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PFAS in food: BfR confirms critical exposure to industrial chemicals

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Per- and polyfluoroalkyl substances (PFAS) are industrial chemicals. Due to their water, grease and dirt repellent properties, they are widely used in industrial processes and are used in numerous consumer products such as paper, textiles, non-stick coated pans and cosmetics. PFAS are difficult to break down and can be found in the environment, in the food chain and in human blood.

The European Food Safety Authority (EFSA) reassessed the health risks posed by PFAS in food in September 2020. In this report, EFSA determined a tolerable weekly intake (TWI) of 4.4 nanograms (ng) per kilogram (kg) of bodyweight per week. This TWI applies for the first time to the sum of four PFAS: Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexanesulfonic acid (PFHxS). It is based on epidemiological studies in which correlations between the PFAS concentrations in the blood and a reduced concentration of vaccine antibodies were observed in children.

The German Federal Institute for Risk Assessment (BfR) has examined the derivation of EFSA's health-based guidance value and recommends using this TWI in future assessments. In the present opinion, the BfR assesses the health risk for various population groups in Germany based on the new TWI from EFSA and the concentration data from the federal states' food control. The results of the external exposure are supplemented by studies on internal exposure in three German cities on the PFAS concentration in the blood. The result: Just as EFSA, the BfR comes to the conclusion that the exposure of some population groups partially exceeds the TWI.

The overall view of the results of the external and internal exposure assessments shows that parts of the population in Germany are exposed to PFOS, PFOA, PFNA and PFHxS to an extent that may be associated with a lower concentration of vaccine antibodies in the blood serum of infants during their first years of life, if they have been breastfed for a long time. This is also possible in children between 1 and 9 years of age with a high PFAS exposure through their diet.

At present, the study data are not sufficiently conclusive to answer the question of whether, at a corresponding level of exposure, there can also be effects on the concentration of vaccine antibodies in the blood serum in adults and adolescents.

At the same time, the BfR emphasizes the uncertainties that still exist in the external exposure assessment. Since the concentrations in the majority of the samples from food control were below the detection and quantification limits, it is recommended to develop more sensitive methods for determining the concentration of PFAS. The BfR also sees a need for research into the question of whether high PFAS concentrations in the blood are actually associated with an increased risk of infection.

Consumers can hardly influence their exposure to PFAS. The BfR recommends measures to further minimise the intake of PFAS with food. The compiled questions and answers on the subject of PFAS are currently being updated on the basis of the present opinion.

BfR risk profile: PFAS in food: reduced formation of antibodies after vaccinations (Opinion number 020/2021)					
A Affected are [1]	**General population Children** 				
B Probability of health impairment if the TWI is exceeded [1]	Very unlikely	Unlikely	**Possible**	Likely	Very likely
C Severity of the health impairment when the TWI is exceeded	No impairment	Mild impairment [reversible/irreversible]	**Moderate impairment [reversible/irreversible]**	Severe impairment [reversible/irreversible]	
D Significance of the available data [1]	High: The most important data are available and are internally consistent	**Medium: Some important data are missing or inconsistent**	Low: A large volume of important data is missing or inconsistent		
E Controllability by the consumer	Controls not Needed	Controllable with precautionary measures	Controllable through avoidance	**Not controllable**	

Fields with a dark blue background indicate the properties of the risk assessed in this opinion
(for more details, see the text of Opinion no. 020/2021 from the BfR dated June 28, 2021).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. The profile is not intended to be used to compare risks. The risk profile should only be read in conjunction with the corresponding Opinion.

[1] Line A – The general population, especially children, are affected
There is currently insufficient data to answer the question of whether, at a corresponding level of exposure, there can also be effects on the level of vaccine antibody titres in adults and adolescents.

[1] Line B – Probability of a health impairment if the TWI is exceeded
So far, the epidemiological data are insufficient to assess whether children with high exposure to the four PFAS mentioned actually have a generally increased risk of infection.

[1] Line D – Significance of the available data
There are currently uncertainties in the external exposure assessment; the internal exposure assessment is not based on representative data surveys for the total population in Germany. There is a need for research into the question of whether the affected population groups are actually at an increased risk of infection.

1 Subject of the assessment

The Federal Institute for Risk Assessment (BfR) has developed an opinion on the health assessment of the presence of the per- and polyfluoroalkyl substances (PFAS) perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexanesulfonic acid (PFHxS) in food.

PFAS are industrial chemicals that are very persistent in the environment and are detectable worldwide in water, soils, plants and animals. They can also be entered into the food chain.

The reason for the opinion is the publication of the opinion of the European Food Safety Authority (EFSA) on health risks related to the presence of PFAS in food. In this report, a tolerable weekly intake (TWI) of 4.4 nanograms per kilogram (ng/kg) of bodyweight (BW) per week was derived for the sum of the four long-chain compounds PFOS, PFOA, PFNA and PFHxS (EFSA 2020a). The feedback received from scientific organisations, citizens, industry and competent authorities in the Member States during a two-month consultation phase between February and April 2020 was published together with EFSA's opinion (EFSA 2020b). The BfR also participated in the commentary.

In its current report, EFSA has derived a sum TWI for several PFAS for the first time. Previous opinions referred exclusively to separate tolerable intake levels for PFOS and PFOA (EFSA 2008, 2018a). EFSA has reassessed these substances, taking into account current scientific knowledge and based on its current methodology for the assessment of combined exposure to multiple chemicals (EFSA 2019). Compared to the TWI values previously derived for PFOS and PFOA, the currently derived sum TWI means a reduction in the tolerable intake levels for PFOS and PFOA.

2 Results

The BfR has checked the derivation of the TWI of 4.4 ng/kg bodyweight per week for the sum of the four long-chain compounds PFOS, PFOA, PFNA and PFHxS by EFSA (2020a) and recommends using this TWI for future assessments of the concentrations of the four PFAS in food. This BfR opinion is also based on the current EFSA TWI (2020a).

The TWI is based on the results of epidemiological studies in which statistical correlations between the concentrations of certain PFAS in the blood serum (internal exposure) and reduced concentrations of vaccine antibodies (antibody titres) after standard vaccinations[1] were observed in children. Using benchmark dose modelling, a critical internal exposure level of 17.5 micrograms per litre (µg/L) in blood serum was calculated for the sum of the four PFAS as a critical reference point for the internal exposure of the infant age group. With blood serum concentrations below this value, there is a high probability that children will not have a 10% or more decrease in antibody titres after vaccinations that are caused by exposure to PFOS, PFOA, PFNA and PFHxS. Also for older children, who are presumably less sensitive, this value of the sum of the four PFAS of 17.5 µg/L can, from the BfR's point of view, be used as a reference point for the assessment of internal exposure in the sense of a conservative approach. The immunological study data available to date for adults and adolescents are not sufficiently conclusive to answer the question of whether this value is also suitable for assessing internal exposure for these age groups.

[1] Standard vaccinations according to the recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute

A reduced concentration of vaccine antibodies in the blood serum is generally considered undesirable, even if this does not necessarily lead to reduced vaccination protection on account of the existing safety margins for vaccinations if the vaccination recommendations of the Standing Committee on Vaccination at the Robert Koch Institute are observed. The current epidemiological data does not yet allow a conclusion to be drawn as to whether the influence of PFOS, PFOA, PFNA and PFHxS on the immune system can lead to a higher incidence of infections.

PFOS, PFOA, PFNA and PFHxS are excreted extremely slowly in humans after being absorbed into the body, which leads to accumulation in the human body. In breastfeeding mothers, the four mentioned PFAS pass into the breast milk and can thus be ingested by infants. Children[2] who have been breastfed for a long time achieve the maximum internal exposure of their life to PFOS, PFOA, PFNA and PFHxS through their breast milk at the end of the breastfeeding period, assuming that the exposure of the population (and thus of mothers) to the four PFASs remains constant over time. This was taken into account when deriving the TWI. For this purpose, the maternal internal exposure level was used as the basis for deriving the TWI (6.9 µg/L in the blood serum for the sum of the four PFAS), which enables the mother to breastfeed for one year without her child exceeding the critical exposure level (17.5 µg/L in the blood serum for the sum of the four PFAS). However, if the internal exposure level of 6.9 µg/L is exceeded (slightly) in adults, this does not mean that the PFAS exposure is critical with regard to the health of the adult person. Which internal exposure level is to be regarded as critical in adults cannot be derived from the immunological study data currently available.

Results on internal exposure in Germany and risk characterisation

Due to their long half-lives, the PFAS concentrations in blood serum or plasma are a good measure of the total exposure in the body ("body burden"). They do not only reflect the individual internal exposure, but also provide a picture of the current exposure in the population when a representative number of samples are examined. However, the available data on internal exposure are not based on representative data surveys for the total population in Germany and must therefore be interpreted with caution.

In current studies on the internal exposure of the adult population in three cities in Germany, the median levels for the sum of the four PFAS in blood serum were 5.8 µg/L (Göckener et al., 2020), 4.1 µg/L (Fromme et al., 2017) and 7.1 µg/L (Menzel et al., 2021). In these studies, the blood serum concentrations in 2 to 36 % of women of childbearing age were above the value of 6.9 µg/L on which the TWI was based. From these data (rough assumption: 25 % of women are above the blood serum concentration of 6.9 µg/L), using current data on breastfeeding behaviour, it can be roughly estimated that at present around 10 % of infants in Germany at the age of one year may exceed the critical exposure level of 17.5 µg/L for the four PFAS.

The data from current studies on internal exposure in children indicate that the blood concentrations of the individual compounds PFOS, PFOA, PFNA and PFHxS in the 95th percentile

[2] In the first 6 months of life, infants should be breastfed, at least until the beginning of the 5th month exclusively. Even after the introduction of complementary foods - no later than the beginning of the 7th month - infants should continue to be breastfed. The total duration of breastfeeding is determined by mother and child. https://www.gesund-ins-leben.de/fuer-fachkreise/bestens-unterstuetzt-durchs-1-lebensjahr/handlungsempfehlungen/stillen/stilldauer/

are below the sum proportions of these compounds of the critical internal exposure level of 17.5 µg/L[3]. Only individual published maximum values of the blood concentrations of the individual compounds of the children examined are well above these total proportions of the exposure level of 17.5 µg/L (Duffek et al., 2020).

Results on external exposure in Germany and risk characterisation

The basis for estimating the long-term external exposure for the sum of these four PFAS in the present opinion is data on concentrations in food (excluding drinking water) from the national food monitoring programs of the federal states for the years 2007 to 2020.

Overall, the estimation of external PFAS exposure is associated with great uncertainties. This is largely due to the fact that the levels in most food groups are to a high percentage below the detection and quantification limits of the analytical methods currently used. This results in large differences between lower bound (LB) and upper bound (UB) estimates[4] of exposure. The BfR shares the view of EFSA (2020a) that, based on the data available here, the exposure assessment in the LB represents a more realistic estimate of the external exposure via food compared to the UB. The following risk characterisation therefore relates to the results of the exposure assessments in the LB. Overall, the present estimate of external exposure can only be viewed as an approximate description of the real exposure situation for the general population in Germany due to the great uncertainties.

In particular, statements on the contributions of individual food groups to the total exposure via food are subject to considerable uncertainty.

As a result, the BfR's current exposure assessment for consumers in Germany confirms the conclusions of earlier opinions by the BfR and EFSA that the main food groups “fish and fish products” and “meat and meat products” contribute significantly to the exposure to PFOS, PFOA, PFNA and PFHxS. Other animal products that have a smaller share of the total exposure are “eggs and egg products” and “milk and milk products”. The role of plant-based foods in the overall exposure to the four PFAS can hardly be assessed on the basis of the available data, since the PFAS levels in the vast majority of the plant-based foods examined are below the detection and quantification limits of the currently used analytical methods. The BfR points out that drinking water can also be relevant for exposure, but was not considered in the present opinion.

As a result of the external exposure assessment, the current data show that the long-term exposure of adults in Germany to PFOS, PFOA, PFNA and PFHxS through the consumption of food other than drinking water at mean concentrations is around twice (mean) to five times (95th percentile) the level of the tolerable weekly intake determined by the EFSA, and for adolescents two to three times (mean) and five to seven times (95th percentile). The median exposure level of adults is in the range of the TWI. This means that the long-term exposure to PFOS, PFOA, PFNA and PFHxS is above the TWI for around 50 % of the participants in the consumption study on which this exposure assessment is based. The median exposure of

[3] Sum proportions of PFOS, PFOA, PFNA and PFHxA in the blood serum concentration of 17.5 µg/L: 7.7 µg/L for PFOS, 8.5 µg/L for PFOA, 0.3 µg/L for PFNA and 1.1 µg/L for PFHxS (EFSA 2020a)

[4] UB, LB: methodical approaches for dealing with analytical results below the detection and quantification limits (see 3.1.3.1.1 and 3.1.3.5). The results of the exposure assessments in the LB and UB represent the upper and lower limits of the range in which, given representative and complete data, the real level of exposure can be expected.

adolescents, with mean concentrations of the sum of the four PFAS in food, also corresponds to the level of the TWI or twice the level of the TWI, depending on the consumption study taken into account. The estimate of the external exposure of younger children (1 to 9 years) to the sum of the four PFAS corresponds to two to three times the level of exposure of adults, partly due to the higher consumption in relation to bodyweight. The exposure of this age group at mean concentrations of PFOS, PFOA, PFNA and PFHxS in food corresponds to about three times (median) to eleven times (95th percentile) the level of the TWI.

Health assessment and conclusion

In addition to data from external exposure assessments, the BfR also uses currently published data on internal exposure in Germany for risk characterisation.
For children aged 1 to 9 years, the calculated exceedance of the TWI of up to eleven times at high exposure (95th percentile) due to external exposure via foods with mean concentrations of PFOS, PFOA, PFNA and PFHxA is not compatible with the results on internal exposure. The results of studies on the internal exposure of this age group indicate that only individual published maximum values for the blood concentrations of the children examined are well above the critical reference point.

- In its overall assessment of the external and internal exposure of children in this age group at high exposure (95th percentile), the BfR therefore shares EFSA's view that there is a possibility that the exposure of some children is at a level associated with decreased concentrations of antibodies in the blood serum following standard vaccinations.

Overall, the data of the external exposure assessment of adults are compatible with the picture that emerges from the results of current studies on internal exposure to the four PFAS in the blood serum of the adult population in Germany, although the internal exposure is apparently somewhat lower than what could have been expected from the data from external exposure.

- The overall view of the results of the external and internal exposure assessments for adults and adolescents shows that the exposure to PFOS, PFOA, PFNA and PFHxS in parts of the general population in Germany is at a level that can be associated with a reduced concentration of antibodies in the blood serum after standard vaccinations during the first years of life in infants, who have been breastfed for a long time.
- The BfR shares EFSA's view that this should be viewed as toxicologically adverse at the population level, not only with regard to vaccination protection, but also with regard to the general immunological defence against other pathogens.
- So far, the epidemiological data is insufficient to assess whether these children with high exposure to the four PFAS mentioned actually have a generally increased risk of infection.
- At the moment there is also insufficient data on the question of whether, at a corresponding level of exposure, there can also be effects on the level of vaccine antibody titres in adults and adolescents.
- Possible risks from a reduced formation of vaccine antibodies in children who have been breastfed for a long time are countered by the numerous and well-studied advantages of long breastfeeding for both child and mother. The National Breastfeeding Commission at the Max Rubner Institute (MRI) has dealt with the risk-benefit assessment and, given the current data, sees no reason to deviate from the existing breastfeeding recommendation. Also worldwide, with knowledge of the findings on PFAS

available to date, no scientific committee has recommended restricting breastfeeding (MRI 2021).

Consumers can hardly influence their exposure to PFAS as a ubiquitous environmental contaminant. The results of the present opinion show that the intake of PFAS with food should be reduced. In principle, it is recommended to include drinking water as a source of exposure. From the results of the risk characterisation and the uncertainties both in the exposure assessment and in the toxicological assessment, the BfR derives recommendations with regard to the necessary collection of data and the need for research in order to reduce the uncertainties.

3 Rationale

3.1 Risk assessment

3.1.1 Hazard identification

Perfluorinated and polyfluorinated alkyl substances (PFAS) are compounds that have been produced industrially since the 1950s and do not occur naturally. Chemically, these are organic compounds in which the hydrogen atoms bonded to the carbon are completely (perfluorinated) or partially (polyfluorinated) replaced by fluorine atoms. The different PFAS differ in the length of their carbon chains and the functional groups present in the molecule, e.g. a carboxy group in the perfluoroalkylcarboxylic acids (PFCA), a sulfonate group in the perfluoroalkylsulfonic acids (PFSA), a hydroxyl group in the fluorotelomer alcohols (FTOH), a phosphate group in the perfluoroalkylphosphoric acid esters (PAP) or a sulfonamide group in the perfluoroalkylsulfonamides (FASA). In addition, a distinction is made between compounds with a branched and unbranched carbon chain, polymeric and non-polymeric compounds; in addition, there is a large number of derivatives in which the perfluorinated carbon chain is interrupted, for example by ether bridges[5].

With regard to the length of the fluorinated carbon chains, a distinction is made between short-chain and long-chain PFAS. Short-chain PFAS are cleared from mammalian organisms, including humans, more quickly than those with longer carbon chains. In PFCA, compounds with shorter carbon chains than perfluorooctanoic acid (PFOA, 8 carbon atoms) are called “short-chain”. The short-chain PFCAs include, for example, perfluorobutanoic acid (PFBA, 4 carbon atoms), perfluoropentanoic acid (PFPeA, 5 carbon atoms), perfluorohexanoic acid (PFHxA, 6 carbon atoms) and perfluoroheptanoic acid (PFHpA, 7 carbon atoms). PFOA, perfluorononanoic acid (PFNA, 9 carbon atoms) and compounds with longer carbon chains are referred to as long-chain PFCA. In PFSA, compounds with shorter carbon chains than perfluorohexanesulfonic acid (PFHxS, 6 carbon atoms) are referred to as “short-chain”. The short-chain PFSA includes, for example, perfluorobutanesulfonic acid (PFBS, 4 carbon atoms). PFHxS, perfluorooctanesulfonic acid (PFOS, 8 carbon atoms) and PFSA with longer carbon chains are called long-chain PFSA (Buck et al., 2011).

The many different compounds from the groups of PFCA, PFSA, FTOH, PAP, FASA, etc. serve as monomers (structural units) for the synthesis of a large number of different oligomers and polymers (molecules made up of several, repeating structural units), so that the PFAS

[5] https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/

substance group now comprises more than 4,700 different compounds (OECD 2018). PFAS are used in numerous industrial processes and technical applications and in numerous consumer products with water-, grease- and dirt-repellent surface treatments such as paper, textiles including upholstered furniture and carpets, non-stick coated cookware as well as in electronic devices, cosmetics or ski waxes. In addition, PFAS are used for the surface treatment of metals and plastics, in cleaning agents and pesticides, in the vehicle and construction industry, in the energy sector, in paints and fire-fighting foams and in a large number of other areas (Glüge et al., 2020).

Monomeric PFAS may be contained in the various consumer products as residues from the manufacturing process and can be released from them. Due to the strong chemical bond between carbon and fluorine atoms, PFAS are chemically and physically very stable. Therefore, they are hardly broken down by natural degradation mechanisms such as solar radiation, by microorganisms and other processes. In the environment, there is only partial degradation of PFAS, with the compounds from the PFCA and PFSA groups being regarded as terminal degradation products that cannot be further degraded in the environment. As a result, these PFAS are very long-lasting in the environment. Some of these PFAS can be transported to remote areas by the environment. PFAS can be detected worldwide in water, soils, plants and animals, and can therefore enter the food chain.

Analytical methods for a number of monomeric PFAS are available for quantifying the content of PFAS in food. In its current opinion, EFSA was able to use data on the levels of 28 different PFAS in food (EFSA 2020a). For 11 of these compounds, all analytical results were below the respective quantification limit; therefore, no exposure assessment has been carried out for these substances. An exposure assessment was carried out for 17 compounds for which the levels in various foods could be quantified. A health assessment was carried out for the sum of the following four PFAS: PFOS, PFOA, PFNA and PFHxS. These four long-chain PFAS have comparably long half-lives. In total, these four PFAS represent around 90 % of the PFAS levels currently detected in human blood samples (see 3.1.2.2).

Perfluorooctanesulfonic acid (PFOS; CAS No. 1763-23-1) is the lead substance for the PFSA group, because it can be detected most frequently in the environmental samples examined so far and is also toxicologically well characterised. PFOS arises from a large number of related compounds (e.g. perfluorooctanesulfonamide; FOSA) and can be released from certain polymers that are based on polyfluorinated compounds with eight carbon atoms (“C8-based”). The term PFOS generally refers to the acid and the salts derived from it. PFOS is readily soluble in water, but also has lipophilic (fat-soluble) properties. PFOS has been used in certain fire extinguishing foams in the past. In addition, PFOS-related compounds were reportedly 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 board for packaging (including those for food contact) were also coated with dirt, grease and water-repellent coatings.

Perfluorooctanoic acid (PFOA; CAS No. 335-67-1) is considered the lead substance of the PFCA group; it has been very well investigated in toxicological terms and is 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). PFOA is more water-soluble than PFOS and 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 and in side-chain fluorinated polymers[6] (e.g. fluorocarbon resins), trace levels of PFOA can occur as a manufacturing-related residue, unintentional by-product or impurity. Side-chain fluorinated polymers are also used to make textiles and leather repellent to water, oil and dirt, e.g. in sports and outdoor clothing, home textiles, upholstered furniture, carpets and protective clothing. In addition, side-chain fluorinated polymers can be used for the surface treatment of paper, cardboard and cardboard for packaging. Impregnating agents can also contain such polymers. Side-chain fluorinated polymers can release FTOH during the use and waste phase, which in turn oxidizes to PFCA (Holmquist et al., 2016).

There are also a number of technical uses of PFOA and its precursors (e.g. in fire-fighting foams). PFOA is used to a lesser extent in the photographic sector and as a surfactant in the semiconductor industry.

PFOA can also arise from non-polymeric precursors such as fluorotelomer phosphates, acrylates and iodides.

