with regard to the evidence of causality and clinical relevance of the effects on which the TWI derivation was based. For this purpose, the BfR entered into a scientific discourse with EFSA, which was documented and published in a "Meeting Report" (EFSA 2018b). Among other things, the BfR addressed questions on epidemiological studies, which in part show negative associations between concentrations of PFOS/PFOA in blood and titres of vaccine antibodies in the blood. Overall, the BfR sees the evidence available to date on the question of reduced formation of vaccine antibodies, possibly caused by PFOS/PFOA, or increased susceptibility to infection as inadequate and sometimes contradictory. Furthermore, the BfR addressed questions regarding the suitability of the observed increases in total cholesterol in the epidemiological studies as biomarkers for cardiovascular diseases. Other issues included the clinical relevance of elevated cholesterol levels against the background of other factors affecting the risk of cardiovascular disease such as age, gender, weight, blood pressure and smoking. In addition, questions were discussed on the causal relationship between PFOS/PFOA in the blood and total cholesterol, in particular with regard to a possible coincidence of elevated serum levels of PFOS and PFOA and higher cholesterol levels, which could be due to, for example, mutual reabsorption from the gut via common membrane transport systems.

The question of the clinical relevance of this parameter (total blood cholesterol), which EFSA has used to derive the TWI, is identified by EFSA itself as an uncertainty. EFSA has announced that its current opinion on PFOS and PFOA will be revised due to the existing uncertainties as part of an ongoing assessment of further poly- and perfluorinated compounds. Based on this announcement, the BfR interprets the current TWI values, derived by EFSA, as provisional.

Despite uncertainties regarding the derivation of TWI values and the need for further scientific research, the BfR recommends using these newly derived TWI values from EFSA in future assessments of PFOS and PFOA concentrations in foods.

- *Risk Characterisation*

According to EFSA's exposure assessment, the new TWIs for PFOS and PFOA in Europe are exceeded by parts of the population when considering mean concentrations in food as well as mean and high consumption quantities.

The exposure assessment based on consumption data from studies in Germany shows for PFOS that the TWI value is not exceeded with mean consumption quantities and is exceeded at high consumption levels (95^{th} percentile) in the age group of infants (1 to <3 years, 14.6 ng/kg body weight per week) and seniors (65 to <75 years, 13.7 ng/kg body weight per week).

For mean consumption quantities, the exposure of infants (9.4 ng/kg body weight per week) and children aged 3 to 10 years (6.4 to 7.1 ng/kg body weight per week) exceeds the TWI for PFOA according to the exposure assessment for Germany. At high consumption quantities (P95), the TWI for PFOA for the population in Germany is exceeded by a factor of 2 to 3 in the age groups of infants (<1 year, 14.2 ng/kg body weight per week), toddlers (21.0 ng/kg body weight per week), children aged 3-10 years (14.6 ng/kg body weight per week to 12.7 ng/kg body weight per week) and adolescents (10 to <18 years, 5.4 to 9.3 ng/kg body weight per week).

For the assessment of long-term total exposure to PFOS and PFOA, concentrations of compounds in the blood are a good parameter because of their long half-lives in humans. This assumption is confirmed by measurements of concentrations of PFOS and PFOA in the blood of the general population: a trend towards decreasing concentrations has been observed in Germany since 2009. For example, recent studies in an urban region in Germany in 2016 also show that those blood concentrations which provide the basis for the newly derived TWI values are not exceeded. These studies are not based on representative data collection for the total population and therefore can only be used to a limited extent for the risk assessment. Nevertheless, from the BfR's point of view, the results indicate that the blood concentrations on which the newly derived TWI values are based are currently not exceeded in the general population through the intake of PFOS and PFOA.

Based on the current level of knowledge, the BfR does not see any reason to not breastfeed children for a prolonged period, according to the recommendations, in case of internal exposure at background levels.

- *Data base on concentrations of PFOS and PFOA in food, EFSA and BfR*

The data base on concentrations of PFOS and PFOA in food was significantly increased compared to the data base used in previous exposure assessments. The data on concentrations of PFOS and PFOA included in EFSA's exposure assessment were mostly collected in Germany (>60%). The EFSA exposure assessment (EFSA, 2018) was compared by the BfR with current concentration and consumption data from Germany. For PFOS, the mean lower bound concentrations according to EFSA (2018) for some of the high-consumption foods such as meat (beef, pork, poultry), milk, eggs and some freshwater fish such as salmonids and carp are significantly lower than those values available to the BfR from the official food control in Germany including the monitoring. For PFOA, the mean lower bound concentrations according to EFSA (2018) for some of the high-consumption foods such as beef and pork as well as milk are lower than those available to the BfR from the official food control in Germany including the monitoring.

Therefore, it cannot be ruled out that the actual exposure in Germany is higher than the result of the exposure assessment based on the occurrence data from Europe (caused by po-

tentially higher PFOS/PFOA concentrations in Germany than in the Europe-wide comparison).

- *Uncertainties in the data base on concentrations of PFOS and PFOA in food*

However, it should be noted that both the occurrence data used by EFSA and the occurrence data available to the BfR are subject to considerable uncertainty. The higher concentrations of some food groups in the German market, when compared to Europe, may also be due to uncertainties in sampling and analytics. It should be emphasised that the concentrations in the majority of the food samples were below the limit of detection when using current analysis methods.

- *Conclusion*

In light of these findings regarding exposure through food, the BfR cannot uphold its 2008 statement that a health risk to consumers is unlikely due to current exposure to PFOS and PFOA through food.

The possibility that long-term TWI exceedances, according to EFSA's current opinion, will be accompanied by changes in lipid metabolism (increase in total cholesterol) cannot be ruled out. Cholesterol is one of the known risk factors for cardiovascular diseases. Epidemiological studies show this correlation for persons over the age of 40 years. However, there are other factors that have a significant impact on the risk of cardiovascular disease, such as age, gender, lifestyle habits such as smoking and blood pressure levels. So far, there is no reliable epidemiological evidence for a relationship between PFOS and PFOA concentrations in the blood and a higher risk of these diseases in particularly exposed population groups. Therefore, the current assessment of health risks from exposure to PFOS/PFOA based on the current TWI values of EFSA (2018) is subject to uncertainties.

In addition, external intake levels of PFOS and PFOA that are in the range of TWI for a period of time need not immediately lead to blood levels in the critical range. The lower limit of the 95% confidence interval of the benchmark dose of 5% ($BMDL_5$ - *Benchmark Dose Lower Bound*) for PFOA is 9.3 nanograms (ng) per millilitre (ml) of blood serum, for PFOS 22 ng per ml of blood serum (see also Section 3.2.4). Depending on the value of blood levels already present, it may take years until intake levels at around the TWI values will result in blood levels in the critical range.

From the point of view of the BfR, there are therefore considerable uncertainties with regard to the exposure data and the evidence of causality and clinical relevance of the effects assumed for the TWI derivation.

- *Recommendations of the BfR*

The BfR recommends implementing measures to further minimise the exposure of consumers to PFOS and PFOA via food. In principle, it is recommended to include drinking water as a source of exposure.

It is the view of the BfR that there is also a need for research, in particular with regard to the evidence of causality and clinical relevance of the results from epidemiological studies used for the TWI derivation.

There is also a need to improve the data base for estimating external and internal exposure of consumers in Germany.

From the point of view of the BfR, representative human biomonitoring (HBM) data for the concentrations of PFOS, PFOA and other compounds from the group of per- and polyfluoroalkyl substances should be generated promptly for the population in Germany.

On the one hand, in order to improve the quality of the PFOS and PFOA occurrence data for food, sampling at federal state level should be representative and, on the other hand, consumption-oriented sampling should be carried out within the German federal states. This applies in particular to those foods which, according to current understanding, contribute significantly to exposure.

The occurrence data used by EFSA contain a high proportion of measurements below the limit of quantification. This results in large differences for the exposure assessment, depending on whether a lower-bound or upper-bound estimate is selected. According to EFSA (2018), uncertainties in the exposure assessment, especially uncertainties in food occurrence data, have the biggest impact on the overall uncertainties in the risk assessment. Therefore, from the point of view of the BfR, the development and establishment of more sensitive analysis methods for PFOS and PFOA in food control is necessary in order to reduce the uncertainties in the exposure assessment, to register changes in the occurrence and to derive recommendations for risk management options.

- *Initiatives of the BfR*

Perfluorinated substances, as a group of substances, are assigned as a new area of expertise to the National Reference Laboratory for Dioxins and PCBs in Food and Feed. On 14.11.2018, the BfR already carried out an initial orientation workshop on the analysis of PFAS for the food control laboratories. The issue was taken up again in the NRL Workshop on 22/23 May 2019.
Furthermore, in addition to the food monitoring for PFAS in selected foods already planned for 2019, the BfR has also submitted an additional application for project monitoring in order to improve the data situation in the short term.

In addition, a project has been initiated to help elucidate the potential molecular link between increased human PFOA exposure and elevated cholesterol levels in the blood.

3 Justification

3.1 Hazard identification

Perfluorooctane sulfonic acid (PFOS, CAS No. 1763-23-1) and perfluorooctanoic acid (PFOA, CAS No. 335-67-1) are industrial chemicals belonging to the group of per- and polyfluoroalkyl substances (PFAS). PFOS and PFOA are C8 compounds whose chemical backbone consists of a linear chain of 8 carbon atoms in which all hydrogen atoms are replaced by fluorine atoms. This perfluorinated carbon chain has hydrophobic properties and is linked to a hydrophilic headgroup. Due to the extremely stable fluorine-carbon bond, the compounds have high thermal and chemical stability.

PFOS and PFOA, their salts and related C8 compounds have been and are used because of their special properties for numerous technical and technological applications. In addition, a variety of applications exist for polymers based on "C8 chemistry". These polymeric materials may contain residues or impurities of PFOS and PFOA, as well as related C8 compounds (“precursor compounds”) and possibly release them. The related C8 compounds can be degraded to PFOS or PFOA. In addition, the (stable) polymers can be degraded over a long

period of time to PFOS or PFOA (and their related compounds). Due to their high mobility, airborne particle-bound transport and poor degradability (high persistence) in the environment, the compounds have developed into global environmental contaminants. Also in Germany, PFOS and PFOA are detectable in the environment, in the food chain and in humans.

PFOS is considered the leading compound in the perfluorinated alkyl sulfonic acid group because it is formed from a variety of related C8 compounds (e.g. sulfonamides, sulfonamidoethanols) and can be released from certain C8-based polymers. PFOS is most commonly detected in the environmental samples studied so far and is also very well characterised toxicologically. The term PFOS generally refers to the acid and the salts derived from it. PFOS has been manufactured on an industrial scale for over 50 years. In May 2000, the world's most important manufacturer announced it was phasing out PFOS production by 2002. The use and distribution of PFOS, its salts and derivatives, including those polymers which break down to form PFOS in the environment, were severely restricted in 2006 within the European Community by Directive 2006/122/EC and limited to a number of special applications (EC 2006). This restriction under chemical law was subsequently adopted in Annex XVII of the REACH Regulation (EC) No 1907/2006 (EC 2009). In 2011, the entry for PFOS was removed from Annex XVII of the REACH Regulation (EU 2011), as the restrictions on PFOS were included in Regulation (EC) No 850/2004 concerning persistent organic pollutants (POP Regulation) (EU 2010). For textiles, for example, the limit value for unintentional trace impurities of PFOS (and its salts and derivatives, including polymers) is 1 µg/m^2 of the coated material. Worldwide, PFOS is governed by the Stockholm Convention, which severely restricts its use.

PFOS has been used in certain fire extinguishing foams in the past. In addition, PFOS-related compounds were used as i.a. raw material for preparatory formulations within polymeric surface treatment to impart water and dirt repellent properties to fabrics, upholstery and carpets (Benskin et al., 2010). Papers, cartons and cardboard for packaging (including those for food contact) were also coated with dirt, grease and water-repellent coatings. Back in 2003, the BfR had already deleted all substances and mixtures that could release PFOS into food from its "Recommendations on materials in contact with food". Nowadays, only special applications in the field of electroplating, in the photographic and photolithographic field, for chrome plating and in the space industry (EU 2010) are permitted.

PFOS is not subject to hydrolysis, photolysis or biodegradation under environmental conditions and is environmentally persistent. In laboratory animals, PFOS is not predominantly distributed in adipose tissue, but tends to bind non-specifically to proteins. PFOS is readily soluble in water (solubility in pure water 519-570 mg/l), but also has lipophilic properties (solubility in pure octanol 56 mg/l), is surface-active (surfactant character)[2] and only lightly volatile. From this it can be deduced that PFOS in an aqueous environment will remain in this phase until it is adsorbed onto particles or consumed by organisms (OECD 2002).

There is no standardised method of PFOS analysis. In particular, obtaining evidence from complex matrices is still considered to be extremely challenging and may be associated with

[2] Due to the surfactant structure, alkylcarbonic and alkylsulfonic acids are preferably found at phase boundaries or form micelles. The nonpolar perfluorinated rest favours affinity with hydrophobic matrices. The negative charge of the acid anions permits strong electrostatic interactions, for example in biological matrices with proteins or with the positively charged mineral surfaces of soils and sediments (Fromme et al., 2006).

relatively large errors. According to Recommendation 2010/161/EU, the quantification limits should be 1 µg/kg[3].

PFOA is regarded as a leading compound for the group of perfluorinated alkylcarboxylic acids and is toxicologically very well studied and often found in environmental samples. Similar to PFOS, the term PFOA is used for both the actual acid and its salts. Most of the toxicological studies were performed with the ammonium salt APFO (ammonium perfluorooctanoate, CAS No. 3825-26-1). Like PFOS, PFOA can also be formed from precursors such as fluorotelomer phosphate esters, acrylates and iodides, and perfluoroalkyl sulfonamides.

