Deliverable report for:

Advice on the bioaccumulation potential of perfluoroheptanoic acid (PFHpA) (EC n°: 206-798-9)

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DOCUMENT HISTORY

Version	***Date***	***Reason of change (responsible person)***
1	20201109	Draft_v1
2	20201221	Draft_v2-with processed comments from Belgian CA
3	20210216	Final advice after discussion in WCSR and comments from Belgian CA
4	20210708	Final advice after discussion in WCSR May 2021

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1 Substance identification

Chemical name: perfluoroheptanoic acid (PFHpA)

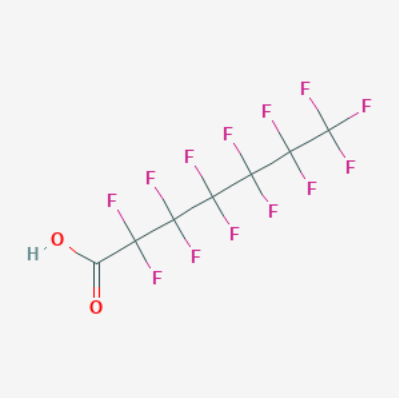
IUPAC Name: 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptanoic acid

EC Number(s): 206-798-9

CAS Number(s): 375-85-9

Structural formula: CF3-CF2-CF2-CF2-CF2-CF2-COOH

Structure:



2 Concern

During the analysis of the properties of the most relevant stable transformation product of FS-65, *i.e.* PFHpA, it became clear that this substance meets the vP and T criteria set in the REACH regulation. In order to be classified as a PBT/vPvB substance, one must thus decide whether the (v)B criterion for PFHpA is met or not. It is clear that PFHpA is not bioaccumulative for aquatic organisms but there are indications that PFHpA bioaccumulates in air-breathing animals and in humans.

An important indication in this framework is the study performed by Zhang *et al*. (2013). In this study it is claimed that the mean elimination half-life of PFHpA in humans is more than 1 year. This is seen as a conclusive argument that PFHpA should be considered as bioaccumulative. However, in the study itself it is already mentioned that uncertainties remain to a certain extent. Besides the study in humans, there is also a study by Numata *et al*. (2014) in pigs. Although it is probably of secondary importance, it can add to a reliable assessment of the bioaccumulation potential of PFHpA.

3 Analysis of available information

A. Zhang *et al*., (2013)

Paired blood and urine samples (n-86) were collected from adult volunteers of one capital city and one industrial city in China in 2010; both cities have about 10 million inhabitants (Zhang *et al.*, 2013). The participants were divided into four groups; young females (age ≤ 50 years, n = 20), older females (> 50 years, n = 19), young males (≤ 50 years, n = 32), and older males (> 50 years, n = 15). All samples were analysed for the presence of several perfluoroalkyl acids (PFAAs) amongst which PFHpA. For all PFAAs except perfluoroundecanoate (PFUnA), levels in urine correlated positively with levels in blood.

The aim was to estimate the rate at which PFAAS were eliminated from the human body (*i.e*. the elimination half-life or clearance). Urinary excretion was assumed to be the major elimination route for short perfluorocarboxylic acids (PFCAs) (C≤8). For young women, the menstrual clearance rate (0.029 ml/day/kg) was considered additionally; it was lower than the renal clearance rate for most PFAAS, including PFHpA. The median elimination half-lives (T1/2) of PFHpA for 1) the young female group and 2) the male and older female group were 1.6 (range: 0.11 – 3.3) and 0.79 (range: 0.12 – 5.1) years respectively, or 584 (group 1) and 288 days (group 2).

The authors stated that these elimination T1/2s should be viewed as upper limits due to the possibility that there might be other significant elimination routes other than via the urine (*e.g*. faeces, nails, lactation).

Renal clearance was taken as measure for elimination. Renal clearance was defined *as the volume of serum from which a chemical is completely removed in a given time period*. Daily renal clearance of individual PFAAs was calculated based on the paired serum and urinary concentrations with the following equation:

$$CLrenal = \frac{Curine\ x\ V}{Cblood\ x\ W}$$

With

- CL_{renal} = renal clearance (ml/kg body bw/day)
- C_{urine} = concentration of an individual PFAA in urine (ng/l)
- V = daily urine excretion volume (l/day): 1.2 l and 1.4 l for females and males respectively (Walser, 1987)
- C_{blood} = individual serum concentration (ng/ml)
- W = body weight (kg): 55 kg for females and 65 kg for males

The median CL_{renal} for PFHpA for group 1 and 2 was 0.17 and 0.41 ml/kg bw/d respectively; for comparison, median CL_{renal} for linear PFOA for group 1 and 2 was lower (0.14 and 0.18 ml/kg bw/d respectively) (Table 1). The renal clearance of PFHxA was not measured.