Perfluorononanoic acid (PFNA; CAS No. 375-95-1), like PFOA, is one of the long-chain PFCA. The pure substance is readily soluble in water. PFNA is mostly used as an ammonium or sodium salt. The substance is used as a surfactant in the production of the polymer polyvinylidene fluoride (PVDF) (Prevedouros et al., 2006). In addition, PFNA is created as a by-product in the synthesis of PFOA and short-chain PFCA such as PFHxA and can therefore also be contained in all consumer products for the manufacture of which these PFCA are used. This includes impregnation of textiles, carpets and upholstered furniture as well as surface coatings of paper, cardboard and metals. Besides PFOA, PFNA can also arise as a main breakdown product of the fluorotelomer alcohol 8:2-FTOH.

Perfluorohexanesulfonic acid (PFHxS; CAS No. 355-46-4), like PFOS, is one of the long-chain PFSA. The pure substance is only poorly soluble in water. The substance is primarily used in the form of its potassium or ammonium salt, whereby the abbreviation PFHxS is used both for the free acid and for its salts. PFHxS was used in the past as an alternative to PFOS and was used in the manufacture of impregnations for textiles, carpets, upholstered furniture and leather goods, as well as surface coatings, chrome plating processes and fire-fighting foams (Norwegian Environment Agency 2018).

Legal framework

The brief summary of the legal framework conditions here represents the status of April 2021. For current changes and for further information, please refer to the website of the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU)[7].

The use and placing on the market of **PFOS**, its salts and derivatives including the polymers that can be degraded to PFOS in the environment, was severely restricted in 2006 in the then European Community with Directive 2006/122/EC and limited to a few special applications. This chemical restriction was subsequently included in Annex XVII of the REACH Regulation (EC) No. 1907/2006. In 2011, the entry on PFOS was removed from Annex XVII of the REACH

[6] Side-chain fluorinated polymers: Non-fluorinated polymer backbone with fluorinated side-chains (Buck et al., 2011)

[7] https://www.bmu.de/faqs/per-und-polyfluorierte-chemikalien-pfas/

regulation, as the restrictions on PFOS were included in regulation (EC) No. 850/2004 on persistent organic pollutants (POP regulation). Worldwide, PFOS comes under the Stockholm Convention, which severely restricts its use.

The use of **PFOA** is severely restricted across Europe, as PFOA was included in the new version of the POP Regulation (EU) 2019/1021 by Regulation (EU) 2020/784. For PFOA, its salts and PFOA-related compounds, low concentration limit values have been in effect since July 4, 2020, provided that they are contained as unintentional trace contamination in products such as food packaging.

PFHxS: Its salts and related compounds were identified as “substances of very high concern” (SVHC) in June 2017 due to their properties (classification as “very persistent and very bioaccumulative”, vPvB) in accordance with REACH regulation (EC) No. 1907/2006 and a restriction procedure was subsequently initiated. Following the submission of a restriction proposal by the Norwegian Environment Agency in June 2019, the Committee for Risk Assessment (RAC) at the European Chemicals Agency (ECHA), together with the ECHA Socio-Economic Analysis Committee (SEAC), prepared a background paper (March 2020) that could be commented until the end of May 2020. The current status of the restriction procedure for PFHxS can be found on the ECHA website: https://echa.europa.eu/de/registry-of-restriction-intentions/-/dislist/details/0b0236e1827f87da.

PFNA was classified as “substance of very high concern” (SVHC) together with PFDA, PFUnDA, PFDoDA, PFTrDA and PFTeDA, the respective salts and related compounds due to their toxicokinetic and toxicological properties (classification as “persistent, bioaccumulative and toxic” (PBT) and “very persistent and very bioaccumulative” (vPvB)) . Under the leadership of Germany and Sweden, a joint restriction process was initiated for these long-chain PFCAs (C9 - C14 PFCA) in 2017. In the meantime, the Committee for Risk Assessment (RAC), together with the Committee for Socio-economic Analysis (SEAC) of ECHA, has drawn up a background paper, which has been available in its final form since November 2018 following the commenting. The current status of the restriction procedure for the C9 - C14 PFCA can be found on the ECHA website: https://echa.europa.eu/de/registry-of-restriction-intentions/-/dislist/details/0b0236e18195edb3

At the European level, activities began in May 2020 to restrict the entire PFAS group. All uses of these substances that are not considered “indispensable for society as a whole” are to be banned in future. The BfR is involved in these activities with a view to assessing properties of these substances that are harmful to human health and their use in consumer products.

3.1.2 Hazard characterisation

The basis for the following chapters on hazard characterisation is essentially the current EFSA opinion (2020a) or the scientific data situation evaluated there. Additional interpretations of the data from the BfR's point of view are identified as such. The literature search for the EFSA opinion (2020a) included the literature published up to August 2019. In the present opinion, selected currently available literature has been supplemented in individual chapters (e.g. see 3.1.4, 3.1.2.1, Table 1, 3.1.2.4.1). Although the exposure assessment and risk characterisation of the BfR exclusively refers to the four long-chain compounds PFOS, PFOA, PFNA and PFHxS, which are also taken into account in the sum TWI of the EFSA (2020a), this chapter includes an overview of the data situation of other PFAS based on the data compiled by EFSA (2020a) in order to enable a more comprehensive overview.

3.1.2.1 Toxicokinetics

After ingestion, PFAS are almost completely absorbed from the gastrointestinal tract into the blood. There the substances bind non-specifically to serum proteins and are distributed to all organs with the blood. The highest PFAS concentrations are found in organs such as the liver and kidneys that are well supplied with blood. They are not primarily found in adipose tissue like other persistent organic contaminants with high fat solubility (EFSA 2020a). PFAS are hardly metabolised in the mammalian organism. The so-called precursor compounds from the subgroups of FTOH, PAP or FASA are oxidised at most up to the homologous compounds from the subgroups of PFCA or PFSA, which are then not further metabolised. For example, 8:2 FTOH is metabolised to i.a. PFOA and PFNA in animal experiments and in human hepatocytes in vitro and could thus contribute to the blood serum concentrations of these compounds (EFSA 2020a).

PFAS are released from the liver into the bile and then largely reabsorbed via enterohepatic circulation. Renal reabsorption plays an important role in excretion via the kidneys, which is almost complete (99.95 %) in humans, for example in the case of PFOA (Han et al., 2012). Compared to experimental animal species investigated so far (with the exception of pigs), long-chain PFAS are therefore only excreted extremely slowly in humans, which leads to long half-lives[8] in the human body. PFSA and many PFCA are excreted primarily in urine and to a lesser extent in faeces. PFNA and PFCA with longer carbon chains than PFNA are mainly excreted in faeces (EFSA 2020a).

The half-lives for the elimination of PFAS depend on the substance and the species and, in some species, also depend on the sex and age (Li et al., 2018, Vanden Heuvel et al., 1991, Zhang et al., 2013a). For all investigated species, the short-chain PFAS are excreted better than the long-chain compounds. While the half-lives for the long-chain substances in many species are in the range from a few hours to weeks, in humans they are 2.7 to 8.5 years for PFOA, 3.1 to 5.4 years for PFOS, 1.7 to 3.2 years for PFNA and for PFHxS 4.7 to 8.5 years (Li et al., 2018, Olsen et al., 2007, Zhang et al., 2013b). The slow excretion of long-chain PFAS in humans is a critical point for the toxicological assessment of the substances.

[8] The half-life (t1/2) for the elimination of substances is defined as the time in which the concentration of the substances falls by half (Nau et al., 2003).

Table 1: Half-lives[a] of PFAS in blood serum or plasma in various species, according to EFSA (2020a) with supplements

Species	Perfluoroalkyl sulfonic acids			Perfluoroalkyl carboxylic acids						
	PFBS	**PFHxS**	**PFOS**	**PFBA**	**PFHxA**	**PFHpA**	**PFOA**	**PFNA**	**PFDA**	**PFUnDA**
Rat	*7.4 h*	0.8 – 2.3 d	18 – 71 d	*1.8 h*	*2.6 – 2.7 h*	*1.2 h*	*3.6 h*	6.4 – 32 d	74.6 d	n.d.
Mouse	n.d.	24.8 – 26.8 d	30 – 38 d	*2.9 - 3.1 h*	*~1.2 h*[b]	n.d.	17 d[b]	25.8[b] - 68.4[b] d	n.d.	n.d.
Monkey[c]	8.1 h – 3.5 d[b]	87 d	110 d	41 h	*2.4 – 19.2 h*[b]	n.d.	32.6 d	n.d.	n.d.	n.d.
Pig[d]	43 d	**2 a**	**1.7 a**	n.d.	4.1 d	74 d	236 d	n.d.	n.d.	n.d.
Human	27.7 d	**4.7 – 8.5 a**	**3.1 – 5.4 a**	2.5 d	32.0 d[e]	**0.17[f] – 1.0[g] a**	**2.7 – 8.5 a**	**1.7[g] – 3.2[g] a**	**4.0[g] – 7.1[g] a**	**4.0[g] – 7.4[g] a**

PFBS, perfluorobutanesulfonic acid; PFHxS perfluorohexanesulfonic acid, PFBA, perfluorobutanoic acid, PFHxA, perfluorohexanoic acid; PFOS, perfluorooctanesulfonic acid; PFHpA, perfluoroheptanoic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluorundecanoic acid
h: hours (*italics*), d: days, **a**: years (**bold**)
n.d.: no data
[a]Half-lives in blood serum or plasma of female dose groups (animal studies) or study participants are listed if different half-lives are described for the sexes. As a rule, half-lives after oral administration of the PFAS are listed in animal studies.
[b]Lau (2015)
[c]Results after i.v. application, as no data are available after oral ingestion
[d]Numata et al., (2014)
[e]Geometric mean; Significantly shorter half-life of 5.1 d described for the α and β phase of elimination (Luz et al., 2019), presentation of a re-evaluation of the data by Nilsson et al. (2013) by Buck and Gannon (2017)
[f]Xu et al., 2020

[g]Zhang et al., (2013b), Determination of the half-life in blood by modelling from renal clearance

In pregnant women, PFAS is transferred from the mother's blood via the placenta and in breastfeeding women via breast milk to the child. From the results of human biomonitoring (HBM) studies of milk and plasma samples, each obtained from the same individuals, the EFSA (2020a) derives a ratio of the concentration in milk to plasma of 0.03 for PFOA/PFNA and 0.015 for PFOS/PFHxS[9].

Breastfeeding thus represents another pathway for excreting PFAS for mothers. According to calculations, the blood serum concentrations of PFHxS decrease by 1 %, of PFNA by 2 % and of PFOS and PFOA by 3 % per month in breastfeeding mothers (Mondal et al., 2014). On the other hand, at the end of the breastfeeding period, the breastfed children achieve the maximum internal exposure for their life (MRI 2021) with constant exposure of the population over time. According to EFSA's calculations (2020a), however, it falls significantly over the course of the first five years of life and after about seven to ten years it becomes equal to the values of the children who have not been breastfed. In a study of children aged 6 to 10 examined during the years from 2007 to 2010, no significant influence of the length of breastfeeding on the level of PFAS could be demonstrated (Harris et al., 2017).

3.1.2.2 Human biomonitoring in Europe

According to EFSA (2020a), the trends over time in some HBM studies in Europe show that the concentrations of PFOS and PFOA in human blood serum and plasma have decreased significantly after the year 2000. For PFNA, perfluorodecanoic acid (PFDA) and perfluorundecanoic acid (PFUnDA), the EFSA (2020a) indicates increasing or constant concentrations in many studies in Europe since 2000, while different trends have been reported for PFHxS.

In the studies evaluated by EFSA (2020a), the following seven compounds show the highest concentrations in human blood serum in Europe[10]: PFOS, PFOA, PFHxS, PFNA, PFDA, PFUnDA and PFHpS. The sum of these seven compounds represents 96.6 % of the PFAS detected in adults and 93.4 % in children. In studies from 2007 to 2018, the sum of the four compounds PFOS, PFOA, PFNA and PFHxS alone represents approx. 90 % of the PFAS measured in human blood, according to EFSA (2020a). The relative proportion of individual PFAS compounds in serum differs between children and adults. According to results from HBM studies from 2007 to 2018, PFOS, PFOA, PFNA and PFHxS account for 64.0 %, 16.0 %, 5.6 % and 5.1 % (total 90.7 %) in adults and in children 35.0 %, 36.6 %, 8.8 % and 6.7 % (total 87.1 %) of the PFAS detected in the serum[10]. This corresponds to median concentrations of 7.7, 1.9, 0.67, 0.61, 0.3 and 0.28 µg/L for PFOS, PFOA, PFHxS, PFNA, PFDA and PFUnDA in adults and 3.2, 3.3, 0.79, 0.60, 0.30 and <0.25 µg/L in children in the median of these studies. The concentrations of all other PFAS are given as <0.25 µg/L[10].

The data on internal exposure in Germany are dealt with in Chapter 3.1.4 Internal exposure.

3.1.2.3 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 moderate (LD_{50} in several animal studies with rats in the range of over 250 to 579 mg PFOS/kg BW

[9]This is based on the arithmetic mean of the medians of the milk/plasma ratios in HBM studies (mean values for PFOA 0.025 µg/L, PFNA 0.039 µg/L, PFHxS 0.018 µg/L and PFOS 0.012 µg/L).

[10]The statement relates to the median value of the median concentrations of PFAS in blood serum reported in individual studies in Europe.

and 250 to 680 mg PFOA/kg BW (EFSA 2008, 2020a). Acute toxicity data are not available for PFNA and PFHxS. LD_{50} values for PFHxA are between 1750 and 5000 mg/kg bodyweight and for PFDA between 120 and 129 mg/kg bodyweight.

3.1.2.3.1 Animal studies with repeated oral exposure

For PFOS, PFOA, PFNA and PFHxS, in animal studies with repeated oral exposure, in some cases comparable target organs of toxic effects and comparable effects were observed, even if the four PFAS differed in terms of their potency with regard to the various endpoints investigated. Earlier derivation of health-based guidance values related to hepatotoxic effects (PFOA) and changes in thyroid hormone levels (PFOS). In studies with repeated exposure to PFOS in rats and cynomolgus monkeys and on the toxic effects of PFOA on reproduction in mice (see 3.1.2.3.2), steep dose-effect curves were described. The liver is a sensitive target organ in rodents. In each of the four PFAS, repeated oral exposure in rats led to increased liver weights associated with hepatocellular hypertrophy, disorders of lipid metabolism (decreased serum levels of cholesterol and triglycerides) and hepatocellular steatosis (EFSA 2018a, 2020a, ATSDR 2018, OECD 2002). For other PFAS (PFBA, PFHxA, PFHpA, PFDA, PFUnDA, PFDoDA, PFTeDA, PFHxDA, PFODA, PFBS, 8:2 FTOH, EtFOSE) there are results from animal studies with repeated exposure in which hepatotoxicity (mostly increased liver weights) is observed (EFSA 2020a). In addition, increased mortality (PFOS, PFOA, PFNA, PFHxA), increased relative kidney weights (PFHxA, PFOA, PFNA, PFDA, PFBS), changes in the nasal mucosa and/or olfactory epithelium (PFHxA, PFOA), as well as changes in thyroid hormone levels (PFBA, PFHxA, PFOA, PFNA, PFBS, PFHxS, PFOS) were observed with several compounds (EFSA 2018a, 2020a).

3.1.2.3.2 Reproductive toxicity

Numerous PFAS induce toxic effects on reproduction in rodents. In addition to PFOS, PFHxS, PFOA and PFNA, this applies to e.g. PFBA, PFHxA, PFNA, PFDoDA, PFDA, PFTeDA, PFODA, PFBS, 8:2 FTOH and EtFOSE (EFSA 2020a). After repeated oral exposure of the dams, the effects most frequently observed were a reduction in the number of live births and the viability of the offspring, reduced birth weights, and reduced bodyweight gain and increased liver weights in the offspring (EFSA 2018a, 2020a).

In mice, PFOA also impaired the development of the mammary glands of the female offspring if the dams were exposed to PFOA during late pregnancy or suckling (Macon et al., 2011, Tucker et al., 2015, White et al., 2007, 2009, 2011). This effect already occurred at low oral doses of PFOA (0.01 to 0.00045 mg/kg BW per day, corresponding to a PFOA blood serum concentration in the dams of 66 µg/L as the Lowest Observed Adverse Effect Concentration (LOAEC) (EFSA 2020a). There are no studies on the developmental toxicity regarding the mammary glands for any other compound belonging to the PFAS group. However, EFSA did not use this sensitive endpoint to derive a health-based guidance value due to uncertainties as to whether this effect is relevant for humans, as well as major uncertainties regarding extrapolation between species (EFSA 2020a).

In male rodents, repeated oral exposure to PFOA, PFOS, PFNA, PFDA, PFDoDA, PFHxA, or PFTeDA led to decreased weights and degenerative changes in the testes or the vesicle gland (*glandula vesiculosa*), decreased sperm counts and/or decreased testosterone levels (EFSA 2020a).

3.1.2.3.4 Neurotoxicity

PFOA and PFOS led to developmental neurotoxic effects in rodents at doses of 0.1 to 0.3 mg/kg BW per day or higher (EFSA 2018a, 2020a). Most of the observations relate to changes in motor activity. Animal studies also exist for PFHxS and PFDA which indicate a developmental neurotoxic potential of the compounds. There are no *in vivo* studies for this outcome for other PFAS including PFNA (EFSA 2020a).

3.1.2.3.5 Immunotoxicity

Some PFAS have an immunotoxic effect in animal experiments (NTP 2016, EFSA 2020a). Studies with rodents have shown that PFOS disrupts the homeostasis of the immune system (No Observed Adverse Effect Level (NOAEL) 1.66 µg/kg bodyweight per day, EFSA 2018a) and that PFOA affects the cellular composition of tissues of the immune system (bone marrow, spleen, thymus) and impairs the function of the immune system (decreased antibody response to T-cell-dependent antigens and increased IgE-specific immune response and inflammatory response). For PFOA, a NOAEL for immunotoxic effects of 1 mg/kg BW per day is derived from animal studies (EFSA 2018a). For PFOA and PFOS it could be shown via animal experiments in rodents that they cause a reduced immune response after repeated exposure to certain allergens, whereby the potency of PFOA regarding this toxicological endpoint was significantly lower than that of PFOS and that clear differences exist between species and sexes in rodents. For PFOS, increased mortality was also observed in mice within 20 days of infection with an influenza virus (H1N1). Immunotoxic effects such as atrophy of the spleen and thymus and changes in certain T cell populations were also observed for PFNA after repeated oral exposure (EFSA 2020a). Effects on the immune system were also observed for PFDA in animal studies with rodents. No animal studies on immunotoxic effects are available for other PFAS, including PFHxS (EFSA 2020a).

3.1.2.3.6 Carcinogenicity and genotoxicity

In animal studies with chronically exposed rats, an increased incidence of adenomas in the liver was observed for PFOS. Chronic exposure to PFOA also led to an increased incidence of adenomas in the liver and testes (Leydig cells) in rats; according to the EFSA, however, the results on the induction of tumours of the pancreas and the mammary gland are ambiguous (EFSA 2018a; 2020a). In a current study on the carcinogenicity of PFOA in rats, increased incidences of tumours of the liver in males and of the pancreas in both sexes were observed (NTP 2019a). The results of a long-term study on the carcinogenicity of PFHxA in rats do not give any indications of a carcinogenic effect of this compound. For PFAS other than PFOS, PFOA and PFHxA, no results are available from long-term carcinogenicity studies in rodents. The mechanisms leading to an increase in tumour incidences are still not fully understood. There is evidence that PFOS and PFOA act as tumour promoters in the liver of rodents and PFOS, PFOA and PFNA in the liver of trout (Benninghoff et al. 2012).

In the overall view of the results of genotoxicity studies *in vitro* and *in vivo*, it is assumed that the carcinogenic effects of PFOS and PFOA are not due to a direct genotoxic mechanism (EFSA 2018a, 2020a). This means that, where the health risk assessment is concerned, it may be assumed that intake levels can be defined for the compounds at which no carcinogenic effects are to be expected. There is only limited availability of data on the genotoxicity of PFAS other than PFOS and PFOA (EFSA 2020a). Based on the available data and the

structural similarities between PFHxS and PFOS as well as PFNA and PFOA, the existence of a direct genotoxic mechanism is also unlikely for PFHxS and PFNA.

3.1.2.4 Epidemiological data

Associations between the blood serum concentrations of various PFAS and various biological parameters have been reported in numerous epidemiological studies. In its previous opinion (EFSA 2018a), EFSA identified four endpoints for potentially critical effects of PFOS and/or PFOA; these were (i) for PFOS and PFOA an increased blood serum level of total cholesterol and low density lipoprotein (LDL) cholesterol as a risk factor for cardiovascular diseases, (ii) for PFOA an increased blood serum level of the liver enzyme alanine aminotransferase (ALT) as a biomarker of damage of hepatocytes, (iii) decreased birth weights and (iv) for PFOS a decreased serum concentration of antibodies after vaccinations. The results of the epidemiological studies on the associations of blood serum levels of PFOS, PFOA and other PFAS with these four endpoints and with other endpoints are summarised below.

3.1.2.4.1 Effects on the immune system

According to (EFSA 2020a), a total of nine epidemiological studies are available that deal with the relationship between peri- or postnatal concentrations of PFAS in the child's blood or concentrations in maternal blood at the time of birth and the concentration of vaccine antibodies (antibody titre) in the child after standard vaccinations.

In a study carried out on the Faroe Islands, where the inhabitants are exposed to a large number of persistent contaminants due to their high consumption of fish and whale meat, blood was taken from 587 children at the age of 5 to determine their vaccine antibody titre (tetanus, diphtheria), as well as the levels of perfluorinated compounds (mean values: PFOS 16.7 µg/L, PFOA 4.1 µg/L) and polychlorinated biphenyls (PCB). A booster vaccination against tetanus and diphtheria was also administered. At the age of 7, the vaccine antibody titre was again examined. There was a clear inverse association with the PFOS and PFOA levels in the blood measured at the age of 5. This was more pronounced for diphtheria antibody titres than for tetanus antibody titres, for which the association with PFOS was not significant. The diphtheria antibody titres measured before the booster at the age of 5 also showed the corresponding inverse association with the maternal PFOS/PFOA exposure measured at birth, albeit less pronounced (Grandjean et al., 2012). At the follow-up examination of 516 children at 13 years of age featuring re-determination of the diphtheria and tetanus antibody titres, as well as the PFAS concentrations in the blood (mean values: PFOS 6.7 µg/L, PFOA 2.0 µg/L), most children showed the expected decrease in antibody titres compared to the previous examination at the age of 7 years. Surprisingly, however, the expected further decrease in antibody titres was not observed in 202 children, although they had apparently not received a booster in the meantime. The evaluations consistently showed inverse correlations between PFOS/PFOA concentrations and diphtheria antibody titres, but only in one of the 6 cases at the level of significance. In the case of the tetanus antibody titres, these relationships were inconsistent; in fact, in most cases positive trends in terms of PFOS/PFOA levels were calculated for this age (Grandjean et al., 2017).