PFOA is mainly used as a processing aid (emulsifier) for the production of fluoropolymers such as e.g. polytetrafluoroethylene (PTFE), which is used i.a. for the non-stick coating of food contact materials (e.g. frying pans) and for membranes in breathable clothing (ECHA 2018). In these coatings as well as in fluorinated polymers for making textiles water, oil and dirt repellent (see below), trace amounts of PFOA may be present (as an unintended by-product/residue or impurity). In addition, there are a number of technical uses of PFOA and its precursors (e.g. in fire extinguishers). To a lesser extent, PFOA is used in the photographic sector and as a surfactant in the semiconductor industry.

Another source of PFOA release from other compounds is C8-based polymers that can be synthesised from fluoroelastomer alcohols (ECHA 2018). These are so-called side-chain fluorinated polymers (also called fluorocarbon resins), which are used i.a. for the surface treatment of textiles and leather to give these materials water, dirt and oil repellent properties. Such a fluorocarbon treatment is used e.g. in sports and outdoor clothing, home textiles, upholstered furniture, carpets and protective clothing. Impregnating agents may also contain such polymers. In addition, side-chain fluorinated polymers can be used to treat the surface of paper, cardboard, and paperboard used in packaging.

Products that contain fluoropolymers such as PTFE or side-chain fluorinated polymers may also contain residues, unintended by-products or impurities of PFOA and related compounds (e.g. 8:2 fluorotelomer alcohol (8:2-FTOH), CAS No. 678-39-7). Therefore, PFOA can be created as a degradation product of 8:2 FTOH.

Toxicologically relevant migration of PFOA to food from non-stick cookware is unlikely subject to good manufacturing practice and proper intended use of the products. In addition to “systems for making coatings on frying and cooking appliances”, in 2016 further listings of substances that could potentially release PFOA were removed from the BfR recommendations on materials that come into contact with food (perfluorinated C8-based surface finishing agents in Recommendation XXXVI) (BfR, 2016).
In 2017, a restriction on PFOA, its salts and precursor compounds was included in Annex XVII of the REACH Regulation (EU Commission, 2017). According to this, from 2020 the compounds mentioned there can neither be manufactured nor distributed. In addition, a prohibition on the manufacture and distributing of products containing PFOA, salts and precursors thereof will also come into force for concentrations above 0.025 mg/kg or 1 mg/kg (for PFOA precursors or combinations of PFOA precursors). Exceptions or longer transitional periods exist for some special uses.
PFOA is more water-soluble than PFOS (3.4-9.5 g/l, 20 °C), surface-active and has a very low vapour pressure.

[3] Commission Recommendation 2010/161/EU of 17 March 2010 on the monitoring of perfluorinated alkyl substances in foodstuffs

There is no standardised method of PFOA analysis and it is considered as challenging as PFOS analysis. According to Recommendation 2010/161/EU, the quantification limits should be 1 µg/kg[4].

3.2 Hazard characterisation

3.2.1 Toxicokinetics

PFOS and PFOA are almost completely absorbed into the blood from the gastrointestinal tract through resorption and bind unspecifically to serum proteins after entering the body through ingestion (Hundley et al., 2006, Han et al., 2003). Both compounds are distributed in the blood and, moreover, preferentially in the internal organs such as liver, kidney and lungs, i.e. not primarily in adipose tissues (Kennedy et al., 2004, Sanchez Garcia et al., 2018). A transfer into breast milk has been shown for both PFOS and PFOA. Their presence in the placenta and umbilical cord blood also demonstrates a transition to the foetus (Manzano-Salgado et al., 2015, Zhang et al., 2013, Mondal et al., 2014, Fromme et al., 2010).

PFOS and PFOA are not metabolised in mammalian organisms. Excretion of PFOS and PFOA occurs primarily via the kidneys and to a lesser extent via faeces. Both substances are recycled via enterohepatic circulation (Johnson et al., 1984). Renal reabsorption also plays an important role in excretion via the kidneys, which is almost complete (99.95%) in humans in the case of PFOA (Han et al., 2012). PFOS and PFOA are therefore excreted extremely slowly by the kidneys in humans in comparison with experimental animal species studied so far, which leads to a prolonged presence in the human body (long half-lives). The half-lives for elimination of PFOS and PFOA, but also of other PFAS, depend on both substance and species and, in addition, gender and age in some species (Li et al., 2018, Vanden Heuvel et al., 1991, Zhang et al., 2013). The shorter half-lives in women compared to men are partly attributed to excretion of the compounds with the menstrual blood (Wong et al., 2014). While the half-lives for the substances in many species range from a few hours to weeks, the half-life in humans is 2.3 to 3.8 years for PFOA and 5.4 years for PFOS (Table 1, Lau 2015, Kudo 2015). Slow excretion in humans is a critical issue for the toxicological assessment of substances.

Table 1: Half-life* of PFAS in blood for different species, supplemented by (Lau 2015); Table according to (Pabel et al., 2017)

Species	Perfluorosulfonic acids			Perfluorocarboxylic acids				
	PFBS	PFHxS	PFOS	PFBA	PFHxA	PFHpA	PFOA	PFNA
Rat	*4.0 h*	29 d	62 - 71 d	*1.0 h* *1.8 h*	*0.4 - 0.6 h*		*2-4 h*	1.4 d
Mouse		25 - 27 d	31 - 38 d	*3 h*	*~1.2 h*		17 d	26 - 68 d
Ape	3.5 d	87 d	110 d	1.7 d	*2.4 - 19.2 h*		30 d	
Pig	43 d	**2 a**	**1.7 a**		4.1 d	74 d	236 d	
Human	28 d	**8.5 a**	**5.4 a**	3 d	32.0 d	**1.2 - 1.5 a**	**2.3 - 3.8 a**	**2.5 - 4.3 a**
Literature	(1); (2)	(1); (2)	(1); (2)	(1)	(1); (2)	(2); (3)	(1); (2)	(1); (3)

PFBS, perfluorobutanesulfonic acid; PFHxS perfluorohexanesulfonic acid, PFBA, perfluorobutanoic acid, PFHxA, perfluorohexanoic acid; PFOS, perfluorosulfonic acid; PFHpA, perfluoroheptanoic acid, PFOA, perfluorooctanoic acid, PFNA, perfluorononanoic acid
(1) Lau 2015; (2) Numata et al., 2014; (3) Zhang et al., 2013
h: hours (*italics*), d: days, **a**: years (**bold**)
Empty cells: no data
*****Half-lives of female animals are listed when different half-lives are described for the sexes

3.2.2 Human biomonitoring

The Commission for Human Biomonitoring (HBM Commission) of the Federal Environment Agency (UBA) has established reference concentrations[4] for PFOS and PFOA in the blood plasma of the German population of 20 µg PFOS per litre for women, 25 µg PFOS per litre for men and 10 µg PFOS per litre for children younger than 10 years and 10 µg PFOA per litre for all population groups (UBA 2009). Data collection took place between the years 2003 and 2007. Due to the European regulatory measures for PFOS and PFOA (see also 3.1), a trend towards decreasing blood concentrations is to be expected in the long term. Measurements of PFOS and PFOA concentrations in the blood of the general population in Germany actually indicate a trend towards decreasing concentrations since 2009 (Yeung et al., 2013a, 2013b). Comprehensive data on current blood concentrations are not available for Germany. However, a recent study on the PFOS and PFOA blood concentrations of 158 people from Munich shows that a further trend towards a decrease in blood concentrations in recent years has to be assumed (Fromme et al., 2017). The median values in this study were 2.1 and 1.1 µg/l for PFOS and PFOA, the values for the 95th percentile were 6.4 or 2.4 µg/l respectively. This trend is also evident in studies of other European and non-European popula-

[4] The reference value for a chemical in a human biological material (here: blood plasma) is a value (usually the 95th percentile), which is derived from a series of corresponding measured values of a sample from a defined population group according to a given statistical method. It is a purely statistically defined value, which has no health significance per se. The reference value enables the current status (so-called background load of a ubiquitous substance) to be described within a reference population (https://www.umweltbundesamt.de/sites/default/files/medien/377/dokumente/konzept.pdf).

tions after the turn of the millennium (Stubleski et al., 2016, Erikson et al., 2017, Olsen et al., 2017, Gebbink et al., 2015).

PFOA and, to a lesser extent, PFOS pass into breast milk and accumulate in the infantile organism during lactation. The concentrations of PFOS and PFOA measured in breast milk are approximately 0.9% to 2% and 1.8% to 9%, according to different studies, of the concentration in the blood of the mother (evaluation of available data in EFSA 2018a). As a result PFOA, in particular, shows accumulation in infants depending on the duration of breastfeeding, which - despite different physicochemical properties - is quantitatively comparable with that of lipophilic compounds such as dioxins and PCBs.

In a study in Bavaria between the years 2007 and 2009, breastfed children (n=27) at the age of 6 and 19 months had average PFOA plasma concentrations of 8.7 and 5.7 µg/l, which were significantly higher than the average maternal value at birth of 2.4 µg/l (Fromme et al., 2010). The accumulation factor at 6 months of age compared to the maternal value at birth averaged 3.6, the maximum 5.5 (Fromme et al., 2010, Verner et al., 2016). Accumulation of PFOS is apparently lower, however, the present studies showed a relatively large range of mean accumulation factors. Pharmacokinetic modelling shows a gradual decline in the concentrations and an evening out of values for breastfed and non-breastfed children within a few years after the maximum of infant blood concentrations upon cessation of breastfeeding (Verner et al., 2016). In fact, in another study with children aged 6-10 years, no significant effect of breastfeeding duration on PFOA and PFOS concentrations was demonstrated (Harris et al., 2017).

3.2.3 Toxicology

Human health risk assessment focuses on toxicity due to long-term intake and accumulation. The acute toxicity of PFOS and PFOA in animal experiments after oral exposure is relatively low (LD_{50} in several animal studies with rats in the range of >250 to <580 mg PFOS / kg body weight, 250 to 680 mg PFOA / kg body weight) (EFSA 2008, 2018). Both PFOS and PFOA are classified as "Harmful if swallowed"[5] and “Harmful by inhalation”[6] under Regulation (EC 2008, CLP Regulation).

3.2.3.1 Animal studies with repeated oral exposure

In studies with repeated administration of PFOS and PFOA, the liver was an important target organ in different species. The primary effects were increased liver weights, hypertrophy of the hepatocytes and induction of peroxisomal β-oxidation of fatty acids. Other effects included a reduction in body weight, disorders of lipid metabolism (decreased serum levels of cholesterol and triglycerides), altered thyroid hormone levels and increased mortality. In its 2008 opinion EFSA applied No Observed Adverse Effect Levels (NOAELs)[7] from these studies to derive TDI[8] values. Due to the effects on the liver, PFOA was classified as hepatotoxic after

[5] Acute Tox 4 H302
[6] Acute Tox 4 H332
[7] No observed adverse effect level (NOAEL): indicates the highest dose at which no health impairment attributable to the studied substance is found
[8] Tolerable daily / weekly intake (TDI/TWI): Health-based guidance value for the tolerable amount of a contaminant that a human being may consume every day/week over the course of a lifetime without causing any appreciable health impairments

repeated exposure according to Regulation (EC 2008, CLP Regulation)[9]. PFOS is also classified according to this Regulation for specific target organ toxicity after repeated exposure, but without specification of target organs[10].

PFOS and PFOA are toxic to reproduction in animal studies and lead to decreased body weight gain after birth and a drastic reduction in live births and viability of offspring. According to EFSA (2018), the most sensitive developmental toxicity effects of PFOS are the impairment of maternal liver weights, the placental physiology and glucose homeostasis, and, in the case of PFOA, an increase in liver weight of the offspring. For PFOA, both EFSA and ECHA also report impairments of mammary gland development in mice (White et al., 2011, Macon et al., 2011, Tucker et al., 2015) and metabolic processes (Hines et al., 2009, Van Esterik et al., 2016) in a relatively low dose range (0.01 mg/kg body weight per day) that were not used to derive a health-based guidance value as they are not considered to be adverse effects. Due to their reproductive toxicity effects, PFOS and PFOA are classified as toxic for reproduction category 1B according to Regulation (EC) No 1272/2008 (CLP Regulation)[11], because they pass into breast milk both substances continue to be labelled "May cause harm to breast-fed babies"[12].

According to the EFSA report (2018), studies in rats with chronic exposure to PFOA showed increased incidences of adenomas in the testes (Leydig cells) and the liver, as well as hyperplasia of the pancreas. Studies in rats with chronic exposure to PFOS showed increased incidences of adenomas in the liver. The mechanisms leading to an increase in tumour incidences are still not fully understood. According to EFSA (2018), there are indications that PFOS acts as a tumour promoter in the liver of rats and trout. It is believed that the carcinogenic effects of PFOS and PFOA are not due to a genotoxic mechanism. This means, for the health assessment, it can be assumed that safe intake levels are definable for the compound for which no carcinogenic effects are to be expected. Health-based guidance values derived on the basis of the most sensitive endpoints for the toxic effects of PFOS and PFOA also protect against the potential carcinogenic effects of PFOS and PFOA. PFOA and PFOS are classified as Category 2[13] carcinogens according to Annex VI of the Regulation (EC 2008, CLP Regulation). The Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) concludes that PFOA-induced tumours are of relevance to humans (ECHA 2015). PFOA has also been assessed as potentially carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer (IARC).

According to EFSA (2018), PFOS and PFOA are neurotoxic in rodents within the dose range of 0.1 to 0.3 mg/kg body weight per day. In addition, both compounds are immunotoxic in animal studies (NTP 2015) in that PFOS interferes with homeostasis of the immune system (NOAEL 1.66 µg/kg body weight per day, EFSA 2018a) and PFOA interferes with the cellular composition of tissues of the immune system (bone marrow, spleen, thymus) and impairs the immune system function (decreased antibody response to T cell-dependent antigens as well as increased IgE-specific immune response and inflammatory response). For PFOA, a NOAEL for immunotoxic effects of 1 mg/kg of bodyweight per day has been derived (EFSA 2018a).