Table 1 Renal clearance (Zhang *et al.*, 2013)

Group	Substance	CLrenal (ml/kg bw/d) - median	CLrenal (ml/kg bw/d) - mean
1. Young women	PFHpA	0.17	0.61
	PFOA	0.14	0.29
2. Man and older women	PFHpA	0.41	0.61
	PFOA	0.18	0.79

Consequently, the clearance was used to calculate the elimination half-life; hereto a one-compartment model was used, meaning that the human body was considered as one compartment, namely blood (no consideration of organs). The elimination T1/2 was estimated with the following formula:

$$T1/2 = \frac{0.693\ x\ V}{CLtotal}$$

With

- T1/2 = elimination half-life (days)
- 0.693 = ln2
- V = volume of distribution i.e. the total amount of a substance in the body divided by its concentration in serum (ml/kg bw).
- CL_{total} = total clearance (ml/kg bw/day); CL_{total} was set equal to CL_{renal} by the authors because
  - of the strong associations between urinary and blood concentrations,
  - urine was the primary elimination route for PFOA in rats and monkeys,
  - no PFHxS was found in the stool, but was detected in the urine samples of a whole Canadian family of seven with unusually high levels of PFHxS in serum (Beesoon *et al.*, 2011)
  - in humans the main nodes of elimination have not been confirmed yet,
  - elimination through hair and nail are likely minor routes, and
  - faecal elimination became important for PFCAs with longer carbon chain (C>8) in rats.

  For the group of young women, the menstrual clearance was added to the renal clearance for calculation of CL_{total}, considering that menstrual clearance (0.029 ml/kg bw/d) is an important clearance pathway.

B. Numata *et al*., 2014

Numata *et al.* (2014) studied the transfer of a mixture of PFAS from contaminated feed into edible tissues of 24 fattening pigs during a 3-week feeding study. Seven PFCAs (PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA) were analysed in every sample. Sampling was performed on feed, tissues (blood, liver, kidney, muscles and urine). The PFAS excretion via faeces were not analysed because they were presumed to be relatively small with respect to the total cumulative PFCAs dose. This assumption was confirmed by mass balance since most of the PFCAs dose was accounted for by tissues (mainly plasma; also fat, and dorsal and ventral muscles) and urine (main pathway for PFHxA) without resorting to the faeces. The authors developed a 2-compartment toxicokinetic model in order to quantify absorption, distribution and excretion of the PFCAs and

calculated elimination T1/2s. The plasma elimination T1/2s for PFOA, PFHpA and PFHxA were 236, 74 and 4.1 days respectively (**Fout! Verwijzingsbron niet gevonden.**).

The authors also calculated biomagnification factors (BMF) for whole pig, meat and liver, as follows:

$$BMF = \frac{Co}{Cd}$$

With

- C_o = steady state concentration in the organism (or tissue) (mg/kg)
- C_d = steady state concentration in the diet (mg/kg)

Mean $BMF_{whole\ pig}$, BMF_{meat} and BMF_{liver} for PFHpA were 2.7, 1.8, and 7.0, respectively. The corresponding values for PFOA, and PFHxA were 7.9/5.3/32.8, and 0.13/0.08/0.42, respectively (Table 2). These values show that meat and liver are reservoirs for PFHxA.