In another study, a subgroup of 50 children aged 3 years from a Norwegian mother-child cohort (recruitment of mothers: 2007/2008) were studied with regard to the titre of vaccine anti-

bodies. Negative associations were found between the maternal PFAS concentrations measured at birth (mean values: PFOS 5.6 µg/L, PFOA 1.1 µg/L) and the antibody titres in rubella, while no significant correlation was observed in Haemophilus influenza type b (Hib), tetanus and measles (Granum et al., 2013). A cross-sectional study carried out between 1999 and 2004 examined the association of perfluorinated compounds in blood serum (mean values: PFOS 20.8 µg/L, PFOA 4.1 µg/L) with the titres of vaccine antibodies against measles, mumps and rubella in 1,191 US American children and adolescents. In the seropositive participants, higher PFAS concentrations were significantly associated with lower titres of antibodies against mumps and rubella. A doubling of the PFAS levels in the blood was associated with a lowering of the titres by 5.9 and 13.3 % for PFOS and by 6.6 and 8.9 % for PFOA. No association was found with measles antibody titres (Stein et al., 2016).

In the studies mentioned, the children were at least 3 years old. Therefore, the comparatively high PFAS exposure at the end of the breastfeeding period as well as a possibly higher sensitivity for effects on the immune system in the first year of life could not be taken into account in these studies. This data gap was recently closed by the publication of a study that was carried out at the end of the 1990s, mainly in Berlin, with 101 children aged one year (Abraham et al., 2020). 21 children were not breastfed, 80 children were exclusively breastfed for at least four months. The PFAS analyses carried out in 2019 in reserved samples showed mean plasma levels of 3.8 µg/L (PFOA) and 6.8 µg/L (PFOS) in the non-breastfed children and 16.8 µg/L (PFOA) and 15.2 µg/L (PFOS) in children who had been breastfed for a long time. The study, which was originally focused on dioxins and PCBs, in which numerous other biological parameters were measured in addition to the immunological parameters, could also be evaluated in relation to PFAS using the new analyses. Significant associations were found between the PFOA concentrations (but not the PFOS concentrations) and the antibody titres against Hib, tetanus and diphtheria adjusted for the time since the last vaccination, with a reduction in the antibody titres (when comparing quintiles Q1 and Q5) of 86, 54 and 53 %, respectively. The PFOA concentrations were also negatively associated with the production of interferon gamma by *ex vivo* lymphocytes after stimulation with tetanus and diphtheria toxoid. The children were vaccinated during the first year of life in accordance with the recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute (Abraham et al., 2020).

In summary, some epidemiological studies indicate statistical relationships between the concentrations of certain PFAS in the blood and reduced antibody titres in children, which indicates a reduced formation of antibodies after certain standard vaccinations.

Epidemiological data on an increased susceptibility to infection

The research results presented are linked to the question of their clinical relevance, i.e. whether PFOS and PFOA may have a general suppressive effect on the immune system, which could lead to an increased incidence or more severe courses of infectious diseases. Studies on the question of general infection susceptibility have so far mainly looked at prenatal PFAS exposure. Several studies are available on the possible association of the PFAS concentrations in maternal blood or umbilical cord blood and the general frequency of infections in children in the first years of life. In some cases, positive associations were reported (Granum et al., 2013; Dalsager et al., 2016; Goudarzi et al., 2017; Impinen et al., 2018), while no or inconsistent associations were found in other studies (Fei et al., 2010; Okada et al., 2012, C8 Science Panel 2012, Impinen et al., 2019). With regard to the comparatively high PFAS exposure of children who have been breastfed for prolonged periods, only the

above-mentioned study by Abraham et al., (2020) is available, in which the detailed questioning of parents about the infections they have had to date in one-year-old children does not indicate any signs of higher susceptibility to infections in the children more exposed to PFOA/PFOS.

The SARS-CoV-2 coronavirus epidemic offers the chance to study the reaction of many people to a new infection as well as to new vaccinations, also depending on the exposure to PFAS. A study on possible relationships between infection-related mortality and the level of exposure to PFAS was recently published (March 2021) from the Italian province of Veneto: In a region with decades of relatively high exposure to PFAS-contaminated drinking water, infection-related mortality increased by a factor of 1.55 compared to the control region (90 % confidence interval: 1.25; 1.92). Individual PFAS analyses were not carried out (Catelan et al., 2021). In the next few years, further publications on this topic are expected, which deal with the question of the clinical relevance of the PFAS influence on the immune system.

From the BfR's point of view, the current epidemiological data does not yet allow a conclusion with regard to the question of whether the influence of PFOS, PFOA, PFNA and PFHxS on the immune system can lead to a more frequent occurrence and/or more serious courses of infections.

3.1.2.4.2 Cholesterol and cardiovascular diseases

The results of numerous epidemiological studies consistently indicate a positive association between the blood serum concentrations of PFOA and PFOS and the concentration of total cholesterol in the serum (Steenland et al., 2009; Eriksen et al., 2013; Nelson et al., 2010). More recent epidemiological cross-sectional studies, which were taken into account in the current EFSA opinion (2020a), confirm this correlation. It is worth noting that the increase of approx. 5 to 7.5 % total cholesterol observed in these studies is recorded up to the range of the measured mean PFOS/PFOA concentrations, but at even higher concentrations the further increase is only slight. An extensive study is available for children and adolescents (Frisbee et al., 2010), which shows comparable results for these age groups. In some studies, including Steenland et al. (2009), it was shown that higher concentrations of PFOS/PFOA in serum are associated with increased LDL cholesterol levels. Compared to the total cholesterol level, the LDL cholesterol level is assigned a higher relevance as a risk factor for cardiovascular diseases.

In addition to PFOS and PFOA, possible associations between the blood serum concentrations of other PFAS and the cholesterol level were investigated in various epidemiological studies. According to EFSA (2020a), a positive association with the total cholesterol level was observed for PFNA in eight out of nine studies (including Nelson et al., 2010; Seo et al., 2018; Dong et al., 2019). However, when interpreting these results, the high correlation of PFNA with the compounds PFOS and PFOA, which are present in higher concentrations, must be taken into account. For PFHxS and other PFAS such as PFHxA, PFHpA, PFBA, PFDA or PFHpS, no such associations were observed in the majority of studies.

According to EFSA (2020a), the question of whether the observed association between PFAS blood serum concentrations and total cholesterol is a causal relationship has not been finally clarified. It is also possible that both parameters are causally dependent on a third parameter. Assuming that PFAS are reabsorbed from the intestine together with bile acids, people with an individually high rate of reabsorption of bile acids would also have a correspondingly high rate of reabsorption for PFAS. However, a high rate of reabsorption of bile

acids is accompanied by an inhibition of the synthesis of new bile acids. A reduced synthesis of new bile acids, for which cholesterol is the precursor substance, leads to an increased blood serum level of total cholesterol. In this scenario, people with a high reabsorption rate for bile acids and PFAS would stand out as people with high PFAS concentrations in their blood and, at the same time, higher blood cholesterol concentrations, without the higher PFAS concentrations being causally related to the higher cholesterol concentrations. A possible confounding (coincidence of increased serum levels for PFAS and total cholesterol) due to the enterohepatic circulation (excretion into the intestine via bile with subsequent reabsorption from the intestine) cannot therefore be ruled out (EFSA, 2018b).

In its previous opinion, EFSA did not consider the possibility of such a confounding factor in greater detail (EFSA, 2018a). In its current opinion, EFSA takes possible confounding into account and therefore attaches greater importance to the uncertainties with regard to causality between PFAS exposure and total cholesterol blood levels (EFSA, 2020a). As a result, EFSA continues to observe clear evidence in the results of the epidemiological studies for an association between the PFAS blood serum levels and total cholesterol, but no longer relies on these results to derive the health-based guidance value.

The results of a longitudinal study in which decreasing PFOS/PFOA blood serum levels were accompanied by a decrease in cholesterol levels support the assumption of a causal relationship between PFAS exposure and an increase in cholesterol levels (Fitz-Simon et al., 2013). According to information from Steenland et al., (2009), the measured values from people who took cholesterol-lowering drugs contradict any “reverse causality” (increased cholesterol values result in higher PFOS/PFOA levels). Assuming that the cholesterol level influences the PFOA/PFOS level, this should be lower in treated individuals. However, this effect was not observed in the study data.

Changes in serum cholesterol levels after repeated exposure to PFOS or PFOA were also observed in animal studies with rodents. Here, the total cholesterol level was lowered, with significantly higher exposures to PFOS and PFOA in the investigations than in epidemiological studies in which this parameter was investigated (see 3.1.2.3.1).

A prolonged increase in total cholesterol, especially in the LDL fraction, is seen as one of several risk factors for the development of cardiovascular diseases in adults (Ference et al., 2017; Piepoli, 2016). However, the available epidemiological studies do not show a clear association between PFAS blood serum levels and diseases such as arteriosclerosis, high blood pressure, myocardial infarction or stroke. EFSA (2018a, 2020a) lists five cross-sectional studies and four longitudinal studies that examined associations between PFOS/PFOA exposure and parameters of cardiovascular diseases. Six of these studies also examined possible associations between other PFAS (including PFNA and PFHxS) and cardiovascular disease. Even if some more recent studies (Bao et al., 2017; Huang et al., 2018; Mastrantonio et al., 2018) indicate a positive association between exposure to PFAS and cardiovascular diseases, in its current opinion EFSA considers the data as not yet sufficient as a basis for deriving a health-based guidance value (EFSA, 2020a).

3.1.2.4.3 ALT blood level

Alanine aminotransferase (ALT) is an enzyme found primarily in hepatocytes. In laboratory diagnostics, the ALT activity in blood serum is measured as one of several parameters for the detection of liver damage. Increased ALT activity in blood serum correlates with increased death of hepatocytes and is therefore an indicator of liver damage.

The association between exposure to PFOA and increased ALT activities in blood serum, observed in epidemiological studies, was already presented in the earlier opinion by EFSA (2018a). The current opinion by EFSA (2020a) now shows that, in several epidemiological studies, a positive association between the blood serum concentrations of other PFAS, including PFOS, PFNA and PFHxS, and the ALT activity in blood serum was observed (Salihovic et al., 2018; Jain et al., 2019). According to EFSA (2018a, 2020a), the moderately increased ALT activities measured in the blood samples were mostly within the reference range of this laboratory parameter. Only in individual studies was it observed for PFOA, branched derivatives of PFOS and PFNA that high blood serum concentrations were associated with measured ALT values above the reference range (Gallo et al., 2012; Nian et al., 2019; according to EFSA 2020a). With regard to increased values for other classic blood parameters that indicate damage to the liver, such as alkaline phosphatase (ALP), γ-glutamyltransferase (GGT) or bilirubin, study results show no clear correlation with increased PFAS blood serum concentrations. In addition, according to EFSA (2020a), the results of epidemiological studies do not consistently indicate a correlation between PFAS blood levels and an increased incidence of liver diseases or liver-associated metabolic diseases such as metabolic syndrome, obesity or diabetes. In its current opinion (EFSA 2020a), EFSA also regards the observed positive association between PFAS blood levels and ALT activities as an unsuitable basis for deriving a health-based guidance value, because only minor increases in ALT activities were observed in the studies and associations with ALT activities outside the reference range have been described in only a few studies.

3.1.2.4.4 Birth weights

In several epidemiological studies, an inverse relationship was observed between the birth weights of newborns and the PFOA and PFOS blood serum concentrations of the mothers (EFSA 2018a, 2020a). In a more recent study, this was also observed for PFNA (Meng et al., 2018). In this Danish cohort study, PFAS concentrations were determined in maternal blood samples which were obtained around the year 2000 and which had significantly higher PFAS concentrations than today (mean concentrations for PFOS 30.1 µg/L, for PFOA 4.6 µg/L, for PFHxS 1.0 µg/L and for PFNA 0.5 µg/L). For other PFAS, the results of epidemiological studies with regard to reduced birth weights were inconsistent, with the blood serum concentrations of these PFAS in some studies being significantly lower than those of PFOS and PFOA (e.g. Kwon et al., 2016; Bach et al., 2016; according to EFSA 2020a).

EFSA considers the clinical relevance and the causality for the relationship between the concentrations of PFOS and PFOA in the blood and the observation of reduced birth weights as being unclear. From EFSA's point of view, the available studies provide indications of a causal relationship between these parameters. A possible confounding factor due to physiological changes during pregnancy (e.g. an increased glomerular filtration rate of the kidneys) cannot be ruled out and no increased risk of birth weights that are defined as “low” (<2500 g) or for the occurrence of an increased incidence of premature births or miscarriages has been reported. In addition, there is no evidence of PFAS-mediated effects on fertility or reproductive capacity in either men or women.

3.1.2.4.5 Other examined associations

Numerous epidemiological studies have looked at other potential health effects of PFAS. Overall, according to EFSA (2020a), it can be said that there is no evidence of associations

between exposure to PFAS and developmental neurological effects, child growth, behavioural problems and psychiatric or cognitive effects. The studies also provided no or only insufficient evidence with regard to an association between PFAS and the function of the thyroid gland and kidneys, or bone density. Population-based studies also investigated whether there is an increased risk of cancer for humans associated with exposure to PFAS. For PFOS and PFOA, the results of these studies available up to August 2019 do not sufficiently support the assumption that such a relationship exists in humans. This means that a connection cannot currently be proven definitively. With regard to other PFAS, human data on carcinogenicity are scarce so far (EFSA 2020a).

3.1.2.5 Derivation of a health-based guidance value

3.1.2.5.1 Selection of the compounds under consideration and approach for evaluating the combination effects

In the previous opinions by EFSA and other international bodies, the two substances PFOA and PFOS were evaluated and a separate value for the tolerable daily/weekly intake (TDI/TWI)[11] was derived as a health-based guidance value for each substance.

Based on data from animal experiments, EFSA published TDI values of 0.15 µg/kg BW per day for PFOS and 1.5 µg/kg BW per day for PFOA in 2008. Other committees as well as EFSA later derived significantly lower health-based guidance values, which initially resulted mainly from the use of other toxicokinetic models to account for differences in the half-lives between laboratory animals and humans (e.g. ATSDR 2018), and later also from the use of epidemiological data as well as the use of effect endpoints for the TWI derivation, which concerned more a risk factor for a disease than an actual disease (e.g. 6 ng/kg BW per week for PFOA and 13 ng/kg BW per week for PFOS in EFSA Opinion 2018a)[12].

In its current opinion (EFSA, 2020a), EFSA has now derived a TWI of 4.4 ng/kg BW per week for the sum of the four compounds PFOS, PFOA, PFNA and PFHxS as a health-based guidance value in accordance with a new guideline on the methodology for the health assessment of combination effects (EFSA 2019) . These four compounds belong to the group of long-chain PFAS. The reason for the selection of these compounds is that they (i) have similar toxicokinetic properties with long half-lives and a high potential for accumulation in the human body (see 3.1.2.1), (ii) show similar effects in animal studies (see 3.1.2.3) and (iii) are the dominant PFAS in human blood samples (see Chapter 3.1.2.2). In the median of the HBM studies evaluated by EFSA (2020a) from 2007 to 2018, the sum of the median concentrations of these four compounds represents approx. 90 % of the PFAS exposure observed in human blood.

As part of a pragmatic approach, it was decided to limit the assessment of the combination effects to the four PFAS that are mainly detected in human blood serum (EFSA 2020a). No health-based guidance value such as a TWI could be derived for the other PFAS previously detected in food, as the currently available database on the toxicology of the individual compounds and on the derivation of potency factors or toxicity equivalence factors, which could

[11]Tolerable Daily/Weekly Intake (TDI/TWI): Health-related guidance value for the tolerable amount of a contaminant (per kilogram of bodyweight), which is not expected to have any adverse effects on health per week if consumed over a lifetime.

[12]In an opinion from the Agency for Toxic Substances and Disease Registry (ATSDR) 2018, Minimal Risk Levels (MRL) for PFHxS and PFNA were also derived (ATSDR 2018).

allow for a health risk assessment of further PFAS as part of a group approach, is insufficient. In its opinion, however, EFSA recognises that there is a need for the collection of toxicological data and the assessment of further PFAS in the future. In the absence of comparative studies on the relative toxicological potency of the four PFAS in relation to the toxicological endpoint used to derive the TWI (see below), an equivalent toxic potential is assumed for the four compounds of the sum TWI in the current EFSA opinion (2020a).

3.1.2.5.2 Selection of the critical effect (most sensitive toxicological endpoint) and the critical study

The EFSA TWI derivation (2020a) is based on the results of epidemiological studies in which an inverse association between the blood serum concentrations of PFOA, PFNA, PFOS and PFHxS and titres of vaccine antibodies was observed in children, which was interpreted as a reduced formation of antibodies (Abraham et al., 2020; Grandjean et al., 2012). This decreased antibody formation after vaccination has been observed in several epidemiological and animal studies at low serum concentrations for various PFAS and is considered to be the most sensitive endpoint. The lowest Benchmark Dose Lower Confidence Limit 10 ($BMDL_{10}$) of **17.5 µg/L** serum, which was calculated in the study by Abraham et al. (2020), for the association of the sum of the four named PFAS with the level of the titre of the diphtheria vaccine antibodies was used as the starting point for the TWI derivation[13]. This value represents the lowest result of the benchmark dose modelling for the data on the association of the sum of the blood serum concentrations of the four PFAS with the antibody titres in children after vaccination against diphtheria and tetanus using four individual models. This means that when blood serum concentrations are below this value in children, a high probability exists that vaccine antibody titres, caused by exposure to PFOS, PFOA, PFNA and PFHxS, will not be reduced by 10 % or more. EFSA and the BfR therefore consider a blood serum concentration of 17.5 µg/L to be a critical reference point for the internal exposure of the infant age group. Even with older children, who are less sensitive according to the benchmark dose calculations of EFSA, this value of the sum of the four PFAS of 17.5 µg/L may also be used as a reference point for assessing internal exposure. The immunological study data for adults and adolescents do not yet allow a conclusion to be drawn on the question of whether application of the value is justified with these age groups.

There is still no generally scientifically coordinated approach to calculate BMDL values based on epidemiological studies. EFSA bases itself on the usual approach for experimental data, which for toxicology generally comes from animal studies. However, this approach had to be modified. The modifications chosen by EFSA are plausible from the perspective of BfR.

The lower concentration of antibodies in the blood serum after vaccinations in children with higher levels of PFOS, PFOA, PFNA and PFHxS in the blood serum indicates that the substances have an effect on the immune system. The underlying mechanism of action has not yet been clarified.

A reduced concentration of vaccine antibodies in the blood serum is generally considered undesirable, even if this does not necessarily lead to reduced vaccination protection due to the existing safety margins for vaccinations if the vaccination recommendations of the Standing

[13]BMDL: Lower limit of the confidence interval associated with the benchmark dose (BMD). The BMD represents the dose determined using mathematical dose-effect modelling, which is associated with a certain effect size within the studies on which the modelling is based (in the case of the BMD 10, e.g. a 10 % increase in the effect).

Committee on Vaccination at the Robert Koch Institute are observed. The current data does not yet allow a conclusion to be drawn as to whether the influence of PFOS, PFOA, PFNA and PFHxS on the immune system can lead to a higher incidence of infections.

At the time of the publication of the previous EFSA Opinion (2018a), the BfR had considered the evidence available at the time on the question of a reduced concentration of vaccine antibodies in blood serum or an increased susceptibility to infection as possibly caused by PFOS/PFOA as being inadequate and in some cases contradictory. The BfR's criticism related to the available data at that time. This data has since been significantly expanded by the publication of a new study (Abraham et al., 2020), so that the BfR no longer believes that insufficient evidence exists on the question of a reduced concentration of vaccine antibodies in blood serum caused by PFOS/PFOA. The new study closes important gaps in the data and was chosen by EFSA as a key study in deriving the TWI.

Also in the EFSA Opinion of 2018a, the TWI derivation was based on the results of epidemiological studies. Here the positive correlation between blood serum concentrations of PFOA or PFOS and an increased blood serum level of total cholesterol was used for the TWI derivations for PFOS and PFOA. Regarding this derivation, the BfR was particularly critical of the evidence for causality and the clinical relevance of the results from epidemiological studies on which the TWI derivation was based.[14]

In its current opinion, EFSA now attaches greater importance to the uncertainties regarding the causality between PFAS exposure and the total cholesterol level in the blood than in its previous opinion (see Chapter 3.1.2.4.2). As a result, EFSA continues to observe clear evidence in the results of the epidemiological studies for an association between the PFAS blood serum levels and total cholesterol in serum, but no longer relies on these results to derive the health-based guidance value.

In its 2020 opinion, as in 2018, EFSA also evaluates the positive association observed between PFAS blood levels and ALT activities as unsuitable for deriving a health-based guidance value based on it, because only small increases in ALT activities were observed in the studies and associations with ALT activities outside the reference range have been described in only a few studies. Although the effect was also observed in animal studies, there are uncertainties regarding the comparability of the effects due to the large differences in the dose-effect curves.

The association of lower birth weights with higher serum concentrations of PFOS, PFOA and PFNA observed in epidemiological studies is considered unsuitable for deriving a health-based guidance value in both the current EFSA opinion (2020a)and in the previous opinion (EFSA 2018a) due to uncertainties regarding clinical relevance and causality.

Impairment of the development of the mammary glands as a developmental toxic effect in mice after exposure to PFOA via the dams *in utero* or during the lactation period was identified as the most sensitive effect in animal studies (Macon et al., 2011, Tucker et al., 2015, White et al., 2007, 2009, 2011). The lowest effective serum concentration LOAEC was 20 µg/L in the offspring, corresponding to an LOAEC of 66 µg/L in the dams. According to EFSA (2020a), deriving a TWI on the basis of this effect would lead to a TWI for PFOA that is around nine times lower than the TWI for the sum of PFOS, PFOA, PFNA and PFHxS in the current EFSA statement. However, the impairment of the development of the mammary

[14] https://www.bfr.bund.de/cm/343/neue-gesundheitsbezogene-richtwerte-fuer-die-industriechemikalien-pfos-und-pfoa.pdf

glands in mice has not been investigated for other PFAS, nor has it been tested in other animal species or in epidemiological studies and has therefore been interpreted as unsuitable for use as a basis for deriving a health-based guidance value.