3.2.3.2 Epidemiology

[9] STOT RE1 H372 "Causes damage to the liver through prolonged or repeated exposure"
[10] STOT RE1 H372 "Causes damage to organs through prolonged or repeated exposure"
[11] H360D "May damage the unborn child",
[12] H362 May cause harm to breast-fed babies
[13] H351 "Suspected of causing cancer"

In its most recent Opinion, EFSA has evaluated extensive findings from some 200 epidemiological studies, most of which were not available at the time of their first opinion.

This shows correlations between PFOS and PFOA concentrations in the blood and changes in lipid metabolism (increase in total serum cholesterol). For PFOS, reduced antibody production after certain vaccinations in children is also considered critical. These relationships are discussed in more detail later in the text. Exposure to PFOA was also associated with an effect on a liver enzyme (alanine aminotransferase).

By contrast, EFSA regards the clinical relevance and causality of the relationship between concentrations of PFOS and PFOA in the blood and a reduction in birth weight as unclear. From EFSA's point of view, the existing studies suggest a causal relationship between these parameters, but potential confounding[14] due to an increased glomerular filtration rate of the kidneys cannot be ruled out and no increased risk for the occurrence of birth weights being defined as "low" (<2500 g) was reported. For other observed impairments also, epidemiological studies do not show sufficient evidence for causal relationships with exposure to PFOS and PFOA from EFSA's point of view. These include the reduction of fertility, the impairment of hormonal development or thyroid metabolism, the impairment of renal function or an effect on uric acid levels. So far, the BfR has not carried out a conclusive assessment of the epidemiological studies on the parameters mentioned in the previous sentence. According to the IARC (2016) assessment, there is limited evidence of a carcinogenic effect of PFOA in humans (“There is limited evidence in humans for the carcinogenicity of perfluorooctanoic acid (PFOA)”). EFSA (2018) views this statement as confirmed by the current evaluation of epidemiological studies on carcinogenicity of PFOA and extends it to cover PFOS.

EFSA has derived the TWI values based on epidemiological studies of changes in lipid metabolism (Steenland et al., 2009, Eriksen et al., 2013, Nelson et al., 2010). Steenland et al. (2009) assess data collected during 2005-2006 in the vicinity of a chemical plant (West Virginia, Ohio) as part of a lawsuit[15]. They can rely on an exceptionally large data pool of over 46,000 records. This evaluation was carefully performed from the point of view of the BfR. The result shows a positive correlation between elevated PFOA/PFOS concentrations and total serum cholesterol, which is supported by numerous other studies with other study populations. The evaluation of other existing epidemiological studies consistently shows higher concentrations of total cholesterol in adults at higher serum concentrations of PFOS and PFOA (Eriksen et al., 2013, Nelson et al., 2010). Of note in the observed relationship is that the increase observed in these studies of approximately 10 to 15 mg total cholesterol per dl (corresponding to an increase of approximately 5 to 7.5%) can be observed down to the range of measured average PFOS/PFOA concentrations, while the further increase at even higher concentrations is only slight. For children and adolescents there is an extensive study involving 12,476 participants (Frisbee et al., 2010), which shows comparable results across the age distribution. Studies focusing on breastfed children and possible changes in cholesterol in the first years of life are not available.

However, the question of whether there is a causal relationship has not been clarified definitively. It is also possible that both parameters are causally dependent on a third parameter. The study design (cross-sectional study) is not suitable to clarify causality. From the point of view of the BfR, possible confounding (coincidence of elevated serum levels for PFOS,

[14] Distortion of the result due to disturbances which influence the effect or the disease which is independent of the exposure to the substance being investigated.
[15] www.c8sciencepanel.org

PFOA and total cholesterol) via enterohepatic circulation (excretion into the intestine via the bile with subsequent reabsorption from the intestine) cannot be ruled out. EFSA did not consider this option further. The results of the study by Fitz-Simon et al. (2013) support the assumption of a causal relationship between PFOS/PFOA exposure and an increase in cholesterol levels, according to the BfR. According to Steenland et al. (2009) the analytical results of persons who took cholesterol-lowering drugs and were therefore not included in the modelling contradict "reverse causation" (elevated cholesterol levels cause higher PFOS/PFOA levels). Assuming that the cholesterol level affects the PFOA/PFOS level, this would have to be lower in treated persons. However, this effect was not observed in the study data.

In several studies, including Steenland et al. (2009), higher concentrations of PFOS/PFOA in serum have been shown to be associated with elevated LDL cholesterol levels. Compared to the total cholesterol level, the LDL level is considered to be more relevant as a risk factor for cardiovascular diseases. Nevertheless, EFSA used the values for total cholesterol for the further evaluations, as a larger data set was available for this parameter compared to LDL cholesterol and the increase in both parameters depended similarly on PFOA/PFOS.

A prolonged increase in total cholesterol in adults is considered a risk factor, among several other risk factors, for the development of cardiovascular disease.

EFSA (2018) lists five cross-sectional studies and four longitudinal studies examining associations between PFOS/PFOA exposure and parameters of cardiovascular disease. According to EFSA (2018), the results of the studies are not consistent with regard to the relationships between exposure to PFOS/PFOA and these parameters. From EFSA's point of view, it would not be possible, based on these studies, to show a potentially existing slight increase in the risk of cardiovascular disease. The BfR points out that another study has recently been published that has investigated this relationship (Huang et al., 2018). This study is based on data collected from seven years of the National Health and Nutrition Examination Survey (NHANES), for which a representative sample of the US population is regularly screened and interviewed. It suggests a positive association of the risk of cardiovascular disease with serum levels of PFOA/PFOS.

Studies cited by EFSA (2018) on the association between total blood cholesterol and cardiovascular disease risks only cover study populations over 40 years of age. The lack of data for younger people including children results in additional uncertainties regarding the health relevance of a possible PFOS/PFOA-induced increase in cholesterol for these age groups.

Epidemiological studies show to some degree negative associations between concentrations of PFOS/PFOA in blood and titres of vaccine antibodies in the blood. The strongest association of these parameters is shown by a study of a group of inhabitants of the Faroe Islands, which has a relatively high exposure to a variety of persistent contaminants due to the high consumption of fish and whale meat. Blood samples were taken from children (n=587) of 5 years of age to determine vaccine antibodies (tetanus, diphtheria) and concentrations of perfluorinated compounds (PFOS and PFOA averages of 16.7 and 4.1 µg/l, respectively) and other compounds and a booster dose against tetanus and diphtheria was administered. The subsequent study of serum vaccine antibodies at 7 years of age showed a marked inverse association with the PFOS and PFOA concentrations in the blood measured at 5 years of age. The association was less pronounced for vaccine antibodies to tetanus (association at PFOS not significant) than for vaccine antibodies to diphtheria, in which the measured antibody titres in the high range of internal PFOS/PFOA exposure were only about half as high as in the low range. The diphtheria antibody titres measured at 5 years prior to the booster

also showed the corresponding inverse association with the maternal PFOS/PFOA exposure measured at birth, but this was less pronounced. At 7 years, 18 or 32 children (3.1% and 5.5%, respectively) were below the antibody titres of 0.1 IU/ml for tetanus and diphtheria considered protective (Grandjean et al., 2012). In the follow-up of 516 children aged 13 years with redetermination of the diphtheria and tetanus titres as well as the PFAS concentrations in the blood (PFOS and PFOA averages of 6.7 and 2.0 µg/l, respectively), most children showed the expected drop in titres between the ages of 7 and 13 years. In the meantime, 68 children may have received a booster dose when visiting an emergency room. Surprisingly, in 202 children, the expected further drop in antibody titres was not observed, although they had evidently not received a booster dose in the meantime. The evaluations of different constellations consistently showed inverse relationships between PFOS/PFOA concentrations and diphtheria antibodies, however, the relationship was statistically significant in only one of the 6 cases reviewed. For tetanus antibodies, these relationships were not uniform, however, the calculated trends were predominantly positive (Grandjean et al., 2017).

Two further studies have also dealt with the above question in children and adolescents. A subgroup (n=50 children) of a Norwegian mother-child cohort was examined at the age of 3 years for titres of vaccine antibodies. There were negative associations with maternal blood PFOS and PFOA concentrations at birth (average 5.6 and 1.1 µg/l, respectively) in rubella, while for Haemophilus influenza type B (Hib), tetanus and measles no significant association was observed (Granum et al., 2013). In a cross-sectional study (n=1191), the association of perfluorinated compounds (PFOS and PFOA averages of 20.8 and 4.1 µg/l, respectively) with the titres of antibodies against measles, mumps and rubella was reported in children and adolescents aged 12 to 19 years. Higher concentrations of the compounds were significantly associated with low titres of antibodies to mumps and rubella in the seropositive subjects, with a 5.9 and 13.3% decrease in titres for PFOS and 6.6 and 8.9% for PFOA, each with a doubling of PFAS concentrations in the blood. No association was found for measles antibodies (Stein et al., 2016).

The results of the study on reduced antibody formation presented here raise the question as to whether a generally suppressive effect of PFOS and PFOA on the immune system could be present, which generally leads to a more frequent occurrence of infectious diseases. However, studies on general susceptibility to infection with regard to the postnatal exposure in long-term breast-fed children considered here are not available. Only in relation to the question of the effect of prenatal PFAS exposure have several studies been published on the possible association of concentrations in maternal or umbilical cord blood and the general infection frequency of infants in the first years of life. Positive associations have been reported in some cases (Granum et al., 2013, Dalsager et al., 2016, Goudarzi et al., 2017, Impinen et al., 2018), while other studies found no association (Fei et al., 2010, Okada et al., 2012, C8 Science Panel 2012).

Overall, the BfR sees the evidence available to date on the question of reduced formation of vaccine antibodies, possibly caused by PFOS/PFOA, or increased susceptibility to infection as inadequate and sometimes contradictory (see also EFSA 2018b). To date, there are only a few studies with predominantly relatively small numbers of subjects whose results are only partially consistent. There are also some doubts as to whether other persistent environmental contaminants were sufficiently considered as possible confounders within the studies. In addition, the question of the clinical significance of the observed findings regarding a potentially reduced vaccination efficacy is fundamentally unclear, since titres of vaccine antibodies are only to be interpreted as surrogate markers and in most vaccinations do not permit any statement about their protective potency. The BfR sees considerable need for research here (see 3.6) to confirm the findings in larger studies, which will have to include functional inves-

tigations of the immune system. In addition, the question of a particularly sensitive time window, which may exist during childhood, is unclear. One focus of further investigations should be on the first years of life. During this period, in which vaccines are often administered as a primary immunisation, there is a relatively high PFOS/PFOA exposure in long-term breastfed children. The studies available so far only examined children who were 3 years or older.

3.2.4 Derivation of health-based guidance values

PFOS and PFOA are the only substances in the PFAS group for which international bodies have so far derived health-based guidance values[16]. Based on data from animal studies, in 2008 EFSA published tolerable daily intake (TDI)[17] values of 0.15 µg/kg of body weight per day for PFOS and 1.5 µg/kg of body weight per day for PFOA. Other bodies later derived significantly lower health-based guidance values, mainly due to the use of other toxicokinetic models to account for differences in half-lives between laboratory animals and humans.

In deriving the TWI values, EFSA (2018) primarily uses the results of epidemiological studies that showed an association between total cholesterol levels and serum PFOS/PFOA concentrations. From the study data (Steenland et al., 2009, Eriksen et al., 2013, Nelson et al., 2010) blood concentrations of 22 ng PFOS per ml blood serum and 9.3 ng PFOA per ml blood serum were determined as the basis for the TWI derivation by means of benchmark modelling. This means that at blood concentrations below these benchmark dose lower confidence limit $(BMDL)_5$ values[18] it is very unlikely that an increase in total cholesterol levels by 5% or more occurs in the population due to exposure to PFOS and PFOA.
There is still no generally scientifically coordinated approach to calculate $BMDL_5$ values based on epidemiological studies. EFSA follows the usual approach for experimental data, which are usually derived from animal studies for toxicology. However, the procedure has to be modified, especially as in epidemiological studies a "control group" without exposure is lacking. The modifications chosen by EFSA are plausible from the perspective of BfR.

EFSA (2018) also performed BMDL modelling for other relationships in epidemiological studies in addition to the association between total cholesterol levels and serum PFOS/PFOA concentrations. For PFOS, BMDL values were also modelled from a study of antibody formation after vaccination in children (reduction of antibody formation after diphtheria vaccination, Grandjean et al., 2012), and for PFOA from a study on the interference with a liver enzyme (serum levels of alanine aminotransferase) (Gallo et al., 2012) and for both compounds from a study on the relation to birth weight (Witworth et al., 2012). The BMDL values for these relationships were not used to derive TWI values. According to EFSA (2018), the BMDL values for the relationship between concentrations of PFOS and PFOA in the blood and a reduction in birth weight are in a similar range as those for the relationship between total cholesterol and PFOS/PFOA concentrations in serum and were not used for the TWI derivation, as EFSA believes uncertainties exist regarding causality of the relationship and adversity. In the study on the influence on the serum level of alanine aminotransferase, a 5% change in the parameter was not observed. The benchmark modelling therefore refers to a

[16] Currently an opinion of ATSDR is available, in which Minimal Risk Levels (MRL) for perfluorhexanesulfonic acid and perfluorononanoic acid were also derived (ATSDR 2018)
[17] Tolerable daily / weekly intake (TDI/TWI): Health-based guidance value for the tolerable amount of a contaminant that a human being may consume every day/week over the course of a lifetime without causing any appreciable health impairments
[18] Benchmark dose (BMD): dose determined by mathematical modelling of the dose-response relationship, which is associated with a specific effect size in the study underlying the modelling. Benchmark dose lower confidence $limit_5$ ($BMDL_5$): lower limit of the 95% confidence interval of BMD of 5%

3% change in the parameter. As a result, the detected BMD_3 or $BMDL_3$ were higher than the BMD_5 or $BMDL_5$, respectively, which were determined for the relationship between total cholesterol level and PFOA concentrations in serum, so this relationship was considered more sensitive/critical for the assessment of PFOA. According to EFSA, the studies on reduced antibody production after vaccination do not allow conclusions to be drawn regarding a possible impairment in adults. EFSA (2018) interprets the study by Grandjean et al. (2012) as showing a greater association of PFOS concentrations in the blood with decreased antibody production compared to concentrations of PFOA in the blood. Considering that the association between PFOA concentrations in the blood and reduction in antibody production could be partly due to the presence of PFOS, $BMDL_5$ modelling for PFOA is not undertaken.