Table 2: Biomagnification factors (Numata *et al.*, 2014)

Substance	Mean BMF – whole pig	Mean BMF – meat	Mean BMF – liver
PFHxA	0.13	0.08	0.42
PFHpA	2.7	1.8	7.0
PFOA	7.9	5.3	32.8

C. Bioaccumulation data

Bioaccumulation of a number of PFAAs was measured in an experimental study with earthworms exposed to different levels in soil (10, 200 and 500 ng/g) (Zhao *et al.*, 2013). The results for PFHxA, PFHpA and PFOA were:

- elimination T1/2 (days): 3.7 (PFHxA), 5.5 (PFHpA) and 6.1 (PFOA)
- elimination rate (k_2) (day^{-1}): 0.187 (PFHxA), 0.126 (PFHpA) and 0.114 (PFOA)
- biota-soil accumulation factors (BSAF) based on wet weight, at
    - 100 ng/g soil: 0.033 (PFHxA), 0.040 (PFHpA) and 0.037 (PFOA)
    - 200 ng/g soil: 0.018 (PFHxA), 0.019 (PFHpA) and 0.024 (PFOA)
    - 500 ng/g soil: 0.013 (PFHxA), 0.008 (PFHpA) and 0.014 (PFOA)
- kinetic BSAF ($g_{oc}\ g_{dw}^{-1}$)[1]:
    - 0.087 (PFHxA), 0.122 (PFHpA) and 0.131 (PFOA)

According to the authors, the PFAAS displayed distinct bioaccumulation; the bioaccumulation ability could be due to the active ingestion of soil through the gut and the high protein content of the earthworm. Bioaccumulation of PFAAS in air-breathing organisms is regarded to operate via a protein-based mechanism. Longer-chain PFAAs had a higher bioaccumulation ability because of the larger uptake rate and the lower excretion rate. The BSAF results showed that the BSAF is dependent on the concentrations of PFASs in soil and that the values decreased as the level of PFASs in soil increased.

Bioaccumulation factors (BAF) for PFAAs in edible crops and fruits were measured by Blaine *et al.* (2014a), for the root, shoot, and fruit compartments (if applicable) of crops grown in industrially impacted soil; the BAFs for PFHxA, PFHpA and PFOA are included in Table 3. The authors concluded that root-soil concentration factors (RCF) for tomato and pea were independent of PFAA

[1] Quotient of uptake rate constant (k_u) and elimination constant (k_e); oc organic carbon, dw dry weight

chain length, while radish and celery RCFs showed a slight decrease with increasing chain length. Shoot-soil concentration factors (SCFs) for all crops generally showed a decrease with increasing chain length. The biggest decrease was seen in fruit-soil concentration factors (FCFs). PFHpA accumulates in plants and fruits to a higher extent than PFOA, but to a lower extent than PFHxA (Blaine *et al.*, 2014a).

Table 3: BAFs in edible crops and fruits (Blaine *et al.*, 2014a)

Crop	Part	PFHxA	PFHpA	PFOA
Radish	Root	1.15	0.80	0.85
	Shoot	3.86	5.50	7.60
Celery	Root	4.77	2.96	1.42
	Shoot	11.91	2.51	0.71
Tomato	Root	1.45	1.88	0.96
	Shoot	8.93	3.79	2.42
	Fruit	2.90	0.86	0.11
Pea	Root	1.04	1.55	0.79
	Shoot	3.46	1.25	0.52
	Fruit	1.47	0.18	0.03

Also in strawberries and lettuce exposed to contaminated irrigation water, bioaccumulation of PFAAs depended on chain length. PFHpA concentrations in strawberries were below the LOQ (Blaine *et al.*, 2014b).

PFHpA was not detected in filet and liver of eelpout from 2 locations of the North Sea and one location in the Baltic sea. Increasing trends over time were detected for the longer PFCAs: PFNA, PFDA and PFDoDA at the Baltic Sea site and for PFDA at one North Sea site (Fliedner *et al.*, 2020).

D. Human biomonitoring (HBM) data

For comparison with the serum levels in Chinese volunteers recruited by Zhan, a search was performed for HBM data from other countries. Data for Germany and the USA were found and are included in Table 4. Plasma samples from 2 German cities (Hall and Münster), collected between 1982 and 2009, were analysed for a suite of PFCAs; all samples had detectable concentrations of PFHpA (0.0191-2.24 ng/ml) (Yeung *et al.*, 2013). The mean values for the most recent campaign (2009) are presented in Table 4. The plasma concentrations for male and female from Halle and male from Münster are about the half of the mean for all serum samples, published by Zhang *et al.* (2013) (serum PFHpA concentrations for female and male separately are not available in Zhang *et al.* (2013)). The mean plasma concentration of females of Münster is about the double of the mean serum values of Zhang *et al.* (2013).
Lee et al (2011) obtained samples from blood donors in California, from 2009. The mean serum concentrations are comparable to the mean concentrations of Zhang *et al.* (2013).
Paired blood-urine concentrations are not available in these two sources.