3.1.2.5.3 Physiology-based toxicokinetic (PBTK) modelling and TWI derivation

With constant exposure of the population over time, long-term breastfed children achieve an internal exposure to PFOS, PFOA, PFNA and PFHxS maximum for their life at the end of the breastfeeding period. Based on the $BMDL_{10}$ value for the sum of PFOS, PFOA, PFNA and PFHxA of 17.5 µg/L in the child's blood serum, the daily intake of the four compounds by mothers that would lead to this total concentration in the blood serum of their one-year-old children was calculated using a PBTK model, assuming breastfeeding for prolonged periods (EFSA 2020). To illustrate the transfer via breast milk, data from HBM studies on the relationship between the levels of compounds in the milk and blood plasma of breastfeeding women were used (see 3.1.2.1). Due to the similarities in the toxicokinetics and the chemical structure of the perfluoroalkylsulfonic acids PFOS and PFHxS or the perfluoroalkyl acids PFOA and PFNA, the assumptions for PFOS were also used for PFHxS and the assumptions for PFOA also for PFNA. The prenatal exposure of the infants and the resulting concentrations in the blood serum of the newborn children were also taken into account in the toxicokinetic modelling.

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). The model developed for PFOA was also used for PFNA in the EFSA opinion (2020a), and the model developed for PFOS was also used for PFHxS. Since the simulation code for the model is described completely, the model calculations are transparent and valid from the point of view of BfR. However, in the PBTK model, the enterohepatic circulation of PFOA and PFOS and their possible (albeit low) excretion via the faeces are not taken into account.

Based on average blood serum concentrations in the study by Abraham et al. (2020) in children aged one year, the $BMDL_{10}$ value of 17.5 µg/L corresponds to values of 7.7 µg/L for PFOS, 8.5 µg/L for PFOA, 0.3 µg/L for PFNA and 1.1 µg/L for PFHxS (proportions of the individual compounds in the total: 43.8 %, 48.4 %, 1.7 % and 6.1 % for PFOA, PFOA, PFNA and PFHxS).

The toxicokinetic model calculates the corresponding maternal blood serum concentrations for women of childbearing age, which must not be exceeded so that the $BMDL_{10}$ of 17.5 µg/L is not exceeded even in children who have been breastfed for a long time.

The modelling showed that a maternal serum concentration of **6.9 µg/L** for the sum of PFOS, PFOA, PFNA and PFHxS (4.9 µg/L for PFSA and 2.0 µg/L for PFCA) assuming 12 months of breastfeeding leads to a serum concentration in the breastfed child that does not exceed the critical value of 17.5 µg/L for the sum of PFOS, PFOA, PFNA and PFHxS (8.7 µg/L for PFSA and 8.8 µg/L for PFCA).[15]

[15]Based on the ratios derived from the HBM between concentrations in maternal blood serum and breast milk of 0.015 for PFSA and 0.03 for PFCA (see 3.1.2.1), the initial concentration in breast milk at this blood serum concentration would be 0.133 µg/L for the total of PFOS, PFOA, PFNA and PFHxS (0.073 µg/L PFSA and 0.06 µg/L PFCA).

This value of 6.9 µg/L indicates the maximum blood serum concentration in mothers so that the $BMDL_{10}$ of 17.5 µg/L in their children is not exceeded even if their children are breast-feeding for a long time.

The modelling also showed that a person who consumes up to 0.63 ng/kg BW of the sum of the four PFAS (0.19 ng PFSA per kg BW and 0.44 ng PFCA per kg BW) daily does not exceed the serum concentration of 6.9 µg/L for the sum of the four PFAS at the age of 35 years[16].

Because of the long half-lives of the four PFAS in human blood serum, this daily intake of 0.63 ng/kg bodyweight per day was multiplied by a factor of 7[17] to calculate a weekly intake **of 4.4 ng/kg bodyweight** for the sum of PFOS, PFOA, PFNA and PFHxS as a TWI.

In the derivation shown for the TWI, EFSA does not use assessment factors to take into account inter-individual variability in toxicokinetics or sensitivity. This takes into account the fact that the inverse association of the levels of PFAS with the concentrations of vaccine antibodies in the blood serum is more a risk factor for a disease than a disease, and that the population group considered in the underlying epidemiological study was infants that are to be regarded as a vulnerable group.

The respective sum of the BMDL values for PFOS and PFOA, which was derived in the earlier EFSA opinion (2018a) for other associations in epidemiological studies, is higher than the blood serum levels in adults correlating with the current TWI for the sum of PFOS, PFOA , PFNA and PFHxS of 6.9 µg/L. The TWI of 4.4 ng/kg BW per week therefore also protects against other effects that have been observed in epidemiological studies and are discussed as PFAS-related.

Because of the long half-lives in human blood serum, PFOS, PFOA, PFNA and PFHxS can accumulate after ingestion with food, drinking water or other sources in the body until an equilibrium is reached between absorption and excretion. Whether exposure exceeding the TWI of 4.4 ng/kg bodyweight per week results in concentrations above the blood serum concentration of 6.9 µg/L on which the TWI is based depends on several factors: the extent of the exceedance, the duration and the amount of substances already present in the body.

Since breastfed infants represent the age group with the highest PFAS levels for the compounds under consideration, the TWI is also seen as protective for other age groups. However, it must be taken into account that only limited data are available to assess a possibly higher vulnerability of older age groups with regard to possible impairment of the immune system by these compounds.

The methodological approach used in deriving the EFSA's TWI takes into account the exposure of breastfed infants by deriving a weekly lifelong intake that is based on the concentration of the four PFAS in the blood serum of 35-year-old women or the related concentration in breast milk. The comparatively high external exposure of infants during the breastfeeding phase should therefore not be compared with the TWI in the context of a health assessment. Apart from this special case, the TWI derivation by EFSA includes all population groups. (Slightly) exceeding the internal exposure level of 6.9 µg/L on which the TWI is based for the sum of the four PFAS in adults is not to be equated with a critical PFAS exposure with regard

[16]Modelling assumption for the onset of pregnancy

[17] Factor 7 for converting the daily tolerable intake to weekly tolerable intake

to the health of the adult person. Which internal exposure level is to be regarded as critical in adults cannot be derived from the data currently available.

3.1.2.6 Uncertainties in the data for the TWI and the derivation of the TWI

According to EFSA (2020a), there are uncertainties with regard to the most sensitive endpoint to be used to derive the health-based guidance value, since studies on the effect on the mammary gland were only carried out in the rodent model with PFOA. No findings exist from animal studies with other species, with other PFAS or from epidemiological studies on this endpoint. In addition, due to the limited amount of data, there are uncertainties with regard to the conclusion on the question of whether the influence of PFOS, PFOA, PFNA and PFHxS on the immune system also leads to a clinically-relevant impairment of the function of the immune system and, for example, there could be a higher incidence of infections. There are also uncertainties and gaps in knowledge with regard to the vulnerability of different age groups.

Further sources of uncertainty in the derivation of the health-based guidance value lie in the assumption of the same effect magnitude for PFOS, PFOA, PFNA and PFHxS and in the methodology of the BMDL derivation and the PBTK modelling (this concerns, among other things, the assumptions on the transfer of PFAS from the maternal serum into breast milk and the calculation of the partition coefficients between blood serum and tissues from animal study data).

In addition, inter-individual variability in the half-life of PFAS in blood serum could not be taken into account.

3.1.3 External exposure

The present estimate of external exposure relates only to food (with the exception of drinking water). Other sources of exposure, such as contact with everyday objects or ingestion of house dust, were not taken into account. The external exposure was estimated on the basis of the available PFAS concentrations from 2007-2020 from food control in Germany and the representative German consumption studies for the age groups from >0.5 to 80 years. The estimate was limited to the sum of the four PFASs included by EFSA in the derivation of the sum TWI (PFOS, PFOA, PFNA, PFHxS). For the respective age groups, exposure with mean consumption results in a range of 4.3 to 19.3 ng/kg BW per week in the LB and 50.6 to 276.8 ng/kg BW per week in the UB.

The large difference between the estimates in the UB and in the LB is mainly due to the uncertainties in the concentration data. This is due, among other things, to the fact that there is a very high proportion of values below the detection and quantification limit. At the same time, despite the exclusion of samples with limits of quantification above 1 µg/kg, the analytical limits are too high, especially for the description of foods that are eaten a lot but have rather low or undetectable levels.

In addition to the uncertainties in the amount of the total exposure, there are also uncertainties in the estimates for the contributions of individual food groups to the total exposure. Sufficient concentration data was only available for the main groups “meat and meat products”, “fish and fish products” and to an extent “milk and dairy products” as well as “vegetables and vegetable products” to enable differentiation between foods with high and low concentrations

in the respective group. In particular, the estimates of the food groups “meat and meat products” and “fish and fish products” are associated with comparably lower uncertainties. The small number of analytical results in other main food groups means that individual main food groups are not well represented by concentration data, individual values in some cases have a very high influence on the overall exposure and the estimate therefore has considerable uncertainties (e.g. "Grains and grain-based products"). Due to these uncertainties, the exposure assessment can only be viewed as an approximate description of the real exposure situation.

Some main food groups could not be included in the exposure assessment due to a lack of concentration data, such as “Legumes, nuts, oil seeds and spices”[18]. Drinking water as a drink was also not included in the exposure assessment. Drinking water proportions in other foods were taken into account in the exposure assessment. Further uncertainties, such as indications of non-representative sampling, are presented in more detail under 3.1.3.4.

Overall, a comparison with the results of the French Total Diet Study (TDS) (Riviere et al., 2014) suggests that the exposure assessment presented here, like the EFSA estimate, may overestimate the PFAS uptake in the average general population.

3.1.3.1 Data set

3.1.3.1.1 Occurrence data

Current data from the food control programs of the federal states from 2007 to 2020 were used as the data set for the evaluation of the PFAS concentrations in Germany.

These data were sent to the BfR by letter dated July 10, 2020 by the Federal Office for Consumer Protection and Food Safety (BVL) on the basis of a data query initiated by the BfR via the BVL by letter dated July 9, 2020 from the food control authorities of the German federal states. The data set includes analytical results from the monitoring programs of the German federal states, as well as from further studies carried out by the federal states' authorities. The data contain measurements for a total of 21 different PFAS. For this report, the BfR has evaluated analytical data of those PFAS, for which a TWI has been derived in the updated EFSA opinion. These are PFOS, PFOA, PFNA and PFHxS (EFSA 2020a). The number of available analytical results for these four PFAS is shown in Table 2. The proportion of values below the quantification limit is high in the data set. PFOS and PFOA were examined more frequently than PFNA and PFHxS. For PFOS, 71.2 % of the concentrations could not be determined, and more than 85 % for the other three PFAS.

Table 2: Overview of the number of measurement results and the proportion of concentrations below the quantification limits of various PFAS in the data obtained from the monitoring programs of the German federal states from January 2007 to June 2020, before the criteria described in the text were applied for exclusion from exposure assessment

PFAS	Number of measurement results	Proportion below the quantification limit [%]
Perfluorooctanesulfonic acid (PFOS)	12,990	71.2

[18] In addition, the following main food groups could not be included in the exposure assessment due to a lack of analytical data: “Animal and vegetable fats and oils”, “Fruit and vegetable juices and nectars”, “Coffee, cocoa, tea”, “Alcoholic beverages”, “Vegan and vegetarian products” and “Sauces and condiments”.

Perfluorohexane sulfonic acid (PFHxS)	7,220	92.7
Perfluorononanoic acid (PFNA)	7,299	87.0
Perfluorooctanoic acid (PFOA)	12,980	85.4

Values below the detection limit or quantification limit were treated with both the LB and the UB. In the LB approach, values below the quantification limit or detection limit were set equal to 0. In the UB approach, values below the detection limit were replaced with the value of the detection limit and values below the quantification limit but above the limit of detection with the value of the quantification limit. If only the quantification limit was given, then values below the detection limit were also replaced with the value of the quantification limit. In contrast to the usual procedure of the BfR, the exposure assessment was carried out with the LB instead of the "modified lower bound"[19] approach. This allows a better comparison with the current EFSA estimate.

A total of 97,857 measurement results were obtained (across all PFAS) from 13,018 examined food samples. The distribution of the measurement results across the various food groups is, however, inhomogeneous. Food of animal origin, especially meat and fish, was examined much more frequently than food of plant origin. For a large part of the foods of plant origin, including some high-consumption foods in this group, no content measurements are available.

84,345 measurements (corresponding to 9,890 samples or partial samples[20]) were excluded from further evaluation, of which:

1) 3,635 samples with a total of 17,796 measurement results, the sampling reason for which suggests non-representative sampling. However, it cannot be ruled out that the other data contain further measurement results from risk-oriented or targeted sampling (see 3.1.3.4).
2) 2,373 samples with 31,585 measurement results with a quantification limit above 1 µg/kg.[21] This exclusion was not made for fish and meat offal, which could usually be detected/determined even with higher detection and quantification limits.
3) 16 samples of milk, with 160 measurement results, as these were sampled with a non-validated method and also had unusually high levels (manual exclusion).
4) 26,998 measurement results due to the exclusion of all results on PFAS except for PFOS, PFOA, PFNA and PFHxS, as these results were not included in the exposure assessment (this did not result in exclusion of samples)
5) 1,397 measurement results for 361 samples as part of the assignment to main food groups. This applies to 79 measurement results on drinking water and food for which the number of samples was not sufficient to evaluate them as a separate food group and which could not be assigned to another food group.
6) A further 7,409 measurement results for 3,505 samples that were not analysed for each of the four PFAS and could therefore not be taken into account in the sum.

The further evaluation of the concentration data hence included 12,512 analytical results for PFOS, PFOA, PFNA and PFHxS from 3,128 samples or partial samples.

[19] In the "modified lower bound", values below the detection limit are replaced with 0 and values below the quantification limit are replaced with the detection limit.

[20] Partial samples occur when, for example, several parts of an animal, such as muscle meat or liver, have been examined.

[21] Measurement results with limits of quantification higher than 1 µg/kg were excluded from the evaluation in line with the EFSA procedure for better comparability.

The samples examined were divided into food groups. Initially, the basis remained the FoodEx2 main group[22] (e.g. “Cereals and cereal-based products”) (EFSA 2015). If little or no foods were examined in a main group like this, the group was evaluated as a whole. When a larger number of food samples had been examined, subgroups were created to allow for a more detailed evaluation. In addition to “meat and meat products” and “fish and fish products”, this also applies to the main group “vegetables and vegetable products”, which could be further subdivided into mushrooms, algae and other vegetables, as well as “milk and dairy products”, which was further divided into processed and unprocessed milk. As a result, the analytical results were assigned to 67 food groups.

For comparison with the TWI, the exposure must be viewed as the sum of the four PFAS, i.e. PFHxS, PFNA, PFOA and PFOS. In order to take into account potential correlations between the levels of PFAS in the food, this total was calculated at the level of the concentration data. The following procedure was used for the formation of this sum:

Handling of measurement results <LOQ/LOD:

- In the LB, the values of the four PFAS for a sample above the quantification limit were added together. Values below the quantification limit were set to 0 and thus not taken into account in the calculation of the total.
- In the UB, different procedures were used depending on whether determinable values were available or not: If it was possible to determine at least one of the four PFAS values of the sample, then only those values which could be determined were added together, analogously to the LB, and the others were set to 0. In the event that all values were below the quantification limit, the value of the highest quantification limit was assigned as the total for the four substances. This prevents the quantification limits from being added together multiple times in the case of several censored values.

Table 3 shows an overview of the mean limits of quantification of the individual PFAS. In most of the main groups, the mean quantification limit for all substances is above 0.5 µg/kg. Exceptions are the main groups “Water and water-based beverages”, “Alcoholic beverages”, “Milk and dairy products” and “Products for babies and toddlers”.

Although measurement results with limits of quantification >1 µg/kg were excluded from further evaluation, the limits of quantification in the evaluated data set are high. The detection and quantification limits were also high in earlier exposure assessments for PFAS, so that the exposure assessments based on them showed great uncertainties. At these limits of quantification, the levels in most of the samples examined for the majority of the main food groups are below the quantification limit.

[22]FoodEx2 is a system developed by EFSA for the classification of food. Based on the main groups, foods are classified further at ever finer levels.

Table 3: Overview of the mean limits of quantification in the various main groups for the PFAS used from the monitoring programs of the German federal states. The information relates to the data set prior to the exclusion of the samples that were not analysed for all four PFAS.

	Mean quantification limit [µg/kg]			
Main food group	**Perfluorohexane sulfonic acid (PFHxS)**	**Perfluorononanoic acid (PFNA)**	**Perfluorooctanoic acid (PFOA)**	**Perfluorooctanesulfonic acid (PFOS)**
Cereals and cereal-based products	0.74	0.74	0.86	0.86
Vegetables and vegetable products	0.59	0.60	0.67	0.66
Starchy roots or tubers and their products	0.99	0.99	0.95	0.95
Fruit and fruit products	0.36	0.42	0.61	0.56
Meat and meat products[a]	0.86	0.84	1.60	1.65
Fish and fish products	0.82	0.82	0.72	0.72
Milk and milk products	0.31	0.27	0.42	0.41
Eggs and egg products	1.00	1.00	0.50	0.52
Sugar, confectionery, and water-based sweet desserts	0.72	0.72	0.66	0.66
Water and water-based beverages	0.01	0.01	0.01	0.01
Alcoholic drinks	n/a	n/a	0.20	0.20
Products for babies and infants	0.29	0.29	0.29	0.29

[a] In the case of offal, data with limits of quantification above 1 µg/kg were not excluded, so values >1 µg/kg may occur here.
n/a: not analysed

Tables 4 to 7 show the number of samples as well as the mean and 95th percentile of the concentrations calculated according to the procedure described above for main food groups, as well as for the subgroups of “Meat and meat products”, “Fish and fish products”, “Vegetables and vegetable products” and “Milk and dairy products”. Most of the samples are in the main groups “Fish and fish products” (n=904) and “Meat and meat products” (n=762).

The number of concentrations above the quantification limit varies between the main food groups. While, for example, in the groups “Starchy roots or tubers and their products” and “Fruit and fruit products” at least one of the four PFAS was determined in only 1.1 % and 0.9 % of the samples, the proportion in the groups “Meat and meat products ”and“ Fish and fish products” is 41.3 % and 45.0 %, respectively.

The main groups "Meat and meat products", "Eggs and egg products" and "Fish and fish products" show the highest concentrations. With an average of 5.38 µg/kg and 52.90 µg/kg, the levels in fish and meat are significantly higher than those of eggs, which have a mean concentration of 0.36 µg/kg. The highest levels in the group “Vegetables and vegetable products” can be traced back to high levels of PFOA in the subgroup algae (23 samples) and PFOS in the subgroup mushrooms (21 samples), which are represented with disproportionate frequency in the present data set in comparison to the amount consumed. A separate evaluation based on the corresponding consumption data was possible for these food groups.

In the main group “Meat and meat products” offal has higher concentrations than muscle meat. Wild boar should be noted as being the animal species with the highest levels. At the same time it should be noted that, regarding the number of samples, both wild boar and offal were sampled disproportionately in relation to consumption. These foods were therefore included in the exposure assessment as a separate food group (taking into account the consumption data for the respective foods). In the subgroup “Fish and fish products”, the highest levels are found in carp, eel and other freshwater fish or their offal.

In the main food group “Cereals and cereal-based products”, results are available for 21 examined samples, of which a content above the quantification limit was reported for only one sample.[23]

Table 4: Concentrations for the sum of PFHxS, PFNA, PFOA and PFOS from the monitoring programs of the German federal states by main food groups in µg/kg using the LB

	Sum (PFHxS, PFNA, PFOA, PFOS)			
Main food group	**No. of samples**	**Proportion of determinable values[a]**	**Mean concentrations [µg/kg]**	**95th percentile concentrations [µg/kg]**
Cereals and cereal-based products	21	4.8 %	0.07	0[b]
Vegetables and vegetable products	184	17.4 %	0.18	1.29
Starchy roots or tubers and their products	95	1.1 %	0.01	0[b]
Fruit and fruit products	108	0.9 %	0.01	0[b]
Meat and meat products	762	41.3 %	52.90	339.87
Fish and fish products	904	45.0 %	5.38	30.00
Milk and milk products	379	13.7 %	0.01	0.04
Eggs and egg products	26	23.1 %	0.36	1.60
Sugar, confectionery, and water-based sweet desserts	34	0 %	0	0
Water and water-based drinks[c]	554	14.4 %	0.001	0.004
Products for babies and infants	61	0 %	0	0

[a] A value was counted as determinable if at least one of the four PFAS was determinable in the sample.
[b] Proportion of determinable values <5 %, therefore in the 95th percentile 0
[c] Without drinking water

[23] Content of PFOA 1.5 µg/kg (LOQ 1 µg/kg), PFOS, PFNA, PFHxS <LOQ (<1 µg/kg), PFPeA 1.5 µg/kg (LOQ 1 µg/kg); Upon request, the BVL confirmed the result as valid after consultation with the examining laboratory

Table 5: Concentrations for the sum of PFHxS, PFNA, PFOA and PFOS from the monitoring programs of the German federal states by food group in the main group "Meat and meat products" in µg/kg using LB.