For children, the lowest $BMDL_5$ value for PFOS was derived for this parameter. According to EFSA, compliance with $BMDL_5$ derived for the increase in total cholesterol in serum in mothers also protects children who are breastfed during the first six months of life from reaching serum concentrations equal to $BMDL_5$ values for decreased antibody production after vaccinations.

EFSA has derived TWI values of 6 ng/kg bw per week for PFOA and 13 ng/kg bw per week for PFOS from the reported $BMDL_5$ values of the serum concentrations using toxicokinetic modelling. These values are significantly lower than health-based guidance values previously derived by EFSA and other international bodies. The toxicokinetic model used for this purpose describes oral intake, distribution in blood, tissue and possibly breast milk as well as renal excretion of PFOA and PFOS in the human body (Loccisano et al., 2011, 2013). Since the simulation code for the model is described completely, the model calculations are fully traceable and valid from the point of view of BfR. However, in the PBPK model, the enterohepatic circulation of PFOA and PFOS and their possible (albeit low) excretion via the faeces are not taken into account.

Because of long half lives in the human body, the quantities of PFOS and PFOA in the body increase, and therefore the blood concentrations, until they reach equilibrium, with a constant supply over a long period of time. This is accounted for in the design of the toxicokinetic modelling during derivation of the TWI values for PFOS and PFOA. As a result, external intake levels of PFOS and PFOA, which are in the range of TWI for some time, do not immediately lead to blood levels within the critical range[19]. Depending on the value of blood levels already present, it may take years until intake levels at around the TWI result in blood levels in the critical range.
According to EFSA's uncertainty analysis, the greatest uncertainty in using the cholesterol level as parameter to derive a TWI value is the clinical relevance issue. Cholesterol is one of the known risk factors, such as age, smoking, and high blood pressure, which determine the risk of cardiovascular disease. According to EFSA's interpretation of the current evidence, no studies have actually established an association between concentrations of PFOS and PFOA in the blood and a higher risk of these diseases in particularly exposed population groups.

Based on the results of these epidemiological studies, EFSA derives toxicological reference values for the health assessment of PFOS and PFOA, which are intended to avoid potential substance-induced increases in cholesterol levels even with long-term, continuous intake of PFOS and PFOA. On the grounds that the TWI values were derived based on a risk factor for certain diseases and the epidemiological studies were carried out on comparatively large

[19] $BMDL_5$ for PFOA 9.3 ng per ml blood serum, $BMDL_5$ for PFOS 22 ng per ml blood serum, see section 3.2.4

cohorts, EFSA has renounced the application of uncertainty factors for interindividual variability.

EFSA's newly derived TWI values also protect against other impairments for which associations with exposure to PFOS or PFOA have been described in epidemiological studies. They also protect against impairments observed in animal studies with significantly higher intake levels of PFOS and PFOA, such as developmental toxicity, hepatotoxic, immunotoxic and carcinogenic effects, and disorders of thyroid function.

3.3 Exposure

3.3.1 Consumption data

The exposure assessment of EFSA (2018) for Germany is based on the following nutrition surveys: the VELS study (Banasiak et al., 2005) for the age group of 0.5 to 5 years, the EsKiMo study for the age group of 6 to 11 years (Mensink et al., 2007) and the National Nutrition Survey II for the age group 14-80 years (MRI, 2008). Within the data of the National Nutrition Survey II, the collected two 24-hour recalls were evaluated.

All of these nutrition surveys are suitable for estimating long-term average intake levels. The intake estimates are evaluated according to the standardised age groups of EFSA (see Table 2). For some age groups, data from two nutrition surveys are available, both of which are presented in a comparative fashion.

EFSA has merged the nutrition surveys in its Comprehensive European Food Consumption Database with FoodEx2 standardised coding.

Table 2: Nutrition surveys for the estimation of the exposure of the population in Germany (EFSA 2018a)

Age group	Nutrition Survey
Infants (<1 year)	VELS
Toddlers (1 - <3 years)	VELS
Children (3 - <10 years)	VELS (up to 5 years)
	EsKiMo (from 6 years)
Adolescents (10 - <18 years)	EsKiMo (up to 11 years)
	NVS II (from 14 years)
Adults (18 - <65 years)	NVS II
Elderly (65 - <75 years)	NVS II
Very elderly (≥ 75 years)	NVS II

3.3.2 Concentrations of PFOS and PFOA in food

A total of 10,191 analytical results for PFOS and 9,828 for PFOA from Europe were included in the EFSA exposure assessment, collected between 2007 and 2015 (EFSA, 2018). Suspect samples, which were explicitly marked as such, were excluded from evaluation. A few datasets were also disregarded since limits of quantification were too high. More than 60% of

the analytical results (for both PFOS and PFOA) were submitted to EFSA from Germany. This does not necessarily mean that the EFSA exposure assessment is dominated by occurrence data from Germany. Firstly, much occurrence data for foods that are rarely consumed, e.g. wild boar liver, have been transmitted by Germany. Secondly, unlike other member states, Germany did not analyse pooled samples and transmit data on it to EFSA. In the evaluation of occurrence data, EFSA weighs pooled samples according to the number of individual samples included in this pooled sample. In case of a pooled sample a result is therefore included with a multiple weighting into the evaluation of the occurrence data. Since no measurement results of pooled samples were sent from Germany to EFSA, all data from Germany were included into the EFSA (2018) exposure assessment with single weighting only. Compared with the results of measurements by other European member states, the actual impact of the measurement results from Germany on the average values of the concentrations in EFSA's Opinion (2018) is therefore lower.

3.3.2.1 PFOS and PFOA concentrations in data from food control in Germany

The Federal Office of Consumer Protection and Food Safety (BVL) has sent a total of 62,034 data sets with PFAS measurements (mostly in food) to the BfR for the present assessment. The survey period dates from 2005-2018. The present assessment takes account of a total of 20,859 data sets with measurements of PFOS and PFOA in food from this data transfer. Data sets that don’t relate to food (e.g. clothing), as well as suspect, follow-up, and complaint samples are excluded from evaluation due to lack of representativeness. Data from the period prior to 2007 are also not taken into account, as older occurrence data may not adequately reflect the current situation. There remain 8710 data sets for each PFOS and PFOA. From eight German federal states, little or no data are available.

The individual food items were grouped into appropriate categories. For the food groups mineral water and drinking water, those datasets were not taken into account where the respective limit of quantification was above the maximum measured value (of the respective food group). For PFOS, this applies to 64 mineral water datasets and 4 drinking water datasets; for PFOA, it applies to 67 mineral water datasets. 308 datasets were not included because the product information was too non-specific (e.g. only "fish"). Food groups for which there was no quantifiable sample were excluded (this applies to i.a. fruit, cereals and cereal products, beer). Due to the high limit of quantification, this does not allow for the conclusion that PFOS/PFOA was not present in these foods.

Also with the remaining measurements of PFOS and PFOA, many values are below the limit of quantification. For a lower-bound estimate, these values are assumed to be 0, while the upper-bound estimate assumes the limit of detection or limit of quantification. The corresponding occurrence data can be found in Table 3 (PFOS) and Table 4 (PFOA).

High mean concentrations of PFOS are found particularly in the offal of game (especially wild boar), some salt-water fish species (order Perciformes) and many freshwater fish (e.g. carp, eel, zander and pike) (see Table 3). It is striking that the concentrations in many samples are not quantifiable. For example, in the potato and vegetable category, PFOS have been detected only in a few cases, which, however, due to the relatively high limit of quantification, does not indicate that PFOS is not present in these food groups.

Table 3: PFOS concentrations in food in Germany (official food control 2007-2018)

Food group	Perfluorooctane sulfonic acid (PFOS)					
	Number of samples [n]	≥LOQ [n (%)]	Lower bound		Upper bound	
			MW [µg/kg]	P95 [µg/kg]	MW [µg/kg]	P95 [µg/kg]
Wild boar						
-Meat	636	226 (36 %)	3.40	5.42	4.03	5.42
-Liver	962	937 (97 %)	224.40	768.95	224.49	768.95
-other offal	45	33 (73 %)	81.89	756.60	82.18	756.60
Roe deer, deer - meat	126	3 (2 %)	0.0087	0.00	0.57	1.00
Game (except wild boar) -other offal	30	22 (73 %)	8.89	68.45	9.38	68.45
Beef						
-Meat	80	15 (19 %)	0.40	1.39	0.88	1.40
-Liver	986	100 (10 %)	0.85	7.00	3.09	7.00
-other offal	21	3 (14 %)	0.43	3.90	1.33	3.90
Pork						
-Meat	16	2 (13 %)	0.41	6.30	0.71	6.30
-Liver	179	42 (23 %)	1.68	12.20	2.12	12.20
-other offal	190	2 (1 %)	0.025	0.00	0.39	1.00
Poultry						
-Meat	154	7 (5 %)	0.12	0.32	1.33	1.07
-Liver	185	20 (11 %)	1.23	6.78	2.64	6.78
-other offal	2	1 (50 %)	0.35	0.70	0.85	1.00
Mutton						
-Meat	56	-	-	-	-	-
-Liver	20	7 (35 %)	3.05	16.85	3.33	16.85
-other offal	9	2 (22 %)	0.78	5.00	1.56	5.00
Goat -Meat	15	9 (60 %)	0.77	6.60	1.05	6.60
Liver sausage	22	5 (23 %)	1.54	15.68	2.04	15.68
Milk	152	2 (1 %)	0.008	0.00	0.64	1.00
Cheese (excl. goat cheese)	70	7 (10 %)	0.12	0.45	0.64	0.73
Goat cheese	10	8 (80 %)	0.67	2.20	0.71	2.20
Eggs	160	16 (10 %)	0.99	5.00	1.70	5.00
Sea fish						
-Herring/ sprat	80	10 (13 %)	0.38	3.70	1.12	3.70
-Perciformes (sea fish)	20	2 (10 %)	69.50	825.50	70.41	825.50
-Flatfish (E.g. plaice)	27	7 (26 %)	0.62	3.72	1.12	3.72
-other sea fish (codling, tuna, …)	263	12 (5 %)	0.10	0.00	1.11	1.00
Freshwater fish						
-Carp, whitefish	405	272 (67 %)	19.97	72.80	20.34	72.80
-Salmonids	850	47 (6 %)	1.57	1.35	2.50	2.56
Perciformes (freshwater)	110	74 (67 %)	106.21	372.35	106.47	372.35
-Eel	240	140 (58 %)	14.46	49.00	14.80	49.00
-Catfish	64	16 (25 %)	1.24	8.88	1.80	8.88
-Esociformes	32	19 (59 %)	26.78	311.00	27.15	311.00
Fish - offal	11	4 (36 %)	1.93	5.80	2.84	5.80
Water molluscs	69	3 (4 %)	0.12	0.81	0.94	1.31
Crustaceans	27	10 (37 %)	0.65	6.56	1.33	6.56
Wild edible fungi	75	16 (21 %)	0.26	1.31	0.63	1.31
Honey	6	-	-	-	-	-
Mineral water	334	32 (10 %)	0.00038	0.0030	0.0014	0.0033
Drinking water	55	3 (5 %)	0.00096	0.010	0.0099	0.011
Potato (raw)	141	-	-	-	-	-

Food group	Perfluorooctane sulfonic acid (PFOS)					
	Number of samples [n]	≥LOQ [n (%)]	Lower bound		Upper bound	
			MW [µg/kg]	P95 [µg/kg]	MW [µg/kg]	P95 [µg/kg]
French fries	113	1 (1 %)	0.011	0.00	1.00	1.00
Carrot	133	1 (1 %)	0.0083	0.00	0.34	0.70
Beetroot	19	-	-	-	-	-
Herbs	7	-	-	-	-	-

High mean concentrations of PFOA were measured especially in wild boar (meat and offal), carp and pike. The proportion of datasets with unquantifiable concentrations is even higher for PFOA than for PFOS. In the groups “potato (raw)”, “carrot” and “beetroot” only isolated detectable concentrations of PFOA were found.