Table 4: PFHpA human blood concentrations

Mean (range) (ng/ml)[a]	Medium	Gender	Sampling year	Geographical region	Reference
0.0420 (0.0081-0.120)	plasma	5 females	2009	Halle (Germany)	Yeung *et al.* (2013)
0.0526 (0.0072-0.0965)	plasma	5 males	2009	Halle (Germany)	Yeung *et al.* (2013)
0.151 (0.0306-0.621)	plasma	5 females	2009	Münster (Germany)	Yeung *et al.* (2013)
0.0333 (0.0073-0.0625)	plasma	5 males	2009	Münster (Germany)	Yeung *et al.* (2013)
0.11	serum	pooled samples	2004-2006	Norway	Haug *et al.* (2011)
0.0972 (<LOD-0.417)	serum	20 males and 20 females	2009	California (USA)	Lee and Mabury (2011)
0.0832 (0.0246-0.162)	serum	10 pooled samples	2009	California (USA)	Lee and Mabury (2011)
0.13	serum (geometric mean)	645 pooled samples, males and females	2000-2001	USA (various states)	Olsen 2011
0.09	plasma (geometric mean)	600 pooled samples, males and females	2006	USA (various states)	
0.05	plasma (geometric mean)	600 pooled samples, males and females	2010	USA (six locations)	Olsen 2012

[a] for comparison: 0.085 (<LOD-0.37) ng/ml in serum for 86 males and females (Zhang *et al.*, 2013)

Plasma concentrations measured by Yeung *et al.* (2013) are higher for PFOA than for PFHpA; mean values for PFHxA are mostly lacking because many measurements are <LOQ. The PFHpA concentrations show no clear time trend.

In a Norwegian study, the PFHpA concentration in eight consecutive multi-year pooled samples increased from <0.05 ng/ml in 1977-1981 to 0.11 ng/ml in 2004-2006 (Haug *et al.*, 2011). However, no significant temporal trend of PFHpA was observed between 1996 and 2010 in pooled serum samples from nursing women in Sweden; the authors mentioned that the levels were all close to or below the quantification limit (Glynn *et al.*, 2012).

Serum concentrations measured by Lee *et al.* (2008) are higher for PFOA than for PFHpA; concentrations of PFHxA are lower than those of PFHpA.

A lower (31%) geometric mean level of PFHpA was found in serum/plasma form American Red Cross donors in 2006 compared to 2000/2001. The percentage decline in geometric mean and P95

between 2000/2001 and 2010 was 62% and 25% respectively (Olsen *et al.*, 2012). The three cohorts were not identical.

All 26 employees at a municipal Swedish airport were sampled for serum and urine, because of groundwater contamination with PFAS-containing firefighting foams (Xu, 2020). For PFHpA, the median urine concentration was 25 ng/l. The serum concentration was calculated from a personal average urine/serum ratio of 0.086; hence the median serum concentration was 290.70 ng/l. The authors reported a modelled T1/2 of 62 days. The model that was used was a linear mixed model with age and sex as covariates.

For a selected group of 2013-2014 NHANES[2] participants (n=2682), paired serum and urine samples were collected at the same time and analysed for 10 PFAS (2 short-chain (PFBS and PFHpA) and 8 long chain). The highest detection frequency in urine was for PFHpA (1.2%) among participants of 12 years and older; the corresponding frequency in serum was 12.6%. PFHpA was not detected in urine of children of 6-11 years, but the detection frequency was 16.2% in these children's serum. PFBS was not detectable in urine, regardless of the age, but detectable in serum of 0.6% and 9.1% of the participants of ≥12 years and 6-11 years respectively. The fact that the two short-chain PFAS were detected more often in the serum than in the urine might be an indication of their shorter persistence in humans in comparison to long-chain PFAS; the T1/2 of PFBS in humans is 26 days (Calafat *et al.*, 2019).