	Total (PFHxS, PFNA, PFOA, PFOS)			
Food group	**No. of samples**	**Proportion of determinable values[m]**	**Mean Concentrations [µg/kg]**	**95th percentile Concentrations [µg/kg]**
Meat from multiple animals[a]	28	0 %	0	0
Meat from beef/veal	11	72.7 %	1.34	2.95
Meat from mutton/lamb	1	0 %	0	0
Meat from pork	39	25.6 %	0.05	0.01
Meat from other non-game mammals[b]	43	0 %	0	0
Meat from wild boar	68	73.5 %	33.77	236.93
Meat from roe deer	38	2.6 %	0.03	0[l]
Meat from deer	12	0 %	0	0
Meat from other game mammals[c]	4	0 %	0	0
Meat from chicken	38	10.5 %	0.19	1.49
Meat from turkey	39	15.4 %	<0,01	0.02
Meat from other non-game poultry[d]	6	16.7 %	2.37	10.65
Meat from game poultry	8	62.5 %	4.17	16.23
Liver from beef/veal	136	56.6 %	3.67	11.08
Liver from pork	89	14.6 %	0.81	5.56
Liver from mutton/lamb	8	62.5 %	3.83	11.46
Liver from wild boar	89	100.0 %	381.15	808.15
Liver from other game mammals[e]	23	78.3 %	3.40	8.37
Liver from chicken	51	27.5 %	1.05	5.75
Liver from other non-game poultry[f]	1	100.0 %	98.70	98.70
Liver from other game poultry[g]	3	100.0 %	61.88	87.16
Other offal from non-game mammals[h]	5	100.0 %	28.88	63.28
Other offal from wild boar[i]	4	100.0 %	706.66	2037.25
Other offal from hens[i]	1	0 %	0	0
Other offal from other non-game poultry[k]	2	50.0 %	15.20	28.88
Meat, unspecified	15	0 %	0	0

[a] Not further specified with regard to animal species, e.g. from bratwurst
[b] Mammalian meat other than beef/veal, pork, mutton/lamb and game (here: goat, domestic rabbit, horse)
[c] Meat from game animals other than wild boar, roe and buck deer (here: hare)
[d] Poultry meat other than chicken and turkey and game (here: duck, goose, quail)
[e] Liver from mammals other than wild boar (here: roe deer, mouflon, buck deer, fallow deer)
[f] Poultry liver other than chicken and game (here: duck, goose, turkey)
[g] Liver from game fowl (here: wild duck)
[h] Offal other than the liver of mammals, non-game (here: kidney, tongue, pig blood)
[i] Wild boar offal except liver (here: kidney, heart, spleen)
[j] Chicken offal except liver (here: heart)
[k] Offal other than liver of poultry, other than chicken and game (duck heart)
[l] Proportion of determinable values <5 %, therefore in the 95th percentile 0
[m] A value was counted as determinable if at least one of the four PFAS was determinable in the sample

Table 6: Concentrations for the sum of PFHxS, PFNA, PFOA and PFOS from the monitoring programs of the German federal states by food group in the main group "Fish and fish products" in µg/kg using LB.

	Total (PFHxS, PFNA, PFOA, PFOS)			
Food group	**No. of samples**	**Proportion of determinable values[a]**	**Mean concentrations [µg/kg]**	**95th percentile concentrations [µg/kg]**
Fish, unspecified	6	0 %	0	0
Eel	42	52.4 %	6.34	28.41
Trout	183	13.7 %	1.21	4.98
Crustaceans	6	33.3 %	0.50	1.85
Herring	46	23.9 %	0.38	3.57
Atlantic cod	12	75.0 %	0.15	0.31
Carp	152	93.4 %	18.93	47.78
Pollack	31	51.6 %	1.23	0.31
Salmon	50	22.0 %	1.89	11.31
Flatfish (plaice, sole)	41	61.0 %	0.25	0.87
Tuna	96	10.4 %	0.09	0.40
Shellfish	56	32.1 %	0.74	5.22
Pangasius	49	32.7 %	0.70	3.28
Other saltwater fish	12	66.7 %	0.66	2.74
Other freshwater fish	102	70.6 %	9.77	31.28
Offal from freshwater fish	19	100.0 %	12.87	29.46
Offal from saltwater fish	1	100.0 %	0.96	0.96

[a] A value was counted as determinable if at least one of the four PFAS was determinable in the sample.

Table 7: Concentrations for the sum of PFHxS, PFNA, PFOA and PFOS from the monitoring programs of the German federal states by food group in the subgroups "Vegetables and vegetable products" and "Milk and milk products" in µg/kg using LB

	Total (PFHxS, PFNA, PFOA, PFOS)			
Food group	**No. of samples**	**Proportion of determinable values[a]**	**Mean concentrations [µg/kg]**	**95th percentile concentrations [µg/kg]**
Vegetables and vegetable products, except algae, mushrooms	140	0.7 %	<0,01	0
Algae	23	65.2 %	0.54	2.64
Mushrooms	21	76.2 %	0.94	1.39
Milk	332	15.7 %	0.01	0.04
Processed milk	47	0.0 %	0	0

[a] A value was counted as determinable if at least one of the four PFAS was determinable in the sample.

3.1.3.1.2 Consumption studies

A total of three different studies were used to determine consumption: The VELS study (consumption study to determine the food intake of babies and infants for the assessment of the acute toxicity risk from pesticide residues), the National Consumption Study II (NVS II) and the EsKiMo study (nutrition study as a module of the nationwide representative child and adolescent health survey KiGGS). Each of these studies looks at a certain age group, so together the three studies cover an age range from half a year to 80 years. A description of the individual studies can be found in Appendix A.

Preparation of the data

In all four data sets, composite foods and dishes were broken down into their ingredients, e.g. rice or zucchini, in order to enable the best possible assignment to the concentration data available at this level from the monitoring programs of the German federal states. In all consumption studies, however, there are codes from the Federal Food Code (BLS) that contain small proportions of ingredients from other food groups not taken into account, e.g. brown bread with onions, which, in addition to the group “Cereals and cereal-based products”, also contains small proportions of the group “Vegetables and vegetable products”.

For each study, the mean daily consumption was calculated for all participants by adding up all consumption events in each food group and dividing them at the end by the number of interview days (one month in the case of Eskimo/DISHES, see Appendix A). Weekly consumption was then determined by multiplying by 7.

3.1.3.2 Exposure assessment

The exposure was calculated at the individual level by multiplying the individual mean weekly consumption for each food group or food consumed by the mean PFAS concentration of the corresponding food group or the corresponding food for each participant in each consumption study. The respective tables show the key statistical figures (mean, median, 95th percentile of the age groups considered in the consumption studies) for exposure at mean concentrations. The consumption of drinking water as a drink was not taken into account in the exposure assessment. The consumption of all other beverages such as tea, coffee, juices, but also mineral water - provided that concentration data were available - was included in the assessment. Since recording in the VELS study does not differentiate between drinking and mineral water, all drinking water consumption was assumed to be mineral water.

No exposure could be estimated for main food groups for which no analytical results were available when using the concentration data from the monitoring programs of the federal states. In main food groups in which only very little concentration data was available, these were assigned to the total consumption amount of the respective main food group. Exposure is shown below for the sum of PFHxS, PFNA, PFOA and PFOS.

The exposure assessment is given for the following age groups:

- Babies (VELS >0.5 to <1 year)
- Infants (VELS 1 to 2 years)
- Other children
  (3 to 9 years: VELS 3 to 5 years, EsKiMo 6 to 9 years)

- Adolescents
  (10 to 17 years: EsKiMo 10 to 11 years, EsKiMo 12 to 17 years, NVS II 14 to 17 years)
- Adults (18 to 64 years)
- Elderly (65 to 74 years)
- Very elderly (≥ 75 years)

These groups correspond to EFSA's commonly used age groups.
All exposure assessments are presented in nanograms per kilogram BW and per week (ng/kg BW per week).

The high quantification limits for PFAS in food in the present data set (Table 3) lead to a high proportion of data/analytical results below the quantification limits and to a comparatively high exposure assessment in the UB. This results in large differences between the results of the exposure assessments in the LB and in the UB. The exposure for all age groups is many times higher in the UB. The exposure assessment in the LB is shown in the following tables. The corresponding tables for the exposure assessment in the UB can be found in Appendix B.

Table 8 shows the exposure using the consumption data from NVS II and the concentration data from the monitoring programs of the federal states in the LB. The median exposure is 4.4 ng/kg BW per week and the 95th percentile at 19.8 ng/kg BW per week. The mean value is well above the median, which is due to some very highly exposed individuals. Men exhibit higher exposure than women. There is hardly any difference in the median between the age groups.

Table 8: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for adolescents and adults in the German population using data from the monitoring programs of the German federal states in the "Lower Bound" (basis: NVS II; all respondents)

	Total (PFHxS, PFNA, PFOA, PFOS)			
Population group	**Number of people**	**Exposure [ng/kg bw per week]**		
	Valid N	**Mean**	**P50**	**P95**
All (14–80 years)	13,926	8.0	4.4	19.8
Male	6,897	8.7	4.7	21.2
Female	7,029	7.4	4.1	18.6
Adolescents (14-17 years)	744	6.2	4.3	17.3
Adults (18-64 years)	10,525	8.0	4.4	19.8
Seniors (65-74 years)	2,008	8.5	4.4	21.3
Very old (≥ 75 years)	649	8.6	4.4	16.6

Table 9 shows the exposure using the concentration data from the monitoring programs of the German federal states and the LB for adolescents from the EsKiMo sub-study for 12 to 17 year olds. The median is 10.5 ng/kg BW per week and the 95th percentile is 27.7 ng/kg BW per week.

Compared to the group of adolescents aged 14 to 17 years in NVS II, the adolescents' age group demonstrates significantly higher exposure. This is explained by two things: On the

one hand due to the different age structure of the two studies (12-17 years vs. 14-17 years) and on the other hand due to the different methodology in the two consumption surveys.

Table 9: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for adolescents in the German population using data from the monitoring programs of the German federal states in the "Lower Bound" (based on: EsKiMo 12–17 years; all respondents)

	Total (PFHxS, PFNA, PFOA, PFOS)			
Population group	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All (12-17 years)	1,351	12.9	10.5	27.7
Male	694	14.7	12.3	32.8
Female	657	11.0	9.1	23.0

Table 10 shows the exposure using the concentration data from the monitoring programs of the German federal states and the LB for the EsKiMo sub-study for 12 to 17 year olds. At 10.5 ng/kg BW per week, the median exposure in this sub-study is the same as the median from the sub-study dealing with 12 to 17-year-olds. "Other children" (6 to 9 years) have a higher median exposure than "adolescents" (10 to 11 years) (8.8 ng/kg BW per week) with a median of 11.6 ng/kg BW. Boys in this sub-study had a higher exposure (median 11.4 ng/kg BW per week) than girls (median 9.7 ng/kg BW per week).

Table 10: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for children and adolescents in the German population using data from the monitoring programs of the German federal states in the "Lower Bound" (based on: EsKiMo 6-11 years; all respondents)

	Total (PFHxS, PFNA, PFOA, PFOS)			
Population group	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All	1155	14.2	10.5	32.0
Male	587	15.6	11.4	38.9
Female	568	12.7	9.7	29.2
Adolescents (EsKiMo 10-11 years)	388	11.6	8.8	30.9
Other children (EsKiMo 6-9 years)	767	15.5	11.6	34.1

Table 11 displays the statistical key figures for exposure of children aged >0.5 to 5 years from the VELS study using the concentration data from the monitoring programs of the German federal states and application of the LB. Due to their higher consumption in relation to bodyweight, exposure is also higher for children of this age group than for adolescents and adults. The median is 14.7 ng/kg BW per week. The exposure of infants is higher than that of young children, which in turn is higher than the exposure of older children. With 15.5 ng/kg BW per week, boys exhibit higher exposure than girls in this age group (13.8 ng/kg BW per week).

Table 11: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for children in the German population using data from the monitoring programs of the German federal states in the LB (based on: VELS; all respondents)

Population group		Total (PFHxS, PFNA, PFOA, PFOS)		
	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All	732	19.5	14.7	48.5
Male	368	20.7	15.5	50.4
Female	364	18.4	13.8	41.9
Other children (VELS 3-5 years)	297	18.3	13.1	44.5
Infants (VELS 1-2 years)	340	20.4	15.3	49.5
Babies (VELS >0.5–<1 years)	95	20.4	19.3	45.2

Exposure via individual main food groups

An overview of the exposure broken down by age group for consumers of the individual main food groups can be found in Appendix C.

If one considers exposure separately according to main food groups, a very similar picture emerges for all consumption studies. Measured by the median, the main food groups “Fish and fish products” and “Meat and meat products” show the highest exposure for consumers of the respective foods.

The main food group “Cereals and cereal-based products” also exhibits high levels of exposure for their consumers. However, it should be noted that this is based only on 21 analytical results with a single determinable concentration. The high consumption quantities within the main food group “Cereals and cereal-based products” leads to a comparatively high exposure in the LB (over 25 % of total exposure), while taking into account the mean value of these 21 analytical results. This result is therefore subject to great uncertainties and contributes significantly to the uncertainties in the total exposure assessment.

Another main group that exhibits high exposure for its consumers when all consumption studies are considered, is the main group “Eggs and egg products”.
Apart from that, the other main groups - if concentration data were available - exhibit lower exposure.

Food groups with high contributions to exposure in highly exposed persons

In order to identify individual food groups that make a high contribution to exposure, the 5 %[24] of participants with the highest exposure were identified within each of the consumption studies under consideration. Then the 10 food groups were determined which, on average, had the highest contributions to the total exposure for these participants.

[24]In VELS, due to the lower number of participants, a value of 10 % was used instead of the 5 % used in the other studies

An overview of the results of this evaluation can be found in Appendix D. Two food groups in all age groups are among the ten foods with the highest contribution to the total exposure of the highly exposed participants. These are “Meat from wild boar” and “Other freshwater fish[25]”. Also within these 10 food groups they belong to the five food groups with the highest exposure. Almost all identified food groups concern foods of animal origin: other fish species such as eel, carp, salmon, pollack and trout, but also meat and offal from other animals, e.g. the liver of beef and veal, or the meat of game poultry. Most food groups represent seldom consumed foods (proportion of consumers <1 %). Notable exceptions are beef and veal, salmon, pollack and the group “Meat from other non-game poultry”[26], which in all consumption studies shows more than 1% consumers.

In the EsKiMo sub-study, which surveyed the consumption of 12 to 17-year-old adolescents, differences exist with regard to the food groups with the highest contributions to exposure compared to other consumption studies, partly due to the methodology of the consumption survey.
The main food groups “Cereals and cereal-based products” and “Eggs and egg products” are also represented here among the 10 food groups with the highest contribution to total exposure.

3.1.3.3 Comparison with the EFSA opinion of 09/2020

Comparison of the data set and the methodological approaches in the exposure assessment

In both the present opinion and the EFSA opinion (EFSA 2020a), the same consumption surveys are used for exposure assessment in Germany (VELS Study, EsKiMo Study and NVS II). In contrast, the two opinions differ in their concentration data used. The data set from the current opinion is comparable to that of EFSA (2020a) with regard to the number of samples and measurements: In the data set of the EFSA opinion there are 11,528 samples with a total of 97,448 measurements, while the data set of the present opinion contains 13,018 samples with 97,857 measured values. It should be noted that there is a considerable overlap between the two data sets. Data from Germany up to 2016 are either completely or at least partially available in both data sets. Differences in the two data sets result from the fact that the data set of the EFSA opinion also contains samples from other member states. In addition, it was possible to include current data from the monitoring programs up to July 1, 2020 within the present assessment. The proportion of analytical results from 2017 to 2020 is around 40 %.

Exclusion criteria (see 3.1.3.1.1) for inclusion of data into the exposure assessment were applied equally in both opinions with regard to the sampling reason, the level of quantification limit and the 16 samples of milk. Differences in the approach between the two opinions result from the fact that samples were included in the EFSA opinion provided that at least one of the PFAS was measured (with the others assumed to be 0). In contrast, the present opinion only includes samples for which results were available for all four PFAS of relevance to risk characterisation.

[25]The group contains the species of freshwater fish for which insufficient samples were available when the group was formed to justify a separate group, i.e. freshwater fish species other than eel, trout and carp

[26]Poultry except chicken, turkey and game

Another difference is that in the present opinion some food groups had to be excluded for which only insufficient numbers of concentration data were available. Inclusion of data from other member states permitted potential consideration of these food groups in EFSA's exposure assessment and/or separate consideration of the corresponding food groups.

The approach with which the concentration data was grouped and linked to the consumption data in both opinions is very similar. In both cases, the main food groups (FoodEx Level 1) were initially used and sub-groups were only formed for those food groups for which sufficient concentration data was available. In both opinions these are “Meat and meat products”, “Fish and fish products” and “Milk and milk products”. The present opinion includes “Vegetables and vegetable products”. However, concentration data were available in the two opinions for different food groups within these main food groups.

In contrast to the present opinion, drinking water was evaluated as a separate food group in the EFSA opinion. The quantities of drinking water used for the preparation of beverages are also taken into account in the present exposure assessment insofar as concentration data was available for the respective beverages. In the case of children (VELS Study), the amounts of drinking water consumed were also taken into account, as these could not be clearly distinguished from mineral water. They were assigned the PFAS content for mineral water.

Comparison of concentration data

In general, the data from the present opinion show slightly higher percentages of food above the quantification limit compared to the EFSA opinion, especially in food groups of animal origin. In the EFSA data set, a higher proportion of values with 0 is included in the mean value calculation in the LB, which - even with the same values for detectable concentrations - leads to a lower mean value.

Differences result from the different exclusion criteria, but also from the fact that some foods in Germany have higher concentrations than in the European comparison and due to a higher proportion of values below the quantification limits in the EFSA data set for some food groups.

When looking at the food groups with the highest concentrations, the data sets of both opinions exhibit good comparability. The highest concentrations are shown both in the data analysed here from food monitoring in Germany and in the data analysis by EFSA (2020a) for food of animal origin. Within the food groups, both data sets show that offal exhibits higher concentrations than muscle meat. In the case of fish, the highest concentrations are recorded in both data sets for the same species (carp and eel).

Comparison of the results of the exposure assessments

Table 12 shows a comparison of the present exposure assessments with the results of the exposure assessment from EFSA’s opinion (EFSA 2020a). All results are shown in the LB. Consumption studies from many member states were used in EFSA's opinion, shown here is the range between minimum and maximum exposure assessments within the member states, as well as the result using consumption data from Germany.

The results of the exposure assessment using the concentration data from the monitoring programs of the German federal states are within the range of exposure assessments based on the consumption studies of the member states in EFSA's opinion.

A direct comparison with the result of the exposure assessment by EFSA (2020a) using consumption data from Germany demonstrates that the results from this opinion exhibit higher exposures for most age groups. This can be explained by the higher average concentrations in the data from the monitoring programs of the German federal states compared to EFSA's concentration data. The only exception are infants, for whom the EFSA exposure assessment shows a significantly higher exposure. This is due to the higher concentrations in baby food in the EFSA data set (2020a).

In the exposure assessments by EFSA (2020a) and in this opinion, comparable food groups have the largest share of total exposure. These are mainly game, offal and various fish species. In the case of game, particular mention should be made of wild boar meat, which has the highest concentrations and contributes, to a large extent, to the exposure of those who are highly exposed. In the case of animal offal, all exposure assessments show high exposures for consumers of these foods. This is especially true for offal from game. In the case of the various species of fish, particularly carp and eel are represented in both opinions with high levels and a high contribution to exposure for highly exposed persons.

The differences result from the fact that in both opinions different food groups (except fish and meat) are afflicted with very great uncertainties, because these food groups contain relatively few and predominantly indeterminable values, so that the statistical indicators of the concentrations are strongly dependent on whether individual determinable samples occur or not. For example, the high contribution of "Cereals and cereal-based products" in the estimate using the data from the monitoring programs of the German federal states results from a single sample with a concentration above the quantification limit. In the EFSA data set, there is also only one measured value in this group above the quantification limit; however, the significantly higher number of 346 samples in this main food group results in a lower mean exposure. On the other hand, the EFSA data set's "Food for infants and small children" group contains a single measured value above the quantification limit, while all concentrations in the data set for this opinion are below the quantification limit. This means that the contribution of the main food groups to the total exposure in the two estimates differ significantly from one another. The results on the contribution of the main food groups to total exposure are therefore subject to considerable uncertainty in both opinions and are not to be regarded as meaningful, at least for main food groups with a small number of concentration data.

Table 12: Comparison of the exposure assessment for the sum of PFHxS, PFNA, PFOA and PFOS in the present opinion with the exposure assessment from EFSA (2020a) in ng/kg BW per week (mean and 95th percentile of consumption). The results of the exposure assessments are shown using the LB

	Exposure [ng/kg bw per week]					
	Mean			95th percentile		
Age group (Consumption study, age range in years)	Monitoring programmes	EFSA (Europe)[a]	EFSA (Germany)[b]	Monitoring programmes	EFSA (Europe)[a]	EFSA (Germany)[b]
Infants (VELS, >0.5 to <1)	20.4	16.7-85.3	50.5	45.2	31.5-195.2	95.6
Infants (VELS , 1-2)	20.4	10.3-45.6	17.6	49.5	23.5-95.8	47.4
Other children (VELS 3-5)	18.3	5.9-21.5	10.8	45.2	18.6-67.8	25.8
Other children (EsKiMo 6-9)	15.5		9.6	34.1		25.0
Adolescents (EsKiMo 10-11)	11.6	2.9-10.6	7.4	30.9	8.9-36.5	20.2
Adolescents (EsKiMo 12-17)	12.9			27.7		
Adolescents (NVS II, 14–17)	6.2		3.0	17.3		8.9
Adults (18-64)	8.0	3.9-9.4	4.9	19.8	9.1-35.5	12.8
Elderly (65–74 years)	8.5	5.0-14.6	6.4	21.2	12.3-39.1	16.7
Very elderly (≥ 75 years)	8.6	3.0-21.7	6.1	16.6	9.2-69.5	15.5

[a]EFSA Exposure Assessment (2020a), the range of results is given using the consumption studies available from the European member states (minimum - maximum)

[b]EFSA Exposure Assessment (2020a), the result is given using the available consumption studies from Germany for the respective age groups

3.1.3.4 Uncertainties in the exposure assessment

Uncertainties in the concentration data

As already described in the chapter on concentration data, the proportion of concentrations below the detection and quantification limit is high. There are large differences between the main food groups. Sufficient samples were only available for the main groups “Meat and meat products”, “Fish and fish products” and partially for “Milk and dairy products” as well as “Vegetables and vegetable products” to enable a more differentiated analysis of the concentration data of individual foods in these main food groups.

The small number of samples in some main food groups also means that individual values can have a very high influence on the overall exposure, especially in the main food groups with high consumption. For example, a single determinable sample in the main group “Cereals and cereal-based products” (out of a total of only 21 samples) leads to a high contribution

from this main group to the total exposure, while this contribution is estimated to be significantly lower in the EFSA opinion. The estimate of this main food group is therefore subject to particularly high uncertainties.