Table 4: PFOA concentrations in food in Germany (official food control 2007-2018)

Food group	Perfluorooctanoic acid (PFOA)					
	Number of samples [n]	≥LOQ [n (%)]	Lower bound		Upper bound	
			MW [µg/kg]	P95 [µg/kg]	MW [µg/kg]	P95 [µg/kg]
Wild boar						
-Meat	633	112 (18 %)	2.28	7.07	3.08	7.07
-Liver	967	452 (47 %)	12.37	32.01	14.84	32.01
-other offal	45	35 (78 %)	76.71	303.01	77.01	303.01
Roe deer, deer -Meat	126	5 (4 %)	0.041	0.00	0.59	1.00
Game (excl. wild boar) - other offal	33	8 (24 %)	1.26	8.45	2.46	8.45
Beef						
-Meat	80	20 (25 %)	0.46	2.76	0.90	2.79
-Liver	972	18 (2 %)	0.041	0.00	2.19	2.50
-other offal	21	-	-	-	-	-
Pork						
-Meat	16	2 (13 %)	0.23	3.30	0.49	3.30
-Liver	179	13 (7 %)	0.13	0.70	0.62	1.00
-other offal	190	9 (5 %)	0.058	0.11	0.37	1.00
Poultry						
-Meat	154	2 (1 %)	0.014	0.00	1.22	1.00
-Liver	185	5 (3 %)	0.053	0.00	2.00	0.60
-other offal	2	-	-	-	-	-
Mutton						
-Meat	56	1 (2 %)	0.0018	0.00	0.82	1.00
-Liver	20	2 (10 %)	0.030	0.39	0.61	1.95
-other offal	9	-	-	-	-	-
Goat -Meat	15	9 (60 %)	0.35	0.90	0.66	1.00
Liver sausage	22	1 (5 %)	0.06	1.19	0.56	1.27
Milk	152	18 (12 %)	0.36	3.00	0.88	3.00
Cheese (excl. goat cheese)	70	9 (13 %)	0.061	0.60	0.68	0.66
Goat cheese	10	7 (70 %)	0.32	0.70	0.41	0.70
Eggs	164	15 (9 %)	0.48	2.70	1.23	2.70
Sea fish						
-Herring/ sprat	80	-	-	-	-	-
-Perciformes (sea fish)	20	-	-	-	-	-
-Flat fish (e.g. plaice)	27	1 (4 %)	0.071	1.15	0.63	1.55
-Other sea fish (codling, tuna, …)	262	2 (1 %)	0.15	0.00	1.18	1.00
Freshwater fish						
-Carp, whitefish	406	124 (31 %)	1.74	10.12	2.32	10.12

Food group	Perfluorooctanoic acid (PFOA)					
	Number of samples [n]	≥LOQ [n (%)]	Lower bound		Upper bound	
			MW [µg/kg]	P95 [µg/kg]	MW [µg/kg]	P95 [µg/kg]
-Salmonids	850	22 (3 %)	0.19	0.00	1.10	1.00
-Perciformes (freshwater)	110	2 (2 %)	0.13	0.000	1.15	3.40
-Eel	240	14 (6 %)	0.30	0.26	0.96	1.00
-Catfish	64	2 (3 %)	0.033	0.00	0.69	1.00
-Esociformes	32	1 (3 %)	1.53	17.15	2.35	19.75
Fish - offal	11	1 (9 %)	0.22	2.42	0.99	2.42
Water molluscs	69	6 (9 %)	0.28	2.69	1.06	2.69
Crustaceans	27	12 (44 %)	0.27	1.08	1.01	1.12
Wild edible fungi	75	1 (1 %)	0.0084	0.00	0.56	1.10
Honey	6	2 (33 %)	0.14	0.47	0.37	0.50
Mineral water	330	47 (14 %)	0.00026	0.002	0.0011	0.002
Drinking water	59	6 (10 %)	0.005	0.006	0.015	0.006
Potato (raw)	141	1 (1 %)	0.007	0.00	0.42	1.00
French fries	113	-	-	-	-	-
Carrot	132	1 (1 %)	0.015	0.00	0.34	0.50
Beetroot	19	1 (5 %)	0.11	2.00	0.58	2.00
Herbs	7	1 (14 %)	0.43	3.00	1.07	3.00

3.3.2.2 Separate analysis of occurrence data from monitoring in Germany

Analytical results from monitoring are considered separately in the following. Reference is made to the information in the series of tables published by the BVL from 2007-2016.

Table 5: Comparison of data from food monitoring (2007-2016) and official food control (including food monitoring, values from Table 3; 2007-2018) for PFOS, Lower-bound

Food group	Data from monitoring			All data from official food control**		
	Number of samples [n]	≥LOQ [n]	PFOS concentration [µg/kg]	Number of samples [n]	≥LOQ [n]	PFOS concentration [µg/kg]
Wild boar – meat	14	3	0.36*	636	226	3.40
Roe deer, deer – meat	89	0	-	126	3	0.009
Beef – meat	49	5	0.12	80	15	0.40
Beef – liver	56	24	1.56	986	100	0.85
Poultry – meat	79	4	0.69*	179	42	1.68
Poultry – liver	83	4	0.65*	154	7	0.12
Pork – liver	121	30	2.16	185	20	1.23
Goat – meat	11	9	1.05	15	9	0.77
Milk	69	0	-	152	2	0.008
Cheese (excl. goat cheese)	61	4	0.12	70	7	0.12
Eggs	36	3	2.95*	160	16	0.99
Herring/sprat	40	1	0.095*	80	10	0.38
Other sea fish (codling, tuna, …)	78	2	0.099	263	12	0.10
Carp, whitefish	35	23	15.93*	405	272	19.97
Salmonids	207	11	0.21*	850	47	1.57
Perciformes (freshwater)	1	0	-	110	74	106.21
Eel	158	75	7.53*	240	140	14.46
Pike	3	3	5.23*	32	19	26.78
Wild edible fungi	60	16	0.33*	75	16	0.26
Carrot	52	0	-	133	1	0.008

*These food groups contain datasets from the years 2007-2012, where values greater than the limit of detection but lower than the limit of quantification were assumed to be half of the limit of quantification
**Including data from monitoring

In Table 5, the lower bound concentrations from food monitoring are compared to the lower bound of all occurrence data from Germany for PFOS. With regard to the mean values calculated in the tables, it should be noted that for measurements above the limit of detection but below the limit of quantification, half the value of the limit of quantification was used during 2007-2012, whereas the lower and upper bound was used during 2013-2016. Means of food groups in which data (from monitoring) from before 2013 are included (i.e. potentially the concentrations do not reflect the lower bound) are marked accordingly.
It can be seen that lower concentrations of PFOS were measured in food monitoring for beef, poultry and freshwater fish. For liver from beef, pork and poultry and also for eggs, the concentrations in food are higher compared to the total of the data from Germany evaluated in this opinion.

It should be noted that the number of quantifiable measurements for the majority of the food groups considered here is very small and therefore the meaningfulness of the occurrence data from food monitoring is limited. In addition, important food groups such as pork and mineral water/ drinking water are not represented in the food monitoring. As a rule, samples were taken from each food group in roughly 3-5 German federal states. Not all German federal states are therefore adequately represented in food monitoring.

An analogous comparison of the concentration data for PFOA can be found in Table 6.

Table 6: Comparison of data from food monitoring (2007-2016) and official food control (including food monitoring, values from Table 4, 2007-2018) for PFOA, Lower-bound

Food group	Data from monitoring			All data from official food control**		
	Number of samples [n]	≥LOQ [n]	PFOA concentration [µg/kg]	Number of samples [n]	≥LOQ [n]	PFOA concentration [µg/kg]
Wild boar - meat	14	0	-	633	12	2.28
Roe deer, deer - meat	89	0	-	126	5	0.041
Beef - meat	49	10	0.64	80	20	0.46
Beef - liver	56	8	0.29	972	18	0.041
Pork - liver	121	7	0.038	179	13	0.13
Poultry - meat	79	0	-	154	2	0.014
Poultry - liver	83	0	-	185	5	0.053
Pork - liver	121	7	0.038	185	5	0.053
Goat - meat	11	9	0.48	15	9	0.35
Milk	69	15	0.72	152	18	0.36
Cheese (excl. goat cheese)	61	6	0.052	70	9	0.061
Eggs	36	1	0.018*	164	15	0.48
Herring/sprat	40	0	-	80	0	-
-other sea fish (codling, tuna,...)	78	1	0.46	262	2	0.15
Carp, whitefish	35	0	-	406	124	1.74
Salmonids	207	13	0.46*	850	22	0.19
Perciformes (freshwater)	1	0	-	110	2	0.126
Eel	158	6	0.15*	240	14	0.30
Pike	3	0	-	32	1	1.53

Wild edible fungi	60	1	0.011*	75	1	0.008
Carrot	52	0	-	132	1	0.015
Potatoes (raw)	56	1	0.018	141	1	0.007

*For these food groups, for some or all of the values greater than the limit of detection but lower than the limit of quantification, half of the limit of quantification was used
**Including data from monitoring

Compared to the total occurrence data from Germany evaluated in this opinion, higher concentrations of PFOA were measured for milk in food monitoring, and significantly lower values for eggs. For freshwater fish the result is uneven, for carp no quantifiable samples could be detected in the food, but for salmonids significantly higher values were measured. Also for PFOA, the number of measurements above the limit of quantification is very small for most food groups.

3.3.2.3 Comparison of PFOS and PFOA concentrations in Germany with EFSA occurrence data for Europe (2018a)

For some high-consumption foods that may provide a greater contribution to overall exposure to PFOS, the lower-bound estimates of concentrations available to the BfR from official food control in Germany, including monitoring, are compared below with those of EFSA's (2018a) Opinion. It should be noted that the selected food groups of EFSA are not always compatible with the selected food groups of occurrence data from Germany. At this point, only those comparisons are shown in which the food groups can be mapped comparatively well.

Table 7: Comparison of current PFOS concentrations in food in Germany (official food control 2007-2018) with occurrence data according to EFSA (2018a) (data collection 2007-2015)

Occurrence data from official food control in Germany (2007-2018)		Occurrence data according to EFSA (2018a)	
Food group	PFOS concentration Mean lower bound [µg/kg]	Food group	PFOS concentration Mean lower bound [µg/kg]
Pork	0.41	Livestock meat (excl. poultry and beef)	0.024
Beef	0.40	Beef	0.056
Poultry	0.12	Chicken	0.018
Pork liver	1.68	Pork liver	2.70
Milk	0.008	Cow's milk	0.001
Eggs	0.99	Fresh eggs	0.26
Gadiformes, tuna, other sea fish	0.10	Codling, pollack, cod	0.42
		Tuna	0.15
Salmonids	1.57	Salmon and trout	0.34
Carp and other whitefish	19.97	Carp	12.30
Mineral water	0.00038	Mineral water and drinking water	0.001
Drinking water	0.00096		
Carrot	0.0083	Carrot	0.013
Onion	-	Onion	0.002
Round cabbage	-	Round cabbage	0.005
French fries	0.011	French fries	0.011
Apples	-	Apples	0.026
Pear	-	Pear	0.13

For PFOS, the mean lower bound concentrations according to EFSA (2018a) for some of the high-consumption foods such as meat (beef, pork, poultry), milk, eggs and some freshwater fish such as salmon and carp are significantly lower than those available to the BfR from official food control in Germany including monitoring. Deviations result e.g. for salmonids (factor 5), beef (factor 7), poultry (factor 6) and eggs (factor 4). For pork liver, the category “Gadiformes, tuna, other sea fish”, mineral-water and some vegetables (onion, carrot, round cabbage) higher lower bound concentrations were determined according to EFSA (2018a). In addition, EFSA's (2018a) occurrence data, in contrast to the data from official food control in Germany (2007-2018), show values above the limit of quantification for fruits such as apples and pears, although these foods were also sampled in Germany.

An analogous comparison for PFOA is shown in Table 8.

Table 8: Comparison of current PFOA concentrations in food in Germany (official food control 2007-2018) with occurrence data according to EFSA (2018a) (data collection 2007-2015)

Occurrence data from official food control in Germany (2007-2018)		Occurrence data according to EFSA (2018a)	
Food group	PFOA concentration Mean lower bound [µg/kg]	Food group	PFOA concentration Mean lower bound [µg/kg]
Beef	0.46	Beef	0.054
Pork	0.23	Pork	0.010
Beef liver	0.041	Beef liver	0.042
Pork liver	0.13	Pork liver	0.19
Milk	0.36	Cow's milk	0.067
Eggs	0.48	Fresh eggs	0.22
Carp and other whitefish	1.74	Carp	3.45
Mineral water	0.00026	Mineral water and drinking water	0.009
Drinking water	0.005		
Carrot	0.015	Carrot	0.015
Onion	-	Onion	0.001
Beetroot	0.11	Beetroot	0.25
Spinach	-	Spinach	0.010
Potatoes	0.007	Potatoes and potato products	0.011
French fries	-		
Apples	-	Apples	0.01
Pear	-	Pear	0.004
Wheat	-	Wheat	0.001

For PFOA, the mean lower bound concentrations according to EFSA (2018a) for some of the high-consumption foods such as beef and pork as well as milk are lower than those available to the BfR from official food control in Germany including monitoring. For eggs, the corresponding concentrations are higher by a factor of about two, for carp and drinking water, in contrast, the lower bound concentrations according to EFSA (2018a) are higher by a factor of two. According to EFSA (2018a), PFOA also has readings above the limit of quantification for certain types of vegetables, fruits and wheat, which, in contrast to the food control data in Germany, allow a quantification of the concentrations, although these foods were also sampled in Germany.

For many food groups, the vast majority of readings of PFOS/PFOA are below the limit of detection for both the occurrence data used by EFSA for exposure assessment and the data available to the BfR from official food control in Germany. As there is also a large gap between the mean upper bound and lower bound estimates (and therefore a correspondingly high uncertainty exists), it is intended to provide in the following a comparison of the analytical limit of detection of the datasets from official food control in Germany with the data according to EFSA (2018a) (see Table 9). However, the BfR does not have the limits of detection for the data of the detailed food groups that were included in EFSA's occurrence estimate (2018a). Therefore, the mean upper-bound estimate of the EFSA (2018a) occurrence data was used as the upper limit for the limit of detection for the comparison. It should also be kept in mind that for EFSA, the proportion of quantifiable samples refers to the number of analytical readings (including those determined in pooled samples), while the mean concentrations include the weighting of pool samples described above.

Table 9: Comparison of the mean limit of detection of occurrence data from official food control in Germany (2007-2018) with the mean upper bound estimates of concentrations used by EFSA for selected food groups

	Data from official food control in Germany (2007-2018)		Data according to EFSA (2018a)	
Food group	Mean limit of detection [µg/kg]	Proportion of quantifiable values [%]	Mean upper bound [µg/kg]	Proportion of quantifiable values [%]
PFOS				
Beef	0.53	19	0.19	13
Poultry	0.73	5	0.21	4
Milk	0.64	1	0.20	6
Eggs	0.69	10	0.48	11
French fries	1.00	1	1.00	1
PFOA				
Beef	0.53	25	0.19	4
Pork	0.22	13	0.21	6
Milk	0.63	12	0.26	2
Eggs	0.68	9	0.50	17
Potatoes	0.42	1	0.37	9

Table 9 shows that the EFSA (2018a) exposure assessment for some food groups included data collected with more sensitive analytical methods.