4 Discussion

4.1 HBM data

Sampling was performed in 2010 by Zhang. The sampling was performed only once and data on exposure are not available; the participants were from one capital city and one industrial city, both with about 10 million inhabitants, the level of contamination of these cities is not known. The elimination rate may depend on the level of exposure (cfr. Olsen *et al.* (2007) in **Fout! Verwijzingsbron niet gevonden.**). So it may be questionable whether the HBM data are relevant as state-of-the-art data for China, but also for the EU. Plasma and serum concentrations from the same sampling period (2009) are available for Germany and the USA. These values show that there is no argument to consider the serum concentrations of Zhang *et al.* (2013) as not relevant for European population. Earlier measured serum concentrations in Sweden (2004-2006) and in the USA (2010) were a little higher and a little lower respectively. The German HBM data show no clear time-trend for PFHpA. Norwegian serum concentrations increased between 1977 and 2006. However, no significant temporal trend was observed between 1996 and 2010 in a Swedish study. Zhang *et al.* (2013) provided no time-trend.

Conclusion: PFHpA is present in human blood in different geographical regions; the concentrations show no clear time trend. Serum concentrations of Zhang *et al.* (2013) are in line / comparable with values in Europe and thus relevant for the European population.

4.2 CL_{total}

For men and older women, Zhang *et al.* (2013) considered CL_{renal} to be equal to CL_{total}. For young women menstrual clearance was considered. For this group, the median CL_{total} was CL_{urine} +

[2] National Health and Nutrition Examination Survey of the Centers for Disease Control and Prevention of the USA

$CL_{menstrual}$ = 0.17 + 0.029 ml//kg bw/d. The corresponding T1/2 was 1.6 years; if $CL_{menstrual}$ is not considered, the T1/2 value would be 1.9 years. This value (1.6 years) is twice as high as the median T1/2 of men and older women (0.79 years). One of the reasons for this large difference between median T1/2 for young women (1.6 years) and men and older women (0.79 years) could be the higher variability of the urinary clearance in the group of young female (n=12; mean: 0.61 (95% CI 0.022-1.2)) than in the other group (n=31; mean: 0.61 (95 % CI 0.38-0.83)); additionally, the number of samples was lower in the group of young females. If the mean value (0.61 for both groups) was used instead of the median value (0.17 for young women versus 0.41 for the other group), the difference was smaller (mean T1/2 of 1,5 years for young women and 1,2 years for men and older women).
Considering CL_{total} as equal to CL_{renal} is in line with findings of Numata *et al.* (2014) who calculated that faecal elimination is a minor pathway for PFCAs in pigs.
Ohmori *et al.* (2003) showed that plasma protein binding, estimated *in vitro*, was over 98% for a number of PFCAs (including PFHpA) tested, indicating that CL_{renal} is responsible for the difference in CL_{total} between the PFCAs tested. The values of CL_{tot} in rats were in the order of PFHA>PFOA>PFNA≈PFDA in male rats, and PFHA≈PFOA>PFNA≥PFDA in female rats. There was a close relationship between CL_{total} and CL_{renal} (r^2 = 0.981) (Ohmori *et al.*, 2003).

Conclusion: renal clearance is by far the major clearance route; hence CL_{renal} can be considered as equal to CL_{total}, unless indications show otherwise (e.g. Zhang *et al.* (2013) also considered menstrual clearance).

4.3 Elimination half-life (T1/2)

To calculate the T1/2, Zhang *et al.* (2013) assumed that

- the total clearance is the same as the renal clearance (see 4.2), and
- the concentration in the body is the same as the concentration in the blood

According to Zhang *et al.* (2013), their calculated elimination T1/2s should be considered as upper limit estimates. The authors acknowledged that other clearance mechanisms, might play a role, but believe them to be minor, with the exception of faecal elimination which might be important for some substances. 3.2% of PFHpA ingested by sheep was excreted via the faeces (Numata *et al.*, 2014). Taking into account other elimination routes besides urine will decrease the T1/2. Hence the T1/2 values of Zhang are in fact 'lower than' values: < 584 (group 1) and < 288 days (group 2).

Zhang *et al.* (2013) used a one-compartment model, meaning that the body was considered as one compartment (blood) and that the PFHpA distribution to organs was ignored. Numata *et al.* (2014) however showed that about 25% of PFHpA ingested by pigs via feed was distributed to muscles and fat. The T1/2 for pigs, estimated with a two-compartment model was 74 days, 4 to 8 times lower than the median values calculated for group 2 (288 days) and 1 (584 days) respectively, by Zhang.