Another example is the main group “Products for infants and toddlers” in the VELS study for infants. No determinable concentrations are available for this group in this opinion, while in the case of EFSA, one determinable value led to a significantly higher exposure. Accordingly, considerable uncertainties exist in particular in the assessment of the contribution of high-consumption food groups to total exposure, for which only limited concentration data are available.

It should also be taken into account that for some main food groups no concentration data is available at all. Therefore, only part of the total exposure is described, which results in a potential underestimation of the exposure.

The high proportion of values below the detection and quantification limit in combination with the high quantification limits leads to considerable differences between the exposure assessment in the LB and in the UB. Since the exposure of the population can in principle lie within the entire range between the two estimates, this leads to a very high level of uncertainty for the exposure assessment and, as a result, also in the risk characterisation.

Uncertainties due to the regional distribution of concentration data

The BfR has statistically analysed the spatial uniform distribution of sampling intensity (sample size per spatial unit) on the basis of the PFAS concentration data in foods evaluated for this opinion[27]. In the combined analysis for all foods as well as in separate analyses for selected food groups (wild boar, veal/beef, trout and carp), a statistically significant, geographically inhomogeneous sampling intensity was identified for the study period. For three German federal states, no measurements of PFAS concentrations in food were available. Sampling intensity was then examined to identify any correlation to the proportion of measured values above the detection and quantification limits[28]. As a result, sampling intensity proved itself to be a significant predictor for the proportion of detectable measured values.

There are thus indications of a geographically inhomogeneous sampling intensity and a correlation between sampling intensity and concentration data. This could be explained by the increased sampling of food in regions with known higher concentrations in food. The findings could also be explained by a geographically differentiated selection of the sampled food groups. Accordingly, it cannot be ruled out that in regions with higher expected PFAS concentrations in food, food groups were selected for which higher concentrations are usually measured. In addition to the identified uncertainties regarding geographic aspects, potential overestimation of PFAS concentrations may arise on the basis of the data from the German federal states' food monitoring programs.

[27] Square Test (Cressie, N. and Read, T.R.C., 1984) using 30 spatial squares over the entire study area per study year.

[28] Linear models with the proportion of measurements above the detection and quantification limits as a dependent variable and sampling intensity as an independent variable (“predictor”).

Uncertainties in consumption data

All three of the consumption studies used are comparatively old: All data were collected more than ten years ago, and in the case of the VELS study more than 15 years ago. Consumption habits may have changed since then, although it is unclear to what extent and in which direction this affects exposure.

The methodology in the consumption survey for the four (partial) studies is not identical. In the EsKiMo sub-study for 11 to 17 year olds in particular, a different methodology was used from the other three sub-studies, which makes it difficult to compare the results. The other three (sub-) studies also differ in the methodology, but especially in the number of survey days. While the NVS II estimates are based on two 24-hour recalls, EsKiMo records the period of the previous four weeks retrospectively. This affects the comparability of the results of the exposure assessments using the various consumption surveys. This becomes particularly clear when comparing the exposure assessments in overlapping age groups. Both in the EFSA opinion (2020a) and in the exposure assessments of the present opinion there is an overlap between the age groups of the NVS II and the EsKiMo study in the age range of 14-17 years. This means that there are two exposure assessments for this section of the adolescent age group. In both cases, the assessment based on the EsKiMo study for mean consumption is significantly higher than that of NVS II (see Table 12). The difference illustrates the influence of the method used to collect consumption data on the result of the exposure assessment.

Conclusion of uncertainty analysis

Overall, there are great uncertainties in the exposure assessment, which is particularly evident in the large difference between the LB and the UB for the concentration data and, as a result, for the exposure. The present exposure assessment can therefore only be viewed as a rough estimate of the exposure for the population in Germany. There are considerable uncertainties in particular with regard to the estimation of the contribution of high-consumption food groups, for which only a small number of analytical results are available, to the total exposure. EFSA concludes (also in comparison with data from HBM) for its data set that the LB estimates reflect the exposure of the population better than the UB estimates. In the BfR's view, this applies to the same extent to the data from the food monitoring programs of the German federal states, with the restrictions already described.

The results show that the food sampling in the present data set is not evenly distributed across the federal states and regions in Germany. The cause of this heterogeneous sample density could be risk-oriented sampling. The finding indicates that in areas with a higher sample density, significantly higher proportions of concentration measurements are found above the detection and quantification limits. This suggests that the average PFAS concentrations measured in the German federal states' monitoring programs should be viewed as an overestimation of the average levels in Germany.

Furthermore, due to the assignment of food groups with large consumption quantities to concentration data with a very small number of samples and individual values above the quantification limit, it can be assumed that exposure is still being overestimated in the LB; however, it is unclear to what extent.

Comparison with the results of the French TDS (Riviere et al., 2014) also shows that the concentrations and exposure in that study are significantly lower than those presented here. This

might be due to regional differences in the concentrations in food or to the sampling method. Comparison with the results of the BfR MEAL study ("Meals for Exposure Assessment and Analysis of Food", the first German total diet study) will provide further information on this question. However, comparison with the French TDS also indicates that the exposure assessment presented here, like the EFSA assessment, may overestimate the PFAS uptake in the average general population.

3.1.3.5 Summary of the external exposure assessment

Overall, estimation of the external exposure to PFOS, PFOA, PFNA and PFHxS is associated with great uncertainties. In particular, statements on the contribution of different food groups to the total exposure are still subject to considerable uncertainty.

As a result, the BfR's current exposure assessment confirms the conclusions of earlier opinions by the BfR and EFSA that the main food groups "fish and fish products" and "meat and meat products" contribute significantly to exposure to PFOS, PFOA, PFNA and PFHxS. Other animal products that have a smaller share of the total exposure are "eggs and egg products" and "milk and milk products". The role of plant-based foods in the total exposure to the four PFAS can hardly be assessed on the basis of the available data, since the PFAS levels in the vast majority of the plant-based foods examined are below the detection and quantification limits of the currently used analytical methods. The BfR points out that drinking water can also be relevant for exposure, but was not considered in the present opinion.

Food groups with a high contribution to consumer exposure are primarily foods with comparatively high concentrations that are only rarely consumed in most consumption studies, such as wild boar, carp, eel, and other freshwater fish or offal. Some consumption studies identify foods with a high contribution to total consumer exposure and which are consumed more frequently as being beef and veal, salmon, pollack and the group "Meat from other non-game poultry".

As a result, the long-term exposure to PFOS, PFOA, PFNA and PFHxS through the consumption of food other than drinking water in the LB in adults is in the range of 4.4 to 19.8 ng/kg BW per week (median to 95th percentile of consumption).

Overall, the exposure estimate for women is lower than for men in the LB (15 % lower for mean consumption in adult women).

If adolescents aged 14 to 17 years from the study population of the NVS II are considered separately, the mean exposure is somewhat lower compared to adults (23 % lower exposure). Adolescents aged 12 to 17 years and 10 to 11 years within the EsKiMo consumption survey, on the other hand, have a significantly higher exposure than adolescents of the NVS II (108 % and 87 % higher exposure). Here, too, the female participants are less exposed to PFOS, PFOA, PFNA and PFHxS than the male participants (25 % lower exposure in 12 to 17-year-old participants in the EsKiMo consumption survey).

The exposure of younger children (1 to 9 years) to PFOS, PFOA, PFNA and PFHxS is significantly higher than the exposure of adults (factor 2 to 3) and is in the range (median to 95th percentile) from 10.5 to 32.0 ng/kg BW per week (children 6 to 9 years, EsKiMo) or 14.7 to 48.5 ng/kg BW per week (children 1 to 5 years, VELS). Here, too, the exposure of the girls is lower than that of the boys (11 % in the younger children to 19 % in the older children). The

highest bodyweight-related exposure is 19.3 to 45.2 ng/kg BW per week (median to 95th percentile of consumption) in the age group of the infants (>0.5 to <1 year). It should be noted that the consumption survey only takes into account non-breastfed babies.

The results of the exposure assessments in the LB and UB represent the upper and lower limits of the range in which, given representative and complete data, the real level of exposure can be expected. Since the PFOS, PFOA, PFNA and PFHxS concentrations in most food groups within the present data set are, to a high percentage, below the detection and quantification limits of the analytical methods currently used, large differences exist between LB and UB estimates. The BfR shares EFSA's view (2020a) that the UB estimate represents a considerable overestimation of the long-term exposure of the general population in this case, also due to the high quantification limits. The results of the UB exposure assessments in the present BfR results are higher by a factor of 3 to 12 than the LB results[29]. The BfR shares EFSA's view (2020a) that the LB exposure assessments based on the available data represent a more realistic assessment of the external exposure via food compared to the UB exposure assessments. This conclusion is supported by the results of the studies on the internal exposure of the general population, which is more compatible with the LB level of the assessment of external exposure than with the UB.

Risk characterisation should therefore refer to the results of LB exposure assessments. This is associated with a possible underestimation of the total exposure level. Other uncertainties, on the other hand, tend to lead to the assumption that the LB exposure assessment still represents an overestimation of the real exposure situation. Due to these uncertainties, the present exposure assessment can only be viewed as an approximate description of the real exposure situation.

3.1.4 Internal exposure in Germany

The internal exposure of the PFAS accumulating in humans can be determined individually by taking a blood sample and obtaining serum or plasma. Due to the high persistence, these levels are a good measure of the total exposure in the body via all intake routes (“body burden”). They not only reflect the individual internal exposure, but also provide a picture of the current exposure in the population when a representative number of samples are examined. In general, at the current detection limits, the compounds PFOA, PFOS, PFNA and PFHxS can be quantified in blood serum or plasma when the exposure is at background level. For this reason, too, these four compounds were used by EFSA for its 2020 assessment. EFSA used data from an epidemiological study on the vaccination response of one-year-old children as critical effect. Using benchmark dose modelling, a critical internal PFAS exposure level of 17.5 µg/L was calculated for the sum of these four PFAS (“PFAS sum”) as a reference point for this age group and used for the subsequent derivation of a TWI. In a further modelling step, the maternal exposure level corresponding to the exposure level of the one-year-old child was derived (PFAS sum 6.9 µg/L), which enables the mother to breastfeed for one year without her child’s exposure exceeding the level of 17.5 µg/L. In a last modelling

[29]Adults, NVS II: UB exposure higher by a factor of 5 to 12 than in the LB (factor 6.9 in mean, 11.6 in median, 4.9 in P95); Adolescents NVS II: UB exposure higher by a factor of 3 to 12 than in the LB (6.5 in mean, 12 in median, 3 in P95); Adolescents EsKiMo 12-17 years UB exposure higher by a factor of 6 to 8.4 than in the LB (factor 7.4 in mean, 8.4 in median, 6 in P95), adolescents EsKiMo 10-11 years UB exposure higher by a factor of 5 to 11 (factor 8.2 in mean, 10.7 in median, 4.9 in P95), (see Appendix B)

step, the TWI was derived as the weekly intake of the PFAS sum, which does not result in the sum PFAS exposure level of 6.9 µg/L being exceeded in women aged 35.

At the end of the risk assessment, the important question is to what extent certain population groups exceed the TWI. However, in the case of the PFAS assessment, the question on the extent to which the blood serum concentration (internal exposure), on which the TWI is based, is exceeded among adults (PFAS sum 6.9 µg/L) is also important for two reasons: On the one hand, the TWI derived from the blood serum concentration is subject to higher uncertainties than the underlying blood serum concentration of 6.9 µg/L itself, because an additional modelling step was required for its derivation. On the other hand, there are great uncertainties in the external exposure estimate (see 3.1.3.4). For this reason, an estimate of the proportion of the population in Germany who currently have internal exposure above the blood concentration of 6.9 µg/L, corresponding to the TWI, is made on the basis of the available data for internal exposure. The BfR sees this estimate as a reliable addition to the health risk assessment based on external exposure.

3.1.4.1 Adult internal exposure data

The following is a presentation and assessment of the data situation for internal PFAS exposure in Germany. First of all, it should be noted that the concentrations measured in serum/plasma have decreased significantly over the past few decades. Data from the Federal Environmental Specimen Bank show that since 1986 the exposure to the compounds with the highest levels in serum has decreased by more than 70 % (PFOA) or more than 90 % (PFOS) (Umweltbundesamt 2020, Göckener et al., 2020). Current data (from 20 to 29 year olds from Münster) originate from 2017 and 2019 (n=20 each) with median values of 1.7 µg/L (PFOA), 2.6 µg/L (PFOS), 0.4 µg/L (PFNA) and 0.5 µg/L (PFHxS) (n=40, Göckener et al., 2020 and Supplement). A median of 5.8 µg/L (maximum 16.3 µg/L) is calculated for the PFAS sum.

A larger number of samples from adults were examined in 2016 (Fromme et al., 2017). The 158 subjects examined as a control group were healthy blood donors from Munich. The median values were 1.1 µg/L (PFOA), 2.1 µg/L (PFOS), 0.4 µg/L (PFNA) and 0.5 µg/L (PFHxS). From the individual data kindly made available by Prof. Fromme, a median for the PFAS sum of 4.1 µg/L (maximum 23.3 µg/L) was calculated.

In the BfR's RBVD study (Risks and Benefits of a Vegan Diet, Weikert et al., 2020), PFAS was also studied in the 72 test subjects from Berlin examined in 2017[30] (Menzel et al., 2021). The median values were 1.6 µg/L (PFOA), 2.7 µg/L (PFOS), 0.3 µg/L (PFNA) and 1.8 µg/L (PFHxS). A median for the PFAS sum of 7.1 µg/L (maximum 21.6 µg/L) was calculated. Half of the study group consisted of persons with a mixed diet and half were vegans. Those with a mixed diet had significantly higher values for PFOS (median 3.6 vs. 2.3 µg/L) and PFNA (median 0.41 vs. 0.12 µg/L) compared to the vegans. The PFAS sum did not differ significantly in the two groups (median 7.7 vs. 6.4 µg/L, $p = 0.33$). Possible causes for the observed differences are discussed in the work (Menzel et al., 2021).

When comparing the study results from Munich (Fromme et al., 2017) and Berlin (Menzel et al., 2021), a significantly higher internal exposure is noticeable among the Berlin test subjects (median PFAS total 4.1 vs. 7.1 µg/L). The study groups did not differ significantly in age

[30]The analyses were carried out in the same laboratory of the Bavarian State Office for Health and Food Safety as the analyses in the study by Fromme et al., (2017).

(median 39.5 vs. 38.0 years), in the gender ratio (m82: w76 vs. m36: w36) and in the year of the study (2016 vs. 2017); in addition, the samples were analysed in the same laboratory using the same methodology. Due to the design of the study, the doubtless higher proportion of vegans in the Berlin study (50 %) even has a dampening effect on the difference. Examination of the four individual PFAS shows that in the Berlin group PFOA (median + 43 %) and PFOS (median + 32 %) were moderately higher, while PFHxS (median + 269 %) was significantly higher when compared to the Munich test subjects. One can only speculate about the reasons for the differences. For example, regional differences in the PFAS concentrations in drinking water, as well as differing food preferences may be of relevance. Several studies also found positive associations with socio-economic status, for example in the German environmental survey among children and adolescents (GerES V, Duffek et al., 2020, see below). Since the social status was not ascertained during the examination of the blood donors in Munich, no comparison can be made with the Berlin group for this parameter.

According to the results of numerous studies, women have significantly lower PFAS exposure than men. This is probably due to several factors, such as physiological differences including urinary excretion, due to menstruation as well as pregnancy and breastfeeding (EFSA 2020a) or lower external exposure. In the Munich group (Fromme et al., 2017) the median values for the PFAS sum were 5.3 µg/L (n=82 men) and 3.5 µg/L (n=76 women), in the Berlin group (Menzel et al., 2021) 8.2 µg/L (n=36 men) and 6.0 µg/L (n=36 women).

The blood serum concentration of 6.9 µg/L, derived by EFSA (2020a) for the PFAS sum, relates - as shown above - to the internal exposure of a woman, which enables her to breastfeed for one year without her child exceeding the internal exposure level of 17.5 µg/L for the PFAS sum. Therefore, when considering the internal exposure of the population, the proportion of women of childbearing age (18 to 45 years) with PFAS sum blood serum levels above 6.9 µg/L is particularly relevant. For the three studies considered above, this proportion is 30 % (6 of 20, max. PFAS sum 16.3 µg/L, environmental specimen bank Münster 2017/2019), 2 % (1 of 52, max. PFAS sum 7.2 µg/L, Munich 2016) or 36 % (10 of 28, max. PFAS sum 21.4 µg/L, Berlin 2017). These data indicate that there may be large regional differences in PFAS exposure and that a major, representative study on internal PFAS exposure is required in order to make more precise statements about the proportion of women in Germany who have blood serum concentrations above 6.9 µg/L. Relevant data will probably only be forthcoming from the Health and Nutrition Study in Germany (gern study), which will medically examine 12,500 adults nationwide over a period of two years. The start of the study jointly carried out by the Robert Koch Institute and the Max Rubner Institute has been postponed in 2020 due to the coronavirus pandemic and has not yet taken place.

When interpreting the figures mentioned, it should be remembered that the blood serum concentration of 6.9 µg/L for the sum of the four PFAS is not the measure of a critical exposure with regard to women's health, but that exposure below this value permits prolonged breastfeeding without infants exceeding the critical internal PFAS exposure level of 17.5 µg/L at the end of the breastfeeding period. According to a current data collection, 41 % of the infants in Germany are still (partially) breastfed (in addition to complementary food) at the end of the first year of life (Kersting et al., 2020). From the study data on internal exposure presented above (rough assumption: 25 % of women are above the internal exposure level of 6.9 µg/L), it can therefore be roughly estimated that currently around 10 % of infants among the general population in Germany may exceed the PFAS sum of 17.5 µg/L at the age of one year. Due to the sometimes significantly higher exposure of mothers in regions with a high additional release of PFAS into the environment, it is to be expected that the proportion of affected infants who have been breastfed for a long time is correspondingly higher there.

3.1.4.2 Data on internal exposure of children

Relatively current and representative data on internal PFAS exposure of 1109 children and adolescents aged 3 to 17 years from Germany for the years 2014-2017 are available from the German environmental study on the health of children and adolescents (GerES V) (Duffek et al., 2020). The median values were 1.3 µg/L (PFOA), 2.4 µg/L (PFOS) and 0.4 µg/L (PFHxS), the median of PFNA was below the quantification limit. The values for the 95th percentile were 3.2 µg/L (PFOA), 6.0 µg/L (PFOS), 0.7 µg/L (PFNA) and 1.3 µg/L (PFHxS). The median value for the PFAS sum cannot be calculated because the individual values were not published. Interpretation of the data for the age group is also not easy, since concentrations (especially in the first years of life) are heavily dependent on the length of breastfeeding and overall on age, due to the different consumption quantities in relation to bodyweight and due to growth, which leads to a dilution of the concentrations in the blood. In addition, for young children only a few years old, the EFSA concept suggests orientation towards the critical internal exposure level of 17.5 µg/L for PFAS sum, while for older (female) adolescents, with a view to subsequent pregnancy and breastfeeding, orientation on the blood serum concentration of 6.9 µg/L for the PFAS sum would have to be made. In its opinion, EFSA modelled the expected development of PFAS concentrations during childhood for children subject to both prolonged breastfeeding and formula-feeding (EFSA 2020a, Figure 14); it becomes clear that, depending on the level of PFAS exposure of the mothers, prolonged breastfeeding in particular is an important factor for high internal exposure in the first years of life.

3.1.4.3 Human biomonitoring values (HBM values)

In recent years, the German Human Biomonitoring Commission (HBM Commission) has dealt intensively with the data situation on PFAS for various endpoints. In 2016 it derived HBM-I values of 2 and 5 µg/L in blood plasma for PFOA and PFOS (Hölzer et al., 2021). The HBM-I value indicates the concentration of a substance in a body medium below which no risk of health impairment is to be expected and therefore there is no need for action. In 2019 the HBM Commission derived HBM-II values for PFOA and PFOS of 5 and 10 µg/L in the blood plasma for women of childbearing age, and of 10 and 20 µg/L for the other population groups (Schümann et al., 2021). The HBM-II value indicates the concentration of a substance in a body medium above which there is an increased risk of adverse health effects and therefore there is an acute need for measures to reduce exposure and for the provision of medical advice.

For several reasons (different assessment concept, partly different study data and data interpretation, individual values for PFOA and PFOS have been derived), the HBM values cannot be compared directly with the blood serum concentration for the PFAS sum of 6.9 µg/L, on which the EFSA TWI (2020a) is based. However, the HBM-I values for PFOA and PFOS (with the largest proportions of internal exposure in terms of content) in sum meet the stated EFSA value.

3.1.5 Risk characterisation

The risk characterisation is based on the TWI of 4.4 ng/kg BW per week for the sum of the long-chain compounds PFOS, PFOA, PFNA and PFHxS (EFSA 2020a) and the exposure estimate for the four PFAS using the data on their concentrations in food (excluding drinking water) from the national food monitoring programs of the German federal states 2007 to

2020. In addition to data from external exposure assessments, the BfR also uses current published data on internal exposure in Germany for risk characterisation.

The TWI is based on the results of epidemiological studies in which statistical relationships between concentrations of certain PFAS in the blood serum and reduced concentrations of vaccine antibodies (antibody titres) after standard vaccinations[31] were observed in children. The comparison of the study data carried out by EFSA showed that long-term breastfed children are most sensitive at the age of one year (Abraham et al., 2020). Using benchmark dose modelling, a critical internal exposure level of 17.5 µg/L in blood serum was calculated for the sum of the four PFAS as a critical reference point for the internal exposure of the infant age group. With blood serum concentrations below this value, there is a high probability that children will not have a 10 % or more decrease in antibody titres after vaccinations that are caused by exposure to PFOS, PFOA, PFNA and PFHxS. Also for older children, who are presumably less sensitive, this value of the sum of the four PFAS of 17.5 µg/L can, from the BfR's point of view, be used as a reference point for the assessment of internal exposure in the sense of a conservative approach. The immunological study data available to date for adults and adolescents are not sufficiently conclusive to answer the question of whether this value is also suitable for assessing internal exposure for these age groups.

When EFSA derived the TWI, a further modelling step was used to derive the internal maternal exposure level (sum of the four PFAS 6.9 µg/L) corresponding to the critical internal exposure level of the one-year-old child (sum of the four PFAS 17.5 µg/L), which enables the mother to breastfeed for a year without her child exceeding the critical exposure level. However, if the internal exposure level of 6.9 µg PFAS/L blood serum is exceeded (slightly) in adults, this does not mean that there is critical PFAS exposure with regard to the health of the adult person. Which internal exposure level is to be regarded as critical in adults cannot be derived from the immunological study data currently available.