3.3.3 Exposure assessment

In the following, the EFSA (2018a) exposure assessment for Germany is presented based on the PFOS and PFOA occurrence data from EFSA for Europe. So while the occurrence data are summarised from all over Europe, the consumption data refer exclusively to Germany.

3.3.3.1 PFOS exposure in Germany

The exposure assessment based on PFOS occurrence data from Europe (EFSA 2018a) and consumption data for Germany (see Table 2) are visible in Table 10.

Table 10: Exposure assessments for PFOS via food at mean concentrations (lower bound and upper bound) at average and high (P95) consumption levels for Germany according to the EFSA 2018 exposure assessment

Age group		PFOS intake with mean consumption [ng/kg bw per week]		PFOS intake with high (P95) consumption [ng/kg bw per week]	
		Lower bound	Upper bound	Lower bound	Upper bound
Infants (<1 year)		1.89	14.21*	8.33	44.52*
Toddlers (1 - <3 years)		5.39	38.78*	14.63*	79.94*
Children (3 - <10 years)	VELS	4.34	32.20*	10.99	60.76*
	EsKiMo	4.90	27.93*	12.81	55.58*
Adolescents (10 - <18 years)	EsKiMo	4.48	21.07*	8.40	39.20*
	NVS II	1.26	8.89	3.50	21.98*
Adults (18 - <65 years)		3.50	10.15	8.82	23.52*
Elderly (65 - <75 years)		5.60	12.25	13.72*	28.14*
Very elderly (≥75 years)		4.83	11.62	11.83	24.85*

*Exceeds the TWI values of 13 ng PFOS/kg bw per week

On the basis of the upper bound concentrations the group of high consumers (95th percentile of the intake levels) exceeds the TWI for PFOS (EFSA 2018a) in all population groups. Assuming average intake levels, exceedances occur in the group of infants, toddlers and children under 10 years (upper bound). Based on the lower bound concentrations, the TWI is not exceeded at average consumption, at high consumption levels (95th percentile), exceedances occur in the groups of infants and the elderly. Overall, infants, children under the age of 10 and seniors aged 65-75 are the most exposed population groups.
The main contributions to exposure are provided by the following food groups (referring to the lower bound estimate) (EFSA, 2018a): Fish and seafood (especially for adults, particularly fish meat), meat and meat products (especially for seniors aged 65-75 years with particular significance of the category of livestock offal , whilst there are relevant contributions through cooked sausages for infants and children under 10 years) as well as eggs and egg products (especially for infants).

3.3.3.2 PFOA exposure in Germany

The estimated exposure to PFOA based on EFSA occurrence data and consumption levels from Germany is shown in Table 11.

Table 11: Exposure assessments for PFOA via food at mean concentrations (lower bound and upper bound) at average and high (P95) consumption levels for Germany according to the EFSA 2018 exposure assessment

Age group		PFOA intake with mean consumption [ng/kg bw per week]		PFOA intake with high (P95) consumption [ng/kg bw per week]	
		Lower bound	Upper bound	Lower bound	Upper bound
Infants (<1 year)		3.78	23.45*	14.21*	64.05*
Toddlers (1 - <3 years)		9.45*	49.14*	21.00*	100.66*
Children (3 - <10 years)	VELS	7.14*	39.69*	14.56*	76.09*
	EsKiMo	6.44*	37.24*	12.74*	64.82*
Adolescents (10 - <18 years)	EsKiMo	4.76	27.30*	9.31*	49.21*
	NVS II	2.17	10.99*	5.39	27.09*
Adults (18 - <65 years)		2.10	10.64*	4.55	24.36*
Elderly (65 - <75 years)		1.89	11.27*	4.27	25.62*
Very elderly (≥75 years)		1.96	11.76*	4.76	26.67*

*Exceeds the TWI values of 6 ng PFOA/kg bw per week

Using upper bound concentrations, PFOA exposure is above TWI even at mean intake levels for all age groups. Assuming lower bound concentrations, at mean intake levels the exposure of toddlers and children under 10 years of age exceeds TWI, in the case of high consumption (95^{th} percentile), exposure in the adolescent and infant age groups also exceeds the TWI. Also concerning PFOA, toddlers and children under 10 years of age are the population group which is most exposed according to the EFSA (2018a) exposure assessment.

The main contributions to exposure to PFOA are provided by the following food groups (referring to the lower bound estimate) (EFSA, 2018a): Milk and dairy products (especially for toddlers), drinking water (especially for infants) and fish and fish products (with emphasis on the very elderly (seniors older than 75 years)). Another important contribution to the intake of PFOA for adults aged 18-65 years is made by eggs and egg products.

3.3.3.3 Discrepancy of lower bound and upper bound estimates

The exposure assessment for PFOS and PFOA shows that the treatment of analytical results below the limit of quantification has a significant influence on the result. For example, in the case of PFOS the mean upper bound concentrations are 2-8 and for PFOA 4-7 times as large as the mean lower bound concentrations. This implies a great deal of uncertainty caused by a large number of analytical results below the limit of quantification. EFSA considers the true value to be closer to the lower bound than to the upper bound, for the following reasons: Firstly, it is argued based on literature that in studies with very sensitive analytical methods, the analytical results are rather in the range of the lower bound values. In addition, studies of PFOS/PFOA in blood (within the European population) would show that the median (of PFOS/PFOA concentrations in blood) is consistent with the lower bound concentrations in food. Although these arguments suggest that the use of lower bound concentrations is closer to reality, it remains to be noted that this is an underestimation of actual exposure.

3.3.3.4 PFOS/PFOA intake in Germany within a European comparison

The following section presents the exposure estimates for Germany within a European comparison. The results in Table 12 and Table 13 show for both PFOS and PFOA that the level of exposure in Germany is in the lower to middle range in the European comparison.

Table 12: Exposure assessment for PFOS via food at mean concentrations in foods (lower bound) and average (mean) and high (P95) consumption levels for Germany in a Europe-wide comparison according to the EFSA 2018a exposure assessment

Age group		PFOS intake (mean) [ng/kg bw per week]		PFOS intake (P95) [ng/kg bw per week]	
		Germany	Europe Min-max (median)	Germany	Europe Min-max (median)
Infants (<1 year)		1.9	1.7-8.6 (2.7)	8.3	6.3-30.4 (8.3)
Toddlers (1 - <3 years)		5.4	3.1-16.5 (5.3)	14.6	8.8-28.7 (14.6)
Children (3 - <10 years)	VELS	4.3	3.1-20.9 (5.8)	11.0	7.8-165.9 (17.0)
	EsKiMo	4.9		12.8	
Adolescents (10 - <18 years)	EsKiMo	4.5	1.3-11.1 (3.1)	8.4	3.5-76.3 (9.7)
	NVS II	1.3		3.5	
Adults (18 - <65 years)		3.5	2.0-13.5 (4.3)	8.8	6.9-81.2 (13.7)
Elderly (65 - <75 years)		5.6	3.2-12.7 (4.3)	13.7	9.9-66.4 (13.6)
Very elderly (≥75 years)		4.8	2.3-7.4 (4.6)	11.8	8.1-25.9 (12.8)

Compared to the exposure estimates for PFOS from a total of 35 consumption studies of the EU member states, it is striking that for infants the average intake in Germany is significantly less than the EU-wide median and lies at the lower end of the Europe-wide comparison. For the 95th percentile of this age group, the exposure in Germany lies in the middle of the European estimate. For children between the ages of 3 and 10 years, exposure estimates are lower in Germany compared to the European median for both average and 95th percentile of the consumption levels. The situation is similar with the age group of adults between 18 and 65 years. For the elderly (65-75 years) age group, the exposure estimate for average consumption is higher than the European median, whilst for the 95th percentile of consumption such a trend cannot be confirmed. The exposure estimates for the other age groups in Germany are within the range of the median of Europe-wide estimates.

Table 13: Exposure assessment for PFOA via food at mean concentrations in foods (lower bound) and average (mean) and high (P95) consumption levels for Germany in a Europe-wide comparison according to the EFSA 2018a exposure assessment

Age group		PFOA intake (mean) [ng/kg bw per week]		PFOA intake (P95) [ng/kg bw per week]	
		Germany	Europe Min-max (median)	Germany	Europe Min-max (median)
Infants (<1 year)		3.8	3.5-10.1 (4.9)	14.2	10.6-26.3 (12.6)
Toddlers (1 - <3 years)		9.4	2.4-18.3 (14.1)	21.0	14.8-37.6 (27.2)
Children (3 - <10 years)	VELS	7.1	2.4-15.1 (7.0)	14.6	5.0-25.1 (14.4)
	EsKiMo	6.4		12.7	
Adolescents (10 - <18 years)	EsKiMo	4.8	1.8-6.0 (3.5)	9.3	4.8-11.2 (7.1)
	NVS II	2.2		5.4	
Adults (18 - <65 years)		2.1	1.5-4.2 (2.2)	4.6	3.8-7.8 (4.6)
Elderly (65 - <75 years)		1.9	1.5-3.1 (2.2)	4.3	3.6-6.7 (4.8)

Age group	PFOA intake (mean) [ng/kg bw per week]		PFOA intake (P95) [ng/kg bw per week]	
	Germany	Europe Min-max (median)	Germany	Europe Min-max (median)
Very elderly (≥75 years)	3.8	1.5-3.4 (2.3)	4.8	3.4-6.0 (4.4)

Exposure to PFOA is lower for infants according to the EFSA exposure assessment (2018a) in Germany compared to the median value for other EU countries when considering mean consumption levels and is at the lower end of the assessment for European member states. For high consumers (95th percentile of consumption), however, the exposure when looking at consumption levels for Germany is higher compared to the EU-wide median of consumption. In the age group of toddlers (1-3 years), the PFOA intake was estimated to be lower for the population in Germany, for both average consumers and the 95th percentile, than for the median consumption levels in the EU member states. For the other age groups, it should be mentioned that in the over 65-years age group with average intake, PFOA intake for the German population is slightly below the EU-wide median. At the 95th percentile of consumption, however, no significant deviations from the EU median were found.

3.4 Risk characterisation

According to the EFSA exposure assessment, in Europe the new TWI values for PFOS (13 ng/kg bw per week) and PFOA (6 ng/kg bw per week) are exceeded by parts of the population when considering mean concentrations in foods.

The following age groups are examined: Infants (<1 year), toddlers (1- <3 years), children (3- <10 years), adolescents (10- <18 years), adults (18- <65 years), the elderly (65- <75 years) and the very elderly (≥75 years) (see Tables 10 to 13).

- *PFOS, no TWI exceedances with average consumption for all age groups in Germany*

For PFOS, exposure via food is below the TWI across Europe, according to the EFSA exposure assessment at average intake levels for all age groups. This also applies to Germany.

- *PFOS, exceedances of TWI at high consumption levels in the age groups of toddlers and the elderly in Germany*

For Germany, exposure also at high consumption (P95) is below the TWI for most age groups. Exceptions are the age groups of toddlers (14.6 ng/kg body weight per week) and the elderly (13.7 ng/kg body weight per week).
In total, in more than 50% of the other European member states, the exposure of high consumers exceeds TWI for PFOS within the age groups of toddlers, children aged 3-10 years, adults and the elderly.

- *PFOA, exceedances of TWI at average consumption levels in the age groups of toddlers and children in Germany*

In the case of PFOA, consumer exposure across Europe exceeds the TWI amongst toddlers and children between the ages of 3 and 10 already at average consumption levels in more than 50% of the member states (including Germany). In Germany the exposure estimate for toddlers is 9.4 ng/kg body weight per week and for children between 3 and 10 years it is 7.1 ng/kg body weight per week (based on VELS) or 6.4 ng/kg body weight per week (based on EsKiMo).

- *PFOA, exceedances of TWI at high consumption levels in the age groups of infants, toddlers, children and adolescents in Germany*

At high consumption levels, TWI exceedances for PFOA are present across Europe in more than 50% of studies for infants, toddlers, children aged 3 to 10 years old and adolescents. Exposure of toddlers exceeds the TWI 4- to 6-fold in 50% of the studies. For Germany, high intake levels (P95) result in TWI exceedances for PFOA in the age group of infants (14.2 ng/kg bodyweight per week), toddlers (21.0 ng/kg bodyweight per week), children aged 3 to 10 years (based on VELS 14.6 ng/kg bodyweight per week or EsKiMo 12.7 ng/kg bodyweight per week) and adolescents (9.3 ng/kg bodyweight per week). As a result, exposure to PFOA is 2 to 3 times greater than the TWI. On the other hand, assuming high consumption levels in accordance with NVS II, the exposure estimate for adolescents at 5.4 ng/kg bodyweight per week is below the TWI for PFOA.

External intake levels of PFOS and PFOA, which are within the range of TWI for a period of time, need not immediately lead to blood levels in the critical range[20]. Depending on the value of blood levels already present, it may take years until intake levels at around the TWI result in blood levels in the critical range.

For the assessment of long-term total exposure to PFOS and PFOA, concentrations of compounds in the blood are a good parameter because of their long half lives in humans. Due to the regulatory measures for PFOS and PFOA, a trend towards decreasing blood concentrations is to be expected in the long term. Measurements of PFOS and PFOA concentrations in the blood of the general population in Germany actually indicate a trend towards decreasing concentrations since 2009 (Yeung et al., 2013a, 2013b). Studies in 2016 within an urban region in Germany show for example, that those blood concentrations that form the basis for the newly derived TWI values for PFOS and PFOA ($BMDL_5$: 22 ng/ml and 9.3 ng/ml for PFOS and PFOA respectively) are not exceeded in the investigated group (median blood concentrations 2016 in 158 samples PFOA 1.1 µg/l and PFOS 2.1 µg/l; 95th percentile PFOA 2.4 µg/l, PFOS 6.4 µg/l according to Fromme et al., 2017). However, data collection in these studies is not representative of the total population. Nevertheless, from the BfR's point of view, the results indicate that the blood concentrations on which the newly derived guidance values are based are currently not exceeded in the general population through the intake of PFOS and PFOA.