Elimination rates and T1/2s are acknowledged as useful metrics indicative of the bioaccumulation potential (ECHA, 2017a). An overview of elimination T1/2 values is presented in **Fout! Verwijzingsbron niet gevonden.**.

Zhang *et al.* (2013) published the concentrations of PFHpA as mean/median/min/max values for all the samples of females and males together. However, the CL_{renal} and elimination T1/2 values were published for two groups separately: 1. Young females, 2. All males and older females. Therefore, the numbers calculated for the renal clearance and elimination T1/2 calculated thereof cannot be verified.

Three parameter values used by Zhang *et al.* (2013) need discussion.

1. It is questionable whether the body weight (bw) used by Zhang is representative for the European population. The REACH guidance (R8) recommends a human body weight of 70 kg (ECHA, 2012); Zhang uses 55 kg (females) and 65 kg (males).
2. The daily urine volume published by Apel *et al.* (2017) is 0.02 l/kg bw/day. This would mean a daily urine volume of 1.4 l for 70 kg bw, which is the same as the urine volume of men, applied by Zhang *et al.* (2013).
3. Volume of distribution (see 4.5)

Calculations of renal clearance and T1/2 starting from median measured concentrations in blood serum and urine of Zhang *et al.* (2013), 1.4 l daily urine volume, and 70 kg bw are presented in Table 5 for PFHpA; PFOA is added for comparison with PFHpA, as T1/2 increases (proxy for increasing bioaccumulation potential) with chain length.

Table 5: Human elimination T1/2 (own calculation)

Parameter	**Description**	**PFHpA**	**PFOA[3]**	**unit**
C_{blood}	= $C_{whole\ blood}$		0.029	ng/ml
C_{blood}	= C_{serum}	0.058	0.053*	ng/ml
C_{urine}		0.82	0.44	ng/l
V	daily urine volume	1.4	1.4	l
W	body weight	70	70	kg
Cl_{renal}**	= C_{total}	0.283	0.167	ml/day/kg bw
ln2		0.693	0.693	
V	volume of distribution	170	170	ml/kg
T1/2	elimination half-life	417	706	days
		1.14	**1.93**	year
T1/2 (Zhang *et al.*, 2013)	for comparison	0.79 – 1.6 (group 2 - 1)	1.7 – 1.8 (group 2 - 1)	year (median)

* Own calculation based on the assumption that the serum level in blood is approximately the same as the plasma level in blood. Blood consists of 55% plasma (Hayat K, 2012); **calculated with V=1,4l and W=70 kg (equation in section 3.A) instead of V=2l and W= 55 kg (f), 65 kg (M) as Zhang (2013) did (Table 1 in this advice)

For PFHpA, the result is an elimination T1/2 of 1.14 year. This value is between the median half-life of 0.79 (for man and older women) and 1.6 (young women) calculated by Zhang *et al.* (2013). For comparison: the half-life of PFOA is longer (1.93 year). An elimination T1/2 of 1.14 year (PFHpA) and 1.93 year (PFOA) corresponds with an elimination rate (=ln 2/T1/2) of 0.00167 and 0.000982 day^{-1} respectively.

An alternative method to calculate T1/2 without V, is based on the total mass in the serum and the daily elimination of mass via urine (see Annex 1):

$$T1/2\ (days) = \frac{ln2}{elimination\ \ rate\ (day-1)}$$

[3] Linear

$$T1/2\ (days) = \frac{mass\ in\ serum\ (ng) * ln2}{elimination\ \ via\ urine\ \left(\frac{ng}{d}\right)}$$

$$T1/2\ (days) = \frac{153\ ng * ln2}{1.07\frac{ng}{d}} = 99\ days$$

based on median serum and urine concentrations of Zhang *et al*. (2013).

For comparison; the median T1/2 values of Zhang (2013) are 288 (group 2) and 584 days (group 1), which is 8 to11 times higher.

This alternative method avoids the use of the volume of distribution, which is a parameter contributing to the uncertainty of the T1/2 value (see 4.4); as a measured value is not available for PFHpA, the value of PFOA was used by Zhang *et al*., 2013. The T1/2 for mean serum and urine concentrations calculated with the alternative method is 63 days, 4 to 6 times lower than the corresponding T1/2 values (438-548 days) of Zhang 2013. For comparison: the T1/2 calculated by Xu (2020) was 62 days, based on median paired serum and urine concentrations. The T1/2 for pigs is 74 days; pigs are a recommended biomedical model of human physiology (Groenen *et al.*, 2012). The T1/2 of PFBA in humans (1.7 days) is lower than for PFHpA.