Using a final modelling step, EFSA derived a weekly intake for the sum of the four PFAS (external exposure via food) as a TWI (4.4 ng/kg BW per week for the sum of the four PFAS), which would not lead to the internal exposure level of 6.9 µg/L blood serum for the sum of the four PFAS being exceeded in women, if they are subject to this weekly exposure up to the age of 35.
The methodological approach used in deriving the EFSA's TWI takes into account the exposure of breastfed infants by deriving a weekly lifelong intake that is based on the concentration of the four PFAS in the blood serum of 35-year-old women or the related concentration in breast milk. The comparatively high external exposure of infants during the breastfeeding phase should therefore not be compared with the TWI in the context of a health assessment. Apart from this special case, the TWI derivation by EFSA includes all population groups.

Overall, the estimation of external PFAS exposure is associated with great uncertainties. Since the concentrations in the majority of the studied foods in most of the food groups lies below the detection and quantification limits of the analytical methods currently used, large differences exist between LB and UB estimates. Results of the UB exposure estimates are higher by a factor of 3 to 12 than in the LB. The BfR shares the assessment of EFSA (2020a) that the exposure assessment in the LB currently represents a more realistic assessment of the external exposure via food compared to the UB. The following risk characterisation therefore relates to the results of the exposure assessments in the LB.

[31] Standard vaccinations according to the recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute

The mean value of the long-term exposure of adults in Germany to PFOS, PFOA, PFNA and PFHxS through the consumption of food other than drinking water with mean concentrations in the LB corresponds approximately to twice the level of the tolerable weekly intake derived by EFSA (2020a) for the sum of these four compounds of 4.4 ng/kg BW per week (Tab. 8). The median exposure of adults is in the range of the TWI. This means that the long-term exposure to PFOS, PFOA, PFNA and PFHxS is above the TWI for around 50 % of the participants in the consumption study on which this exposure assessment is based[32]. The median exposure of adolescents also corresponds to the level of the TWI (when considering the adolescents in the NVS II separately) or twice the level of the TWI (when considering the adolescents aged 10 to 17 years in the EsKiMo study). The high (95th percentile) long-term external exposure of adults due to the intake of PFOS, PFOA, PFNA and PFHXs with food (mean concentrations) corresponds to five times the level of the TWI, the high exposure (95th percentile) of adolescents is five to seven times the level of the TWI. The estimate of the external exposure of younger children (1 to 9 years) to the sum of the four PFAS corresponds to two to three times the level of exposure of adults, partly due to the higher consumption in relation to bodyweight. The exposure of this age group with mean concentrations of PFOS, PFOA, PFNA and PFHxS in food corresponds to about three times (median) to eleven times (95th percentile) the level of the TWI.

When assessing TWI exceedances in the age group of children, it must be taken into account that, according to a toxicokinetic modelling by EFSA (2020a), exposure that corresponds to twice the level of the TWI at the age of 1 to 10 does not result in blood levels above 17.5 µg/L. The data from current studies on internal exposure indicate that the blood concentrations of the individual compounds PFOS, PFOA, PFNA and PFHxS in the 95th percentile lie below the sum proportions of these compounds of the $BMDL_{10}$ of 17.5 µg/L[33]. Only individual published maximum values of the blood concentrations of the individual compounds of the children examined are well above these sum proportions of the $BMDL_{10}$ of 17.5 µg/L (Duffek et al., 2020). The exceedance of the TWI, which was calculated to be up to eleven-fold, due to external exposure via food in this age group is therefore not compatible with the results for internal exposure.

- In the overall view of the results of the external and internal exposure assessment for children in this age group at high exposure (95th percentile), the BfR therefore shares EFSA's view that there is a possibility that the exposure of some children is at a level associated with decreased concentrations of antibodies in the blood serum following standard vaccinations.

Overall, the data of the external exposure assessment via food for adults are compatible with the picture that emerges from the results of current studies on internal exposure to the four PFAS in the blood serum of the adult population in Germany, although the internal exposure is apparently somewhat lower than what could have been expected from the data on external exposure.[34] In women of childbearing age from three German cities, it was found that between 2 and 36 % of these women had blood serum concentrations above 6.9 µg/L and were thus subject to long-term exposure above the TWI. From this data (rough assumption: 25 % of women are above the blood serum concentration of 6.9 µg/L), using current data on breastfeeding behaviour, it can be roughly estimated that around 10 % of infants in Germany

[32]NVS II, age 14 to 80 years.

[33]Sum proportions of PFOS, PFOA, PFNA and PFHxA in the blood serum concentration of 17.5 µg/L: 7.7 µg/L for PFOS, 8.5 µg/L for PFOA, 0.3 µg/L for PFNA and 1.1 µg/L for PFHxS (EFSA 2020a).

[34]Median values for the sum of PFOS, PFOA, PFNA and PFHxA are 5.8 µg/L (Göckener et al., 2020), 4.1 µg/L (Fromme et al., 2017) and 7.1 µg/L (Menzel et al., 2021).

at the age of one year may exceed the sum of the four PFAS of 17.5 µg/L (see 3.1.4.1.). With these estimates it should be pointed out that the available data on internal exposure are not based on representative data surveys for the total population in Germany and must therefore be interpreted with caution.

- The overall view of the results of the external and internal exposure assessments for adults and adolescents shows that the exposure to PFOS, PFOA, PFNA and PFHxS in parts of the general population in Germany is at a level that can be associated with a reduced concentration of antibodies in the blood serum after standard vaccinations in long-breastfed[35] infants in the first years of life.
- The BfR shares EFSA's view that this should be viewed as toxicologically adverse, not only with regard to vaccination protection, but also with regard to the general immunological defence against other pathogens.
- So far, the epidemiological data is insufficient to assess whether these children with high exposure to the four PFAS mentioned actually have a generally increased risk of infection.
- At present, there is also insufficient data on the question of whether, at a respective level of exposure, there can be effects on the level of vaccine antibody titres or a clinically relevant functional restriction of the immune system (higher susceptibility to infections, more serious infection processes) also in adults and adolescents.
- Possible risks from reduced formation of vaccine antibodies in children who have been breastfed for a long time are countered by the numerous and well-studied advantages of long breastfeeding for both child and mother. The National Breastfeeding Commission at the Max Rubner Institute has dealt with the risk-benefit assessment and, given the current data, sees no reason to deviate from the existing breastfeeding recommendation. Even worldwide, with knowledge of the findings on PFAS available to date, no scientific committee has recommended restricting breastfeeding (MRI 2021).

3.2 Framework for action and recommendations

Consumers can hardly influence their exposure to PFAS as a ubiquitous environmental contaminant. The results of the present opinion show that the intake of PFAS with food should be reduced. In principle, it is recommended to include drinking water as a source of exposure.

From the results of the risk characterisation and the uncertainties presented both in the exposure assessment and in the toxicological assessment, the BfR derives the following recommendations:

- Toxicology

From the perspective of the BfR, there is a need for research to clarify the molecular mechanisms of the toxicity of PFAS. On the one hand, this concerns the causes of the observed re-

[35] In the first year of life, infants should be breastfed, at least until the beginning of the 5th month exclusively. Even after the introduction of complementary foods - no later than the beginning of the 7th month - infants should continue to be breastfed. The total duration of breastfeeding is determined by mother and child https://www.gesund-ins-leben.de/fuer-fachkreise/bestens-unterstuetzt-durchs-1-lebensjahr/handlungsempfehlungen/stillen/stilldauer/

lationships between PFAS blood serum concentrations and reduced antibody titres after certain vaccinations in children, which are currently largely unclear at the molecular level. Furthermore, the question has to be clarified, via which molecular mechanisms PFAS interact with the immune system and negatively affect its function. Molecular immunological studies can provide valuable information on whether and to what extent PFAS can have an influence on various clinical pictures that are associated with the immune system (e.g. susceptibility to infection or inflammatory diseases).

There is a need for further research to elucidate the molecular effects of PFAS on lipid metabolism, in particular on cholesterol metabolism. Such studies could make a valuable contribution to assessing the adverse nature of the observed effects of PFAS on lipid metabolism in humans.

Overall, there is a need to expand the database on toxicology beyond PFOS, PFOA, PFNA and PFHxS for shorter-chain PFAS and other, exposure-relevant PFAS as well as with regard to possible combination effects.

- Analytics

For the investigation of the levels of PFAS along the food chain, more sensitive methods for the quantitative determination of PFAS must be developed. A high percentage of the PFAS levels in the food groups examined is currently below the detection and quantification limits. This leads to great uncertainties in the exposure estimates. Not only foods of animal origin should be taken into account, but also plant-based foods, especially those that are widely consumed. Since the contribution of feed to the exposure of farm animals to PFAS cannot be ruled out in the case of food of animal origin, correspondingly sensitive analytical methods should also be available for certain feed matrices (e.g. basic feed, compound feed). In the future, the spectrum of the examined PFAS analytes should be continuously expanded to include the standard substances available on the market.

- External exposure

For all age groups of consumers, more data on PFAS levels in food are required for more reliable statements on the level of exposure and the relative contributions of individual food groups.

In regions with special sources of entry of PFAS into the environment, comparatively higher levels can result in regionally produced foods. When collecting data on the levels of PFAS in food, it must be taken into account that these regions are not fully known. It is therefore not possible on the basis of the available data to make a comprehensive statement about the content of PFAS in foods without special sources of entry (the so-called background exposure). In order to reduce these uncertainties in the data on the levels of PFAS in foods, spatially representative sampling would be helpful in the context of studies on the levels of PFAS in foods, especially in foods that are frequently consumed but for which little or no data are currently available.

- Internal exposure and HBM

When estimating exposure, the determination of internal PFAS exposure is of particular importance due to the long half-lives of many PFAS. For this purpose, from the perspective of the BfR, representative HBM data for the population of Germany should be generated

promptly for the levels of PFOS, PFOA, PFNA and PFHxS and other compounds from the PFAS group.

- Human studies on the question of possible PFAS effects in humans

The current TWI derivation of EFSA (2020a) is based on the results of epidemiological studies in which associations between the blood serum concentrations of PFOA, PFNA, PFOS and PFHxS and reduced vaccine antibody titres were observed in children. Overall, however, the data situation still gives an incomplete picture. Further studies, especially with children at the end of the first year of life who have been breastfed for prolonged periods, are necessary in order to generally substantiate the evidence, to answer questions about the strength of the effect of individual PFAS, and to elucidate the underlying mechanism of a reduced immune response. The study should be prospective and include the recording of clinical aspects such as an increased susceptibility to infection. Due to the generally lowered exposure level in Germany, meaningful results can only be expected if the study focuses on regions that were exposed to particularly high levels of PFAS contamination.

In addition to studies on the association between the blood serum concentrations of PFAS and a reduced formation of antibodies in children after vaccinations, such effects should also be investigated in more detail in the long-term in epidemiological studies in older population groups.

New human studies should also be carried out to clarify possible further PFAS effects in humans, e.g. on the question of whether the observed associations between PFAS concentrations and cholesterol levels in the blood are based on a causal relationship and whether or to what extent this actually leads to an increased occurrence of cardiovascular disease and type 2 diabetes.

- PFAS transfer along the food chain

Like other environmental contaminants, PFAS can accumulate via the path “soil - plants/feed - farm animals” along the food chain and thus contribute to consumer exposure, especially through the consumption of food of animal origin.

Currently there are hardly any reliable concentration data on background values in feed for food-producing animals, which can serve as a basis for a realistic assessment of a transfer of PFAS from feed to food of animal origin, taking into account both conventional husbandry systems and those types of animal husbandry that take greater account of animal welfare requirements.

To estimate the transition of PFAS from feed into food of animal origin - including PFAS other than those assessed by EFSA (e.g. short-chain PFAS) and especially with a view to precursor substances for the toxicologically relevant, long-chain PFAS - different experimental approaches must be pursued.

On the one hand, practical studies are necessary to generate the urgently needed background values for PFAS in food of animal origin, while taking into account the main types of husbandry. These data on background concentrations in foods of animal origin form the indispensable basis for a discussion on the derivation of maximum concentrations for foods of animal origin. Initial discussions on this have already begun at EU level.

Furthermore, targeted feeding experiments are to be carried out under controlled conditions, which deal with the diverse and different metabolic behaviour of PFAS in different animal species. The necessity of such investigations is based on the fact that the pattern of PFAS in feed often differs considerably from the pattern of PFAS in food of animal origin. The first results of such experiments are available for selected animal species or types of production, but require specific additions.

4 References

Abraham K, Mielke H, Fromme H, Volkel W, Menzel J, Peiser M, Zepp F, Willich SN, Weikert C (2020) Internal exposure to perfluoroalkyl substances (PFASs) and biological marker in 101 healthy 1-year-old children: associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. Arch Toxicol, 94, 2131–2147

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 12.04.2021

Bach CC, Bech BH, Nohr EA, Olsen J, Matthiesen NB, Bonefeld-Jørgensen EC, Bossi R, Henriksen TB (2016) Perfluoroalkyl acids in maternal serum and indices of fetal growth: the Aarhus birth cohort. Environ Health Perspect, 124, 848–854, https://doi.org/10.1289/ehp.1510046

Banasiak U, Heseker H, Sieke C, Sommerfeld C, Vohmann C. (2005) Abschätzung der Aufnahme von Pflanzenschutzmittelrückständen in der Nahrung mit neuen Verzehrsmengen für Kinder. BGBL, 1, 98

Bao WW, Qian ZM, Geiger SD, Liu E, Liu Y, Wang SQ, Lawrence WR, Yang BY, Hu LW, Zeng XW, Dong GH (2017) Gender-specific associations between serum isomers of perfluoroalkyl substances and blood pressure among Chinese: isomers of C8 Health Project in China. Sci Total Environ, 607–608, 1304–1312, https://doi.org/10.1016/j.scitotenv.2017.07.124

Benninghoff AD, Orner GA, Buchner CH, Hendricks JD, Duffy AM and Williams DE (2012) Promotion of hepatocarcinogenesis by perfluoroalkyl acids in rainbow trout. Tox Sci, 125, 69–78

Benskin, JP, De Silva, AO, Martin, JW (2010) Isomer Profiling of Perfluorinated Sub-stances 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

Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SP (2011) Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. Integr Environ Assess Manag 7, 513−541, DOI:10.1002/ieam.258

Buck RC, Gannon SA (2017) Perfluorohexanoic acid pharmacokinetics in mouse, rat, micro-minipig, pig, monkey and human. In: 253rd ACS National Meeting & Exposition, San Francisco, CA, United States, 2017. American Chemical Society, San Francisco, CA, United States ENVR-881

C8 Science Panel (2012) http://www.c8sciencepanel.org/prob_link.html, last accessed 13.04.2021

Catelan D, Biggeri A, Russo F, Gregori D, Pitter G, Da Re F, Fletcher T, Canova C (2021) Exposure to Perfluoroalkyl Substances and Mortality for COVID-19: A Spatial Ecological Analysis in the Veneto Region (Italy). Int J Environ Res Public Health 18 (5) 2734

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

Dong Z, Wang H, Yu YYB, Naidu R, Liu Y (2019) Using 2003-2014 U.S. NHANES data to determine the associations between per- and polyfluoroalkyl substances and cholesterol: trend and implications. Ecotox Environ Safe, 173, 461–468

Duffek A, Conrad A, Kolossa-Gehring M, Lange R, Rucic E, Schulte C, Wellmitz J (2020) Per- and polyfluoroalkyl substances in blood plasma – Results of the German Environmental Survey for children and adolescents 2014-2017 (GerES V). Int J Hyg Environ Health 228,113549

ECHA (European Chemicals Agency) (2018) 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 2018, available online at https://echa.europa.eu/documents/10162/61e81035-e0c5-44f5-94c5-2f53554255a8, last accessed 03.03.2021

EFSA (European Food Safety Authority) (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

EFSA (European Food Safety Authority) (2015) The food classification and description system FoodEx 2 (revision 2). EFSA Supporting Publications, 12, EN-804

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 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 17.03.2021

EFSA (European Food Safety Authority) Scientific Committee (2019) Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 17 (3) 5634, 77 pp. https://doi.org/10.2903/j.efsa.2019.5634

EFSA (European Food Safety Authority) (2020a) Scientific Opinion on the risk to human health related to the presence of perfluoroalkyl substances in food. EFSA Journal 18 (9) 6223, 391 pp. https://doi.org/10.2903/j.efsa.2020.6223

EFSA (European Food Safety Authority) (2020b) Outcome of a public consultation on the draft risk assessment of perfluoroalkyl substances in food. EFSA supporting publication 2020: EN-1931. 202 pp. DOI:10.2903/sp.efsa.2020.EN-1931

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 (2) e56969

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

Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss Ronald M, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen M-R, Tokgözoğlu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL (2017) Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel European Heart Journal 38, 2459–2472. DOI:10.1093/eurheartj/ehx144

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 adolescents: results from the C8 Health Project. Arch Pediatr Adolesc Med 164,860-869

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

Glüge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D, Lohmann R, Ng C A, Trier X, Wang Z (2020) An overview of the uses of per- and polyfluoroalkyl substances (PFAS) Environ Sci: Processes Impacts 22, 2345. DOI: 10.1039/d0em00291g

Göckener B, Weber T, Rüdel H, Bücking M, Kolossa-Gehring M (2020) Human biomonitoring of per- and polyfluoroalkyl substances in German blood plasma samples from 1982 to 2019. Environ Int 145,106123

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 4 years 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 as-sociated 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

Hartmann BM, Bell S, Vásquez-Caicedo AL, Götz A, Brombach C (2006) Der Bundeslebensmittelschlüssel – Aktuelle Entwicklungen, Potenzial und Perspektiven. Ernährungs-Umschau, 53, 124-29

Hölzer J, Lilienthal H, Schümann M (2021) Human Biomonitoring (HBM)-I values for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) - Description, derivation and discussion. Regul Toxicol Pharmacol 121, 104862

Holmquist H, Schellenberger S, van der Veen I, Peters GM, Leonards PEG, Cousins IT (2016) Properties, performance and associated hazards of state-of-the-art durable water repellent (DWR) chemistry for textile finishing. Env Int, 91, 251-264. https://doi.org/10.1016/j.envint.2016.02.035

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

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

Impinen A, Longnecker MP, Nygaard UC, London SJ, Ferguson KK, Haug LS, Granum B (2019) Maternal levels of perfluoroalkyl substances (PFASs) during pregnancy and childhood allergy and asthma related outcomes and infections in the Norwegian Mother and Child (MoBa) cohort. Environ Internat 124, 462–472

Jain RB, Ducatman A (2019) Roles of gender and obesity in defining correlations between perfluoroalkyl substances and lipid/lipoproteins. Sci Total Environ, 653, 74–81

Kersting M, Hockamp N, Burak C, Lücke T (2020) Studie zur Erhebung von Daten zum Stillen und zur Säuglingsernährung in Deutschland – SuSe II. 14. DGE-Ernährungsbericht, Vorveröffentlichung Kapitel 3, https://www.dge.de/fileadmin/public/doc/ws/dgeeb/14-dge-eb/14-DGE-EB-Vorveroeffentlichung-Kapitel3.pdf, last accessed 13.04.2021

Kwon EJ, Shin JS, Kim BM, Shah-Kulkarni S, Park H, Kho YL, Park EA, Kim YJ and Ha EH (2016) Prenatal exposure to perfluorinated compounds affects birth weight through GSTM1 polymorphism. JOEM, 58, e198–e205, https://doi.org/10.1097/JOM.0000000000000739

Lau C (2015) Perfluorinated compounds: an overview. J.C. DeWitt (Ed.), Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances, Molecular and Integrative Toxicology, Humana Press, London, pp. 1-21. DOI 10.1007/978-3-319-15518-0

Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, Jakobsson K (2018) 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. Regul Toxicol and Pharmacol 59, 157-175

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

Luz AL, Anderson JK, Goodrum P, Durda J (2019) Perfluorohexanoic acid toxicity, part I: Development of a chronic human health toxicity value for use in risk assessment. Regul Toxicol Pharmacol 103, 41–55. https://doi.org/10.1016/j.yrtph.2019.01.019

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

Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P (2018) Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. EJPH, 28, 180–185. https://doi.org/10.1093/eurpub/ckx066

Meng Q, Inour K, Ritz B, Olsen J and Liew Z (2018) Prenatal exposure to perfluroralkyl substances and birth outcomes: an updated analysis from the Danish National Birth Cohort. Int J Environ Res Publ Health, 15, 1832. https://doi.org/10.3390/ijerph15091832

Mensink G, Heseker H, Richter A, Stahl A, Vohmann C (2007) Forschungsbericht Ernährungsstudie als KIGGS-Modul (Eskimo) (Universität Paderborn, Robert Koch-Institut)

Menzel J, Abraham K, Völkel W, Fromme H, Schwerdtle T, Weikert C (2021) Internal exposure to perfluoroalkyl substances (PFASs) in vegans and omnivores. Int J Hyg Environ Health (in press)

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

MRI, Max Rubner-Institut (2008a) Nationale Verzehrsstudie II, Ergebnisbericht Teil 2- Die bundesweite Befragung zur Ernährung von Jugendlichen und Erwachsenen (Max-Rubner-Institut: Karlsruhe)

MRI, Max Rubner-Institut (2008b) Nationale Verzehrsstudie II. Ergebnisbericht Teil 1. Die bundesweite Befragung zur Ernährung von Jugendlichen und Erwachsenen

MRI, Max Rubner-Institut (2021) Per- und polyfluorierte Alkylsubstanzen (PFAS) und Stillen: Nutzen-Risiken-Abwägungen. Stellungnahme der Nationalen Stillkommission vom 28.01.2021, available online at www.mri.bund.de

Nau H, Steinberg P, Kietzmann M (2003) Lebensmitteltoxikologie - Rückstände und Kontaminanten: Risiken und Verbraucherschutz. Parey Buchverlag. ISBN 3-8263-330-6