With regard to long-term breastfed infants, who accumulate particularly PFOA during the breastfeeding period, based on the level of internal exposure within an urban region in Germany (Fromme et al. 2017) presented in the previous paragraph, it is to be expected that a (presumably small) subset of these subjects will slightly exceed $BMDL_5$ blood levels derived from EFSA (2018a) temporarily. As outlined above (see 3.2.2) kinetic modelling shows a gradual decline in the concentrations and an evening out of values for breastfed and non-breastfed children within a few years after the maximum of infant blood concentrations upon cessation of breastfeeding (Verner et al., 2016). With consideration to all associations between PFOS/PFOA exposure and those changes in biological parameters in humans observed so far in epidemiological studies, the potentially reduced vaccine antibody production and the impairment of the immune system would have to be considered particularly critical for this age group. However, as described in 3.2.3.2, the BfR regards the evidence existing so far for such an effect through PFOS/PFOA as limited and considers that further clarification is required (see 3.6) before these data can be taken into account as part of a quantitative

[20] $BMDL_5$ for PFOA 9.3 ng per ml blood serum, $BMDL_5$ for PFOS 22 ng per ml blood serum, see section 3.2.4

risk assessment. Based on the current level of knowledge, the BfR does not see any reason to not breastfeed children for a prolonged period, according to the recommendations, in case of internal exposure at background levels.

In light of the findings regarding exposure through food, the BfR cannot uphold its 2008 assessment that a health risk to consumers is unlikely due to exposure to PFOS and PFOA through food. The possibility that long-term TWI exceedances, according to EFSA's current opinion, will be accompanied by changes in lipid metabolism (increase in total cholesterol) cannot be ruled out. Cholesterol is one of the known risk factors for cardiovascular diseases. Epidemiological studies show this correlation for persons over the age of 40 years. However, there are other factors that have a significant impact on the risk of cardiovascular disease, such as age, gender, lifestyle habits such as smoking and blood pressure levels. So far, there is no reliable epidemiological evidence for a relationship between PFOS and PFOA concentrations in the blood and a higher risk of these diseases in highly exposed population groups. Therefore, the current assessment of health risks from exposure to PFOS/PFOA based on the current TWI values of EFSA (2018a) is subject to uncertainties.

3.5 Discussion and uncertainties

In 2008, the BfR already undertook a risk assessment for PFOA and PFOS (BfR, 2008). At that time, an average exposure of adults via food (including drinking water) to PFOS of 2.32-3.76 ng/kg bw per day and 1.03-1.34 ng/kg bw per day to PFOA was determined (lower/upper bound). These estimates are significantly higher (at least for the lower bound) than the EFSA estimate (0.5-1.75 ng/kg bodyweight per day for PFOS and 0.27-1.68 ng/kg bodyweight per day for PFOA (for adults and seniors)). The main reasons for the discrepancy amongst both substances are the higher concentrations in fish and - especially in the case of PFOA - significantly higher concentrations in chicken eggs compared to the EFSA occurrence data. Another cause may be that the data collection was not sufficiently representative, as was also described in the BfR opinion at the time. The 2008 BfR exposure assessment for PFOS/PFOA did not include the pork, beef and milk food groups as occurrence data was either lacking or insufficient. Although a concentration value was assumed for milk based on literature data for PFOS and a corresponding exposure share was calculated, this was not included in the estimate of the total exposure.

The EFSA exposure assessment (2018a) for Germany contains some uncertainties. E.g. use of lower bound estimates of concentrations represents a potential underestimation of exposure due to the high number of analytical results below the limit of quantification. Furthermore, only exposure via food was considered while other exposure pathways and sources were not taken into account. This leads to an underestimation of total exposure, which is presumably low (Haug et al., 2011).

The consumption data used by EFSA (EFSA, 2018a) correspond to the data available to the BfR and represent the consumption data currently available in Germany. Nevertheless, due to the age of the studies, it cannot be ruled out that the consumption patterns of the population in Germany, and thereby also the food-borne intake of PFOS and PFOA, have changed due to trends in consumption patterns.
According to EFSA (2018a), uncertainties in the exposure assessment, especially uncertainties regarding data on occurrence in food, have a significant impact on the overall uncertainties in the risk assessment. On the one hand, the high proportion of non-quantifiable samples has to be mentioned, which leads to large differences between the lower and upper bound assumptions. On the other hand, an uncertainty exists concerning the reasons for the large

range of available concentrations both within the EFSA data and within the German data. Overall, EFSA considers the risk assessment as conservative. From the point of view of the BfR, the use of lower bound estimates for concentrations in the exposure assessment may also result in an underestimation of the health risks.

From the point of view of the BfR, considerable uncertainties also exist with regard to the evidence of causality and clinical relevance of the effects used as the basis for the TWI derivation. The question of the clinical relevance of this parameter (total blood cholesterol), which EFSA has used to derive the TWI, is identified by EFSA itself as uncertain.

The BfR entered into a scientific discourse with EFSA on these questions, which was documented and published in a "Meeting Report" (EFSA 2018b). Amongst other issues, the BfR addressed questions regarding the suitability of the observed increases in total cholesterol in the epidemiological studies as biomarkers for cardiovascular diseases. Further discussions dealt with the clinical relevance of elevated cholesterol levels against the background of other factors affecting the risk of cardiovascular disease such as age, gender, weight, blood pressure and smoking. In addition, questions were discussed on the causal relationship between PFOS/PFOA in the blood and total cholesterol, in particular with regard to a possible coincidence of elevated serum levels of PFOS and PFOA and higher cholesterol levels, which could be due to, for example, mutual reabsorption from the gut via common membrane transport systems.

The BfR points out that the "Agency for Toxic Substances and Disease Registry" (ATSDR) has also published updated figures for preliminary minimum risk levels for PFOS[21] and PFOA[22] (ATSDR 2018). The derivations of these values are based on data from animal studies.

3.6 Risk management options, recommended measures

From the overall view of the results of the risk characterisation, which identifies TWI exceedances for consumer groups in Germany, and the uncertainties both in the exposure assessment and in the derivation of the TWI values, the BfR derives the following recommendations for measures:

Consumer exposure to PFOS and PFOA through food should be further minimised. In principle, it is recommended to include drinking water as a source of exposure.

In addition, from the perspective of the BfR, there is a need to investigate the evidence of causality and clinical relevance of the epidemiological study results on which the TWI derivation is based, in particular the relationship between PFOS/PFOA and total cholesterol concentrations in the blood as well as the reproducibility of the results for reduced antibody production after the vaccination of children. Studies should be highly robust, statistically speaking, and preferably prospective, and, in terms of the time window, should include the end of a

[21] Minimal risk level for PFOS for intermediate oral exposure: 2 ng/kg bodyweight per day based on delayed eye opening and reduced weight of offspring in rats, human equivalent dose (HED) of NOAEL 0.515 µg/kg bodyweight per day, uncertainty factor 300 (3 for interspecies extrapolation, 10 for intraspecies extrapolation, additional modifying factor 10 to account for the uncertainty that immunotoxicity may be a more sensitive endpoint than developmental toxicity)

[22] Minimal risk level for PFOA: intermediate oral exposure 3 ng/kg bodyweight per day based on developmental neurotoxic effects and skeletal effects in mice, HED of LOAEL 0.821 µg/kg bodyweight per day, uncertainty factor 300 (3 for interspecies extrapolation, 10 for intraspecies extrapolation)

long period of breastfeeding (ages 1 to 1.5 years) in which the highest PFAS concentrations are expected amongst long-term breastfed children. These studies should not only determine the titres of vaccine antibodies, but also include functional immune system studies and metabolic parameters for a broad range of meaningful results. In addition, other research approaches should also be used to advance the clarification of the general question of the effects of PFAS on the human immune system and to identify their mechanisms.

A research project was initiated by the BfR to investigate a possible molecular relationship between increased human exposure to PFOA and elevated blood cholesterol.

There is also a need to improve the data base for estimating external and internal exposure of consumers in Germany. From the point of view of the BfR, representative HBM data for the concentrations of PFOS, PFOA and other compounds from the group of per- and polyfluoroalkyl substances should be generated promptly for the population in Germany.

On the one hand, in order to improve the quality of the PFOS/PFOA occurrence data for food, sampling at federal state level should be representative and, on the other hand, consumption-oriented sampling should be carried out within the German federal states. This applies in particular to those foods which, according to current understanding, contribute significantly to exposure: Milk, eggs and commonly eaten freshwater fish. Especially in view of the significantly higher concentrations in Germany compared to the concentrations reported by EFSA for Europe, beef, pork and poultry meat should be given a higher priority for the purpose of clarifying the current situation. In the case of pork, only 16 samples are available that have been tested for PFOS and PFOA (and for each substance only two with quantified concentrations), meaning that in addition to the improved sample control, an increase in the number of samples is required.

The large discrepancy between the lower bound and upper bound estimates indicates a strong influence of the analytical uncertainties (values below the limit of detection or quantification). These uncertainties can only be reduced with better analytical measurement methods. This is particularly important in food groups that exhibit a large discrepancy between lower and upper bound concentrations, and which in general are also consumed frequently. According to the data available at present, this is the case with beef and poultry meat, milk, eggs, sea fish and generally salmonids. In addition, better analytics would also be important in determining the concentrations of PFOS and PFOA in potatoes and vegetables. This also applies to the food groups fruit as well as cereals and cereal products, which are not included here due to a lack of values above the limit of quantification.

The perfluorinated substances as a substance group are assigned as a new area of responsibility to the former NRL for dioxins and PCBs in food and animal feed, which is the future national reference laboratory for halogenated persistent organic pollutants (POPs) in animal feed and foodstuffs. Already on 14 November 2018, the BfR carried out an initial orientation workshop on the analysis of PFAS for the monitoring laboratories. The issue will be taken up again in the NRL Workshop on 22/23 May 2019. Furthermore, in addition to the food monitoring for PFAS already planned for 2019, the BfR has also submitted an additional application for project monitoring in selected foods in order to improve the data situation in the short term.

Since it is known that the industry is switching to compounds with shorter fluorinated carbon chains (e.g. C4 and C6 compounds) due to the regulatory measures for PFOS and PFOA, these compounds should also be included in monitoring, as far as analytically feasible.

Further information on this subject at the BfR website…

https://www.bfr.bund.de/cm/343/per-und-polyfluorierte-alkylsubstanzen-forschungsaktivitaeten-des-bfr-und-die-neue-efsa-bewertung.pdf

https://www.bfr.bund.de/en/press_information/2016/40/digital_tools_for_more_safety_in_the_food_chain-198818.html

BfR "Opinions app"

4 References

ATSDR (Agency for Toxic Substances and Disease Registry) (2018) Toxicological Profile for Perfluoroalkyls Draft for Public Comment June 2018. Available online at: https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf, last accessed: 12.02.2019

Banasiak U, Heseker H, Sieke C, Sommerfeld C, Vohmann C (2005): Abschätzung der Aufnahme von Pflanzenschutzmittel-Rückständen in der Nahrung mit neuen Verzehrsmengen für Kinder. Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 1 (48): 84–98

Benskink, J. P., De Silva, A. O., Martin, J. W. (2010) Isomer Profiling of Perfluorinated Substances as a Tool for Source Tracking: A Review of Early Findings and Future Applications. In: Reviews of Environmental Contamination and Toxicology. Volume 208 Perfluorinated alkylated substances. Pim De Voogt (Hrsg), S. 111-160

BfR (Bundesinstitut für Risikobewertung) (2008): Gesundheitliche Risiken durch PFOS und PFOA in Lebensmitteln sind nach dem derzeitigen wissenschaftlichen Kenntnisstand unwahrscheinlich. Stellungnahme Nr. 004/2009 des BfR vom 11. September 2008. Available online at:http://www.bfr.bund.de/cm/343/gesundheitliche_risiken_durch_pfos_und_pfoa_in_lebensmitteln.pdf, last accessed: 13.07.2018

BfR (Bundesinstitut für Risikobewertung) (2016): 220. Mitteilung. In: Bundesgesundheitsblatt 59 (2016) 1365–1368

C8 Science Panel (2012) http://www.c8sciencepanel.org/prob_link.html

Dalsager L, Christensen N, Husby S, Kyhl H, Nielsen F, Høst A, Grandjean P, Jensen TK (2016): Association between prenatal exposure to perfluorinated compounds and symptoms of infections at age 1-4years among 359 children in the Odense Child Cohort. Environ Int 96:58-64

ECHA (European Chemicals Agency) (2015): Background document to the Opinion on the Annex XV dossier proposing restrictions on Perfluorooctanoic acid (PFOA), PFOA salts and PFOA-related substances. Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC), 26. Juni 2015. Available online at:https://echa.europa.eu/documents/10162/61e81035-e0c5-44f5-94c5-2f53554255a8, last accessed: 31.01.2019

EFSA (European Food Safety Authority, Scientific Panel on Contaminants in the Food Chain (CONTAM)) (2018a): Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA Journal 2018; 16(5):5194

EFSA (European Food Safety Authority) (2018b): Minutes of the expert meeting on perfluooroctane 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). EFSA/CONTAM/3503. Available online at:

https://www.efsa.europa.eu/sites/default/files/news/efsa-contam-3503.pdf, last accessed: 01.02.2019

EFSA (European Food Safety Authority: Scientific Panel on Contaminants in the Food Chain (CONTAM)) (2008): Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts Scientific Opinion of the Panel on Contaminants in the Food chain. EFSA Journal (2008) 653;1-131

EG (2002): Verordnung (EG) Nr. 178/2002 des Europäischen Parlaments und des Rates vom 28. Januar 2002 zur Festlegung der allgemeinen Grundsätze und Anforderungen des Lebensmittelrechts, zur Errichtung der Europäischen Behörde für Lebensmittelsicherheit und zur Festlegung von Verfahren zur Lebensmittelsicherheit. Amtsblatt der Europäischen Gemeinschaften L31/1