However, the same alternative calculation for PFOA gives a T1/2 of 182 days for median serum/urine concentrations and 53 days for mean concentrations; these values are far below T1/2 values measured by other authors (Table 6); concentrations for PFHxA are not available in Zhang *et al*., 2013. As a control, the T1/2 is calculated for another pair of serum/urine samples with PFOA. Paired serum and urine PFOA concentrations were measured in residents living in a site with contamination due to many year's application of PFOA-containing sludge on the soil (Worley 2018). The mean concentrations were:

- Man: 15200 ng/l serum and 31.4 ng/l urine
- Women: 14100 ng/l serum and 25.2 ng/l urine

The T1/2 values for man and women, calculated thereof with the alternative method are 793 days and 786 days respectively. These values are in line with the values in Table 6 for contaminated sites.

The alternative method calculations confirm the statement of Zhang *et al.* (2013) that the T1/2 values calculated by Zhang are likely too conservative.

Renal clearance of specific PFAS was discussed as part of the toxicokinetics in the recent scientific opinion of EFSA on the risk to human health related to the presence of PFAS in food (EFSA, 2020). Data illustrating that Zhang (2013) probably underestimated renal clearance, were published by Kim *et al.* (2019) (cited in EFSA (2020)), on PFDA. The authors measured a rate constant to urine of 0,681 h^{-1} in female rats; the corresponding human (female) rate constant calculated thereof was 0.174 h^{-1} (scaled with $(BW_{human}/BW_{rat}{}^{4})^{-0.25}$). The half-life estimated by Zhang (2013) for PFDA was 4 years (geometric mean for young women). The rate constant calculated thereof (ln2/T1/2) is 0.00047 $day^{-1,}$ which is much lower than the rate constant of 0.174 h^{-1} calculated by Kim *et al.* (2019). For comparison: the rate constant of PFHpA is 0.0024 d^{-1} (calculated for a geometric mean half-life of 1 year for young women by Zhang (2013)) which is lower than the human (female) clearance for PFDA (0.174 h^{-1}) estimated by Kim *et al*., 2019. Hence human CL_{renal} might be a more substantial elimination route than estimated by Zhang *et al.* (2013).

[4] Body weight: human 70 kg, rat 250 g

However, the model for the translation of rat data to human data developed by Kim *et al.,* (2019) was subject to criticism by the German Federal Institute for Risk Assessment (BfR) (Hethey *et al.*, 2019). BfR had two major critics: (1) the structural model Kim and co-authors set up was not in conformity with the physiological processes of urinary excretion (tubular secretion was neglected) and 2) the allometric extrapolation from rats to humans did not take into consideration marked interspecies differences in the activity of kidney transporters.

It has been demonstrated in rat, mice and monkeys that serum elimination T1/2s of PFCAs increase with increasing chain length (references in ECHA (2017b)). The increasing trend is also apparent for pigs where the elimination T1/2 increases from 4 days for PFHxA, 74 days for PFHpA to 236 days in PFOA. The elimination T1/2s of PFHpA and PFOA are very long compared to the lifetime of a farm pig (~180 days) before slaughter (Numata *et al.*, 2014). The maximum measured T1/2 in rats for PFHxA and PFHpA are comparable (2.6 and 2.5 h respectively) (Ohmori *et al.*, 2003; Chengelis *et al.*, 2009); for PFOA, the T1/2 in rats is 19 h for females and 5.6 days for males (Ohmori *et al.*, 2003). PFOA and PFHxS which were identified as B and vB respectively, have T1/2 values for rats of 135 h (M) and 19 h (F) and 646 h (M) and 41 h (F) respectively.

The trend between T1/2 and chain length also exists for humans where the elimination T1/2 increases:

- from 1.7 days in PFBA (Chang *et al.*, 2008) to 3.8 years (arithmetic mean)/3.5 years (geometric mean) in PFOA in occupational workers (Olsen *et al.*, 2007),
- from 1 year in PFHpA, 1.5 years in PFOA, 1.7 years in PFNA