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

Nian M, Li Q-Q, Bloom M, Qian Z, Syberg KM, Vaughn MG, Wang S-Q, Wei Q, Zeeshan M, Gurram N, Chu C, Wang J, Tian Y-P, Hu L-W, Liu K-K, Yang B-Y, Liu R-Q, Feng D, Zeng X-W, Dong G-H (2019) Liver function biomarkers disorder is associated with exposure to perfluoroalkyl acids in adults: isomers of C8 Health Project in China. Environmental Research, 172, 81–88, https://doi.org/10.1016/j.envres.2019.02.013

Nilsson H, Kärrman A, Rotander A, van Bavel B, Lindström G, Westberg H (2013) Biotransformation of fluorotelomer compound to perfluorocarboxylates in humans. Environ Int 51, 8-12

Norwegian Environment Agency (2018) Investigation of Sources to PFHxS in the Environment. Final Report bipro and ETH Zürich M-961

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, last accessed 17.03.2021

NTP (National Toxicology Program) (2019a) NTP technical report on the toxicity studies of perfluoroalkyl carboxylates (perfluorohexanoic acid, perfluorooctanoic acid, perfluorononanoic acid, and perfluorodecanoic acid) administered by gavage to sprague dawley (Hsd:Sprague Dawley SD) rats. NTP TOX 97. Research Triangle Park, North Carolina, USA, available online at http://ntp.niehs.nih.gov

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, last accessed 13.07.2018

OECD (2018) Toward a new comprehensive global database of per- and polyfluoroalkyl substances (PFASs): summary report on updating the OECD 2007 list of per- and polyfluoroalkyl substances (PFASs) Environment, Health and Safety Publications Series on Risk Management No. 39 ENV/JM/MONO(2018)7, available online at http://www.oecd.org/env/ehs/risk-management/series-on-risk-management-publications-by-number.htm, last accessed 12.04.2021

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, 118-125

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL and Zobel LR (2007) Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect, 115, 1298–1305

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

Prevedouros K, Cousins IA, Buck R, Korzeniowski S H (2006) Sources, Fate and Transport of Perfluorocarboxylates. Env Sci Technol 40 (1). DOI: 10.1021/es0512475

Riviere G, Sirot V, Tard A, Jean J, Marchand P, Veyrand B, Le Bizec B, Leblanc JC (2014) Food risk assessment for perfluoroalkyl acids and brominated flame retardants in the French population: results from the second French total diet study. Sci Total Environ, 491-492, 176-83

Salihovic S, Stubleski J, Kärrman A, Larsson A, Fall T, Lind L, Lind PM (2018) Changes in markers of liver function in relation to changes in perfluoroalkyl substances - a longitudinal study. Environ Int, 117, 196–203. https://doi.org/10.1016/j.envint.2018.04.052

Schümann M, Lilienthal H, Hölzer J (2021) Human Biomonitoring (HBM)-II values for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) - Description, derivation and discussion. Regul Toxicol Pharmacol 121, 104868

Seals R, Bartell SM, Steenland K (2011) Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. Environ Health Perspect, 119, 119-124

Seo SH, Son MH, Choi SD, Lee DH, Chang YS (2018) Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. Environ Int, 113, 149-161. https://doi.org/10.1016/j.envint.2018.01.025

Sieke C, Lindtner O, Banasiak U (2008a) Pflanzenschutzmittelrückstände-Nationales Monitoring: Abschätzung der Verbraucherexposition, Teil 1, Deutsche Lebensmittel-Rundschau, 104, 275-79

Sieke C, Lindtner O, Banasiak U (2008b) Pflanzenschutzmittelrückstände-Nationales Monitoring: Abschätzung der Verbraucherexposition; Teil 2. DLR, 104, 336-342

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

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

Umweltbundesamt (2020) Schwerpunkt PFAS, Magazin des Umweltbundesamtes, Heft 1/2020, available online at https://www.umweltbundesamt.de/publikationen/schwerpunkt-1-2020-pfas-gekommen-um-zu-bleiben, last accessed 12.04.2021

Vanden Heuvel JP, Kuslikis BI, Van Rafelghem MJ, Peterson RE (1991) Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. J Biochem Mol Toxicol 6, 83-92

Weikert C, Trefflich I, Menzel J, Obeid R, Longree A, Dierkes J, Meyer K, Herter-Aeberli I, Mai K, Stangl GI, Müller SM, Schwerdtle T, Lampen A, Abraham K (2020) Der Versorgungsstatus mit Vitaminen und Mineralstoffen bei veganer Ernährungsweise. Dtsch Arztebl Int 117, 575-582

White SS, Calafat AM, Kuklenyik Z, Villanueva L, Zehr RD, Helfant L, Strynar MJ, Lindstrom AB, Thibodeaux JR, Wood C, Fenton SE (2007) Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. Tox Scie, 96, 133–144

White SS, Kato K, Jia LT, Basden BJ, Calafat AM, Hines EP, Stanko JP, Wolf CJ, Abbott BD, Fenton SE (2009) Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. Reprod Toxicol, 27, 289–298. https://doi.org/10.1016/j.reprotox.2008.11.054

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

Xu YL, Fletcher T, Pineda D, Lindh CH, Nilsson C, Glynn A,Vogs C, Norström K, Lilja K, Jakobsson K, (2020) Serum Half-Lives for Short-and Long-Chain Perfluoroalkyl Acids after Ceasing Exposure from Drinking Water Contaminated by Firefighting Foam. Environ Health Persp 128 (7) https://doi.org/10.1289/EHP6785

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) 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 47, 10619–10627

Appendix A: Description of the individual consumption studies

VELS

Consumption data from the VELS study (consumption study to determine the food intake of infants and toddlers for the assessment of an acute toxicity risk from pesticide residues) was used as the basis for data on consumption for children under 6 years of age (Banasiak et al., 2005). This nationwide study was carried out from 2001 to 2002 in Germany, covering 816 infants and young children aged from 6 months to under 5 years old. Parents kept 3-day nutritional logs twice for each child on all food consumed. No children who were still breastfed were included in the consumption survey. The intake calculation was based on consumption data for children between the ages of 2 and 5 with an average bodyweight of 16.15 kg. Due to the presence of single-day consumption data, two three-day nutritional protocols are suitable for exposure assessments for both acute and chronic risks.

EsKiMo

EsKiMo (nutrition study as a KiGGS module) was carried out by the Robert Koch Institute and the University of Paderborn as part of KiGGS, the nationwide representative children's and youth health survey, and financed by the Federal Ministry of Food, Agriculture and Consumer Protection (Mensink et al., 2007). The EsKiMo study was carried out in 2006 with approx. 2,400 children and adolescents aged 6 to 17 throughout Germany. The survey was carried out using two survey methods. With the help of their parents, the 6- to 11-year-old children filled out a food diary on three consecutive days, in which they noted all the food they had eaten and their quantities, along with details on preparation, etc. A "dietary history" interview was undertaken with the 12 to 17 year olds with the help of the "DISHES" programme and enquiries were made into their usual consumption over the last four weeks. In addition, they also filled out a consumption frequency questionnaire. The methodology used for 12 to 17 year olds provides good estimates of the long-term intake of substances when grouping foods into general categories or looking at foods that are consumed regularly. The methodology used for 6 to 11 year olds is suitable for both exposure estimates for acute and chronic risks due to the availability of consumption information on individual days.

National Consumption Study II (NVS II)

NVS II is currently the most recent representative study for food consumption in the German population. The study, which surveyed about 20,000 individuals aged between 14 and 80 on their eating habits using three separate survey methods (dietary history, 24-hour recall and weighing protocol), was conducted between 2005 and 2006 throughout Germany (MRI 2008b, 2008a)

The analyses are based on the data from the two independent 24h-recalls from NVS II, which were surveyed in a computer-aided interview using "EPIC-SOFT" (MRI 2008b, 2008a). Data was evaluated from 13,926 people for whom both interviews were available. Due to the presence of consumption data for individual days, the 24-hour recall method is suitable for use in exposure assessments considering both acute and chronic health risks.

Appendix B: Exposure assessment in the Upper Bound

Table B 1: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for adolescents and adults in the German population using data from the monitoring programs of the German federal states in the UB (based on: NVSII; all respondents)

Population group	Sum (PFHxS, PFNA, PFOA, PFOS)			
	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All	13926	55.2	50.9	97.1
Male	6897	54.4	49.8	96.0
Female	7029	56.0	52.1	98.0
Adolescents (NVS II)	744	55.6	51.8	93.7
Adults	10525	54.9	50.6	97.2
Elderly (65-74 years)	2008	56.2	51.1	103.4
Very elderly (≥75 years)	649	56.3	53.1	98.0

Table B 2: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for adolescents in the German population using data from the monitoring programs of the German federal states in the UB (based on: EsKiMo 12–17 years; all respondents)

Population group	Sum (PFHxS, PFNA, PFOA, PFOS)			
	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All	1,351	96.2	89.1	167.7
Male	694	100.7	93.6	171.8
Female	657	91.4	86.1	160.1
Adolescents (EsKiMo 12-17)	1,351	96.2	89.1	167.7

Table B 3: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for children and adolescents in the German population using data from the monitoring programs of the German federal states in the UB (based on: EsKiMo 6-11 years; all respondents)

Population group	Sum (PFHxS, PFNA, PFOA, PFOS)			
	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All	1,155	120.2	113.8	194.5
Male	587	125.7	118.8	211.0
Female	568	114.5	108.3	181.4
Adolescents (EsKiMo 6-11)	388	95.5	94.1	152.4
Other children (EsKiMo 6-11)	767	132.7	130.0	203.7

Table B 4: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for children in the German population using data from the monitoring programs of the German federal states in the UB (based on: VELS; all respondents)

Population group	Sum (PFHxS, PFNA, PFOA, PFOS)			
	Number of people	Exposure [ng/kg bw per week]		
	Valid N	Mean	P50	P95
All	732	194.6	180.0	326.0
Male	368	198.8	182.5	327.3
Female	364	190.5	176.4	322.8
Other children (VELS 3-5)	297	167.0	159.3	241.4
Toddlers (VELS)	340	196.9	190.4	294.9
Infants (VELS)	95	273.2	276.8	373.9

Appendix C: Exposure according to main food groups

Table C 1: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS via the respective food groups in ng/kg bw per week for adolescents and adults in the German population using concentration data from the monitoring programs of the German federal states (based on: NVS II; only consumers). No concentration data are available in the main food groups listed with "n/a".

	Sum (PFHxS, PFNA, PFOA, PFOS) LB			Sum (PFHxS, PFNA, PFOA, PFOS) UB		
	Exposure [ng/kg bw per week]					
Main food group	**Mean**	**P50**	**P95**	**Mean**	**P50**	**P95**
Cereals and cereal-based products	1.6	1.5	3.2	17.1	15.5	34.0
Vegetables and vegetable products	0.3	<0.1	1.9	4.7	3.8	11.7
Starchy roots or tubers and their products	0.1	0.1	0.2	7.5	6.3	17.0
Legumes, nuts, oil seeds and spices	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and fruit products	0.2	0.2	0.6	6.3	4.9	16.5
Meat and meat products	3.5	0.5	12.2	6.0	3.0	16.9
Fish and fish products	7.6	3.5	19.5	10.4	6.4	25.8
Milk and milk products	0.1	<0.1	0.5	11.4	8.3	32.0
Eggs and egg products	0.8	0.5	2.6	2.0	1.3	6.3
Sugar, confectionery, and water-based sweet desserts	0	0	0	2.9	2.1	8.3
Animal and vegetable fats and oils	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and vegetable juices and nectars	n/a	n/a	n/a	n/a	n/a	n/a
Water and water-based drinks[a]	0.1	<0.1	0.1	0.5	0.4	1.1
Coffee, cocoa and tea	n/a	n/a	n/a	n/a	n/a	n/a
Alcoholic drinks	n/a	n/a	n/a	n/a	n/a	n/a
Products for infants and toddlers	None Consumption	None Consumption	None Consumption	None Consumption	None Consumption	None Consumption
Vegan/vegetarian products	n/a	n/a	n/a	n/a	n/a	n/a
Sauces and condiments	n/a	n/a	n/a	n/a	n/a	n/a

[a] Without drinking water

Table C 2: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS via the respective food groups in ng/kg bw per week for adolescents in the German population using concentration data from the monitoring programs of the German federal states (based on: EsKiMo 12–17 years; only consumers). No concentration data are available in the main food groups listed with "n/a".

Main food group	Sum (PFHxS, PFNA, PFOA, PFOS) LB			Sum (PFHxS, PFNA, PFOA, PFOS) UB		
	Exposure [ng/kg bw per week]					
	Mean	P50	P95	Mean	P50	P95
Cereals and cereal-based products	3.0	2.8	5.7	31.2	29.0	59.8
Vegetables and vegetable products	0.4	0.1	2.0	9.2	7.3	23.2
Starchy roots or tubers and their products	0.1	0.1	0.3	10.4	8.7	23.5
Legumes, nuts, oil seeds and spices	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and fruit products	0.3	0.2	0.8	7.8	5.5	22.9
Meat and meat products	5.6	4.1	14.4	9.3	7.5	22.2
Fish and fish products	2.9	1.1	11.5	3.6	1.6	13.0
Milk and milk products	0.4	0.3	1.1	17.1	13.9	40.1
Eggs and egg products	1.1	0.8	2.9	2.6	2.0	6.9
Sugar, confectionery, and water-based sweet desserts	0	0	0	5.6	4.2	15.5
Animal and vegetable fats and oils	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and vegetable juices and nectars	n/a	n/a	n/a	n/a	n/a	n/a
Water and water-based drinks[a]	0.1	0.1	0.2	0.7	0.6	1.5
Coffee, cocoa and tea	n/a	n/a	n/a	n/a	n/a	n/a
Alcoholic drinks	n/a	n/a	n/a	n/a	n/a	n/a
Products for infants and toddlers	no consumption	no consumption	no consumption	no consumption	no consumption	no consumption
Vegan/vegetarian products	n/a	n/a	n/a	n/a	n/a	n/a
Sauces and condiments	n/a	n/a	n/a	n/a	n/a	n/a

[a] Without drinking water

Table C 3: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS via the respective food groups in ng/kg bw per week for children and adolescents in the German population using concentration data from the monitoring programs of the German federal states (based on: EsKiMo 6-11 years; only consumers). No concentration data are available in the main food groups listed with "n/a".

	Sum (PFHxS, PFNA, PFOA, PFOS) LB			Sum (PFHxS, PFNA, PFOA, PFOS) UB		
Main food group	**Exposure [ng/kg bw per week]**					
	Mean	**P50**	**P95**	**Mean**	**P50**	**P95**
Cereals and cereal-based products	3.8	3.6	6.6	39.9	37.6	69.8
Vegetables and vegetable products	0.4	<0.1	2.1	8.3	6.9	19.2
Starchy roots or tubers and their products	0.2	0.1	0.4	13.0	10.8	31.4
Legumes, nuts, oil seeds and spices	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and fruit products	0.4	0.3	1.0	10.8	9.1	26.7
Meat and meat products	4.0	0.9	15.7	8.7	5.8	24.5
Fish and fish products	10.0	6.6	22.2	13.1	9.1	29.7
Milk and milk products	0.6	0.5	1.5	23.2	19.6	54.2
Eggs and egg products	1.8	1.4	5.2	4.4	3.4	12.5
Sugar, confectionery, and water-based sweet desserts	0	0	0	10.1	7.3	30.5
Animal and vegetable fats and oils	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and vegetable juices and nectars	n/a	n/a	n/a	n/a	n/a	n/a
Water and water-based drinks[a]	0.1	0.1	0.1	0.6	0.5	1.2
Coffee, cocoa and tea	n/a	n/a	n/a	n/a	n/a	n/a
Alcoholic drinks	n/a	n/a	n/a	n/a	n/a	n/a
Products for infants and toddlers	no consumption	no consumption	no consumption	no consumption	no consumption	no consumption
Vegan/vegetarian products	n/a	n/a	n/a	n/a	n/a	n/a
Sauces and condiments	n/a	n/a	n/a	n/a	n/a	n/a

[a] Without drinking water

Table C 4: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS via the respective food groups in ng/kg bw per week for children in the German population using concentration data from the monitoring programs of the German federal states (based on: VELS; only consumers). No concentration data are available in the main food groups listed with "n/a".

	Sum (PFHxS, PFNA, PFOA, PFOS) LB			Sum (PFHxS, PFNA, PFOA, PFOS) UB		
Main food group	**Exposure [ng/kg bw per week]**					
	Mean	**P50**	**P95**	**Mean**	**P50**	**P95**
Cereals and cereal-based products	4.0	3.7	6.5	41.6	39.5	68.7
Vegetables and vegetable products	0.7	<0.1	3.6	11.4	10.0	25.9
Starchy roots or tubers and their products	0.2	0.2	0.5	16.8	14.9	38.4
Legumes, nuts, oil seeds and spices	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and fruit products	0.7	0.7	1.6	20.2	18.1	43.2
Meat and meat products	7.2	2.3	29.0	12.3	7.6	35.2
Fish and fish products	9.1	5.8	24.1	12.0	8.3	30.8
Milk and milk products	1.1	0.8	3.1	62.4	57.7	126.6
Eggs and egg products	2.3	1.9	6.3	5.5	4.5	15.1
Sugar, confectionery, and water-based sweet desserts	0	0	0	0.8	0.7	2.0
Animal and vegetable fats and oils	n/a	n/a	n/a	n/a	n/a	n/a
Fruit and vegetable juices and nectars	n/a	n/a	n/a	n/a	n/a	n/a
Water and water-based drinks[a]	0.1	0.1	0.2	0.8	0.7	2.0
Coffee, cocoa and tea	n/a	n/a	n/a	n/a	n/a	n/a
Alcoholic drinks	n/a	n/a	n/a	n/a	n/a	n/a
Products for infants and toddlers	0	0	0	26.9	17.0	82.2
Vegan/vegetarian products	n/a	n/a	n/a	n/a	n/a	n/a
Sauces and condiments	n/a	n/a	n/a	n/a	n/a	n/a

[a] Without drinking water

Appendix D: Food groups with high contributions to exposure in highly exposed persons

Table D 1: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for the consumers of the ten food groups with the highest proportions of mean intake in ng/kg bw per week for adolescents and adults in the German population using concentration data from the monitoring programs of the German federal states (based on: NVS II; only consumers)

No.	Food group	N Consumer	LB		
			Mean	P50	P95
1	Meat from wild boar	31 (<1 %)	241.8	180.2	558.7
2	Carp	22 (<1 %)	199.9	155.5	567.7
3	Other offal from non-game mammals[a]	42 (<1 %)	139.0	122.4	278.6
4	Other freshwater fish	52 (<1 %)	73.1	65.0	141.4
5	Pork liver	3 (<1 %)	22.1	29.6	30.4
6	Meat from other non-game poultry[b]	301(2 %)	14.4	11.0	41.5
7	Liver from beef/veal	75 (<1 %)	17.3	13.5	42.1
8	Eel	24 (<1 %)	16.5	14.9	34.5
9	Meat from game poultry	7 (<1%)	15.9	15.0	24.3
10	Salmon	745 (5 %)	7.7	5.9	21.3

[a] Offal excluding liver from mammals except from game
[b] Meat from poultry except chicken, turkey and game

Table D 2: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for the consumers of the ten food groups with the highest proportions of mean intake in ng/kg bw per week for adolescents in the German population using concentration data from the monitoring programs of the German federal states (based on: EsKiMo 12–17 years; only consumers)

No.	Food group	N Consumer*	LB		
			Mean	P50	P95
1	Carp	12 (<1 %)	12.3	11.2	37.8
2	Other freshwater fish	115 (9 %)	11.4	7.5	33.7
3	Meat from wild boar	10 (<1 %)	11.0	8.4	22.5
4	Other offal from non-game mammals[a]	30 (2 %)	10.9	4.0	41.4
5	Meat from beef/veal	1,324 (98 %)	4.5	3.4	11.9
6	Cereals and cereal-based products	1,351 (100 %)	3.0	2.8	5.7
7	Pollack	533 (39 %)	1.4	0.9	3.6
8	Trout	62 (5 %)	1.3	1.0	3.3
9	Liver from beef/veal	9 (<1 %)	1.3	0.9	3.7
10	Eggs and egg products	1,350 (100 %)	1.1	0.8	2.9

[a] Offal excluding liver from mammals except from game

Table D 3: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for the consumers of the ten food groups with the highest proportions of mean intake in ng/kg bw per week for children and adolescents in the German population using concentration data from the monitoring programs of the German federal states (based on: EsKiMo 6-11 years; only consumers)

No.	Food group	N Consumer*	LB		
			Mean	P50	P95
1	Other freshwater fish	12 (1 %)	89.2	80.8	215.0
2	Meat from wild boar	1 (<1 %)	84.9	84.9	84.9
3	Meat from game poultry	2 (<1 %)	47.9	47.9	47.9
4	Other offal from non-game mammals[a]	12 (1 %)	44.9	38.5	140.9
5	Meat from other non-game poultry[b]	24 (2 %)	20.2	17.1	44.9
6	Trout	11 (1 %)	12.7	14.9	19.9
7	Salmon	28 (2 %)	11.2	8.5	28.5
8	Liver from beef/veal	6 (<1 %)	9.9	11.4	14.9
9	Pollack	196 (17 %)	9.4	8.2	17.6
10	Meat from beef/veal	400 (35 %)	6.4	5.2	17.4

[a] Offal excluding liver from mammals except from game
[b] Meat from poultry except chicken, turkey and game

Table D 4: Exposure to the sum of PFHxS, PFNA, PFOA and PFOS for the consumers of the ten food groups with the highest proportions of mean intake in ng/kg bw per week for children in the German population using concentration data from the monitoring programs of the German federal states (based on: VELS; only consumers)

No.	Food group	N Consumer*	LB		
			Mean	P50	P95
1	Other freshwater fish	3 (<1 %)	87.7	110.2	117.3
2	Meat from wild boar	1 (<1 %)	39.9	39.9	39.9
3	Meat from game poultry	101 (14 %)	24.1	19.7	60.9
4	Pollack	86 (12 %)	13.1	11.9	22.2
5	Trout	8 (1 %)	13.1	11.9	22.2
6	Eel	33 (5 %)	12.2	4.7	39.7
7	Salmon	23 (3 %)	12.7	4.1	44.7
8	Meat from other non-game poultry[a]	49 (7 %)	9.1	8.3	21.1
9	Meat from beef/veal	303 (41 %)	5.4	3.6	15.6
10	Other saltwater fish	112 (15 %)	5.0	4.5	10.0

[d] Poultry meat other than chicken and turkey and game