EG (2006): Richtlinie 2006/122/EG des Europäischen Parlamentes und des Rates vom 12. Dezember 2006 zur dreißigsten Änderung der Richtlinie 76/769/EWG des Rates zur Angleichung der Rechts- und Verwaltungsvorschriften der Mitgliedstaaten für Beschränkungen des Inverkehrbringens und der Verwendung gewisser gefährlicher Stoffe und Zubereitungen (Perfluoroctansulfonate). Amtsblatt der Europäischen Union L 372/32. Available online at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:372:0032:0034:de:PDF EG, last accessed: 30.01.2019

EG (2008) Verordnung (EG) Nr. 1272/2008 des Europäischen Parlaments und des Rates vom 16. Dezember 2008 über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen, zur Änderung und Aufhebung der Richtlinien 67/548/EWG und 1999/45/EG und zur Änderung der Verordnung (EG) Nr. 1907/2006. Amtsblatt der Europäischen Union L 353/1. Available online at: https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32008R1272&from=DE, last accessed: 31.01.2019

EG (2009): Verordnung (EG) Nr. 552/2009 der Kommission vom 22. Juni 2009 zur Änderung der Verordnung (EG) Nr. 1907/2006 des Europäischen Parlaments und des Rates zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH) hinsichtlich Anhang XVII. Amtsblatt der Europäischen Union L 164/7. Available online at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:164:0007:0031:de:PDF, last accessed: 20.01.2019

Empfehlung der Kommission vom 17. März 2010 zur Überwachung von perfluorierten Alkylsubstanzen in Lebensmitteln (2010/161/EU) L 68/22

Eriksen KT, Raaschou-Nielsen O, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K, Sørensen M (2013): Association between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population. PLoS One. 2013;8(2):e56969

Eriksson U, Müller JF, Toms L-ML, Hobson P, Kärrman A (2017): Temporal trends of PFSAs, PFCAs and selected precursors in Australian serum from 2002 to 2013. Environmental Pollution 220 (2017) 168-177

EU (2010) Verordnung (EU) Nr. 757/2010 der Kommission vom 24. August 2010 zur Änderung der Verordnung (EG) Nr. 850/2004 des Europäischen Parlaments und des Rates über persistente organische Schadstoffe hinsichtlich der Anhänge I und III. Amtsblatt der Europäischen Union L 223/29. Available online at: https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32010R0757&from=DE, last accessed: 30.01.2019 EU-Kommission, 2017

EU (2011) Verordnung (EU) Nr. 207/2011 der Kommission vom 2. März 2011 zur Änderung der Verordnung (EG) Nr. 1907/2006 des Europäischen Parlaments und des Rates zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH) in Bezug auf Anhang XVII (Diphenylether-Pentabromderivat und Perfluoroctansulfonat — PFOS). Amtsblatt der Europäischen Union L 58/27. Available on-

line at: https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32011R0207&from=DE, last accessed: 30.01.2019

EU (2017) Verordnung (EU) 2017/1000 der Kommission vom 13. Juni 2017 zur Änderung von Anhang XVII der Verordnung (EG) Nr. 1907/2006 des Europäischen Parlaments und des Rates zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH) betreffend Perfluoroctansäure (PFOA), ihre Salze und PFOA-Vorläuferverbindungen. Amtsblatt der Europäischen union L 150/14. Available online at: https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32017R1000&from=DE, last accessed: 30.01.2019

Fei C, McLaughlin JK, Lipworth L, Olsen J (2010): Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood. Environ Res 110(8):773-777

Fitz-Simon N, Fletcher T, Luster MI, Steenland K, Calafat AM, Kato K, Armstrong B (2013): Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid. Epidemiology 24(4):569-76

Frisbee SJ, Shankar A, Knox SS, Steenland K, Savitz DA, Fletcher T, Ducatman AM (2010): Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adoles-cents: results from the C8 Health Project. Arch Pediatr Adolesc Med. 164:860-869

Fromme H, Mosch C, Morovitz M, Alba-Alejandre I, Boehmer S, Kiranoglu M, Faber F, Hannibal I, Genzel-Boroviczény O, Koletzko B, Völkel W (2010): Pre- and postnatal exposure to perfluorinated compounds (PFCs). Environ Sci Technol. 15;44(18):7123-7129

Fromme H, Tittlemier SA, Völkel W, Wilhelm M, Twardella D (2009): Perfluorinated compounds—exposure assessment for the general population in Western countries. Int J Hyg Environ Health 212:239–270

Fromme H, Wöckner M, Roscher E, Völkel W (2017): ADONA and perfluoroalkylated substances in plasma samples of German blood donors living in South Germany. Int J Hyg Environ Health 220:455–460

Gallo V, Leonardi G, Genser B, Lopez-Espinosa MJ, Frisbee SJ, Karlsson L, Ducatman AM, Fletcher T (2012): Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. Environ Health Perspect 120(5):655-660

Gebbink WA, Glynn A, Berger U (2015): Temporal changes (1997-2012) of perfluoroalkyl acids and selected precursors (including isomers) in Swedish human serum. Environ Pollut 199:166-73

Goudarzi H, Miyashita C, Okada E, Kashino I, Chen CJ, Ito S, Araki A, Kobayashi S, Matsuura H, Kishi R (2017): Prenatal exposure to perfluoroalkyl acids and prevalence of infectious diseases up to 4years of age. Environ Int 104:132-138

Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C (2012): Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 307(4):391-7

Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB, Budtz-Jørgensen E (2017): Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. Environ Health Perspect 125(7):077018

Granum B, Haug LS, Namork E, Stølevik SB, Thomsen C, Aaberge IS, van Loveren H, Løvik M, Nygaard UC (2013): Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. J Immunotoxicol 10(4):373-379

Han X, Nabb DL, Russell MH, Kennedy GL, Rickard RW (2012): Renal elimination of perfluorocarboxylates (PFCAs). Chem Res Toxicol 25:35–46

Harris MH, Rifas-Shiman SL, Calafat AM, Ye X, Mora AM, Webster TF, Oken E, Sagiv SK (2017): Predictors of Per- and Polyfluoroalkyl Substance (PFAS) Plasma Concentrations in 6-10 Year Old American Children. Environ Sci Technol 51(9):5193-5204

Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE (2009): Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. Mol Cell Endocrinol 304(1-2):97-105

Huang M, Jiao J, Zhuang P, Chen X, Wang J, Zhang Y (2018): Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population. Environ Int 119:37-46

IARC (International Agency for Research on Cancer) (2016): IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Perfluorooctanoic acid. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono110-01.pdf, verfügbar am 13.07.2018

Impinen A, Nygaard UC, Lødrup Carlsen KC, Mowinckel P, Carlsen KH, Haug LS, Granum B (2018): Prenatal exposure to perfluoralkyl substances (PFASs) associated with respiratory tract infections but not allergy- and asthma-related health outcomes in childhood. Environ Res 160:518-523

Johnson JD, Gibson SJ, Ober RE (1984): Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium (14C)perfluorooctanoate or potassium (14C)perfluorooctanesulfonate. Fundamental and Applied Toxicology 4, 972-976

Kennedy GL, Butenhoff JL, Olsen GW, O'Connor JC, Seacat AM, Perkins RG, Biegel LB, Murphy SR, Farrar SG (2004): The toxicology of perfluorooctanoate. Critical Reviews in Toxicology 34, 351-384.

Kotthoff M, Müller J, Jürling H, Schlummer M, Fiedler D (2015): Perfluoroalkyl and polyfluoroalkyl substances in consumer products. Environ Sci Pollut Res (2015) 22:14546–14559

Lau C (2014): Perfluorinated compounds: an overview. J.C. DeWitt (Ed.), Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances, Humana Press, London, pp. 1-21

Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, Jakobsson K (2017): Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med. 75(1):46-51

Loccisano AE, Campbell JL, 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

Loccisano AE, Longnecker MP, Campbell JL, Andersen ME and Clewell HJ (2013): Development of PBPK models for PFOA and PFOS for human pregnancy and lactation life stages. Journal of Toxicology and Environmental Health Part A, 76, 25-57

Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L, Fenton SE (2011): Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. Toxicol Sci 122(1):134-145

Manzano-Salgado CB, Casas M, Lopez-Espinosa M-J, Ballester F, Basterrechea M, Grimalt JO, Jiménez A-M, Kraus T, Schettgen T, Sunyer J (2015): Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environ Res Vol. 142, p. 471-478

Mensink GBM, Bauch A, Vohmann C, Stahl A, Six J, Kohler S, Fischer J, Heseker H (2007): EsKiMo – Das Ernährungsmodul im Kinder- und Jugendgesundheitssurvey

(KiGGS). Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 50:902–908

Mondal D, Weldon RH, Armstrong BG, Gibson LJ, Lopez-Espinosa MJ, Shin HM, Fletcher T (2014): Breastfeeding: a potential excretion route for mothers and implications for infant exposure to perfluoroalkyl acids. Environ Health Perspect. 122(2):187-92

Nelson JW, Hatch EE, Webster TF (2010): Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. Environ Health Perspect 118(2):197-202

NTP (National Toxicology Program) (2016): Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf, verfügbar am 13.07.2018

Numata J, Kowalczyk J, Adolphs J, Ehlers S, Schafft H, Fuerst P, Müller-Graf C, Lahrssen-Wiederholt M, Greiner M (2014): Toxicokinetics of seven perfluoroalkyl sulfonic and carboxylic acids in pigs fed a contaminated diet. J Agric Food Chem. 16;62(28):6861-70

OECD (Organisation for Economic Co-operation and Development) (2002): Hazard assessment of perfluorooctane sulfonate (PFOS) and its salts. ENV/JM/RD(2002)17/FINAL. https://www.oecd.org/chemicalsafety/risk-assessment/2382880.pdf, verfügbar am 13.07.2018

Okada E, Sasaki S, Saijo Y, Washino N, Miyashita C, Kobayashi S, Konishi K, Ito YM, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H, Kishi R (2012): Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants. Environ Res, 112, pp. 118-125

Olsen GW, Mair DC, Lange CC, Harrington LM, Church TR, Goldberg CL, Herron RM, Hanna H, Nobiletti JB, Rios JA, Reagen WK, Ley CA (2017): Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000-2015. Environ Res 157:87-95

Pabel U, Kowalczyk J, Numata J, Buhrke T, Lampen A, Lahrssen-Wiederholt M, Wittkowski R (2018): Per- und Polyfluoralkylsubstanzen als persistente organische Kontaminanten in der Lebensmittelkette. UMID: Umwelt und Mensch – Informationsdienst, Nr. 1/2018, S. 43-51

Sanchez Garcia D, Sjödin M, Hellstrandh M, Norinder U, Nikiforova V, Lindberg J, Wincent E, Bergman Å, Cotgreave I, Munic Kos V (2018): Cellular accumulation and lipid binding of perfluorinated alkylated substances (PFASs) – A comparison with lysosomotropic drugs. Chemico-Biological Interactions 281, 1–10

Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V (2009): Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. Am J Epidemiol 170(10):1268-78

Stein CR, Savitz DA (2016): Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5–18 years of age. Environ. Health Perspect 119:1466–1471

Stockholm Convention (2009): UNEP/POPS/COP.7/36 Verfügbar unter: http://chm.pops.int/TheConvention/ConferenceoftheParties/Meetings/COP7/tabid/4251/mctl/ViewDetails/EventModID/870/EventID/543/xmid/13075/Default.aspx, letzter Aufruf 13.07.2018

Stubleski J, Salihovic S, Lind L, Lind PM, van Bavel B, Kärrman A (2016): Changes in serum levels of perfluoroalkyl substances during a 10-year follow-up period in a large population-based cohort. Environ Int 95:86-92

Tucker DK, Macon MB, Strynar MJ, Dagnino S, Andersen E, Fenton SE (2015): The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. Reprod Toxicol 54:26-36

UBA (Umweltbundesamt) (2009): Referenzwerte für Perfluoroctansäure (PFOA) und Perfluoroctansulfonsäure (PFOS) im Blutplasma. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 52(8):878-85

Van Esterik JC, Bastos Sales L, Dollé ME, Håkansson H, Herlin M, Legler J, van der Ven LT (2016): Programming of metabolic effects in C57BL/6JxFVB mice by in utero and lactational exposure to perfluorooctanoic acid. Arch Toxicol 90(3):701-15

Vanden Heuvel JP, Kuslikis BI, Van Rafelghem MJ, Peterson RE (1991): Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. Journal of Biochemical Toxicology 6, 83-92

Verner MA, Ngueta G, Jensen ET, Fromme H, Völkel W, Nygaard UC, Granum B, Longnecker MP (2016): A Simple Pharmacokinetic Model of Prenatal and Postnatal Exposure to Perfluoroalkyl Substances (PFASs). Environ Sci Technol 50(2):978-986

White SS, Stanko JP, Kato K, Calafat AM, Hines EP, Fenton SE (2011): Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. Environ Health Perspect 119(8):1070-6

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, Longnecker MP (2012): Perfluorinated compounds in relation to birth weight in the Norwegian Mother and Child Cohort Study. Am J Epidemiol 175(12):1209-1216

Wong F, MacLeod M, Mueller JF, et al. (2014): Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: evidence from population-based pharmacokinetic modeling. Environ Sci Technol 48:8807–8814

Yeung LW, Robinson SJ, Koschorreck J, Mabury SA (2013a): Part I. A temporal study of PFCAs and their precursors in human plasma from two German cities 1982-2009. Environ Sci Technol 47(8):3865-3874

Yeung LW, Robinson SJ, Koschorreck J, Mabury SA (2013b): Part II. A temporal study of PFOS and its precursors in human plasma from two German cities in 1982-2009. Environ Sci Technol. 47(8):3875-82

Zhang T, Sun H, Lin Y, Qin X, Zhang Y, X, Kannan K (2013a): Distribution of Poly- and Perfluoroalkyl Substances in Matched Samples from Pregnant Women and Carbon Chain Length Related Maternal Transfer. Environ Sci Technol 47 (14), p. 7974–7981

Zhang Y, Beesoon S, Zhu L, Martin JW (2013b): Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol. 17;47(18):10619-27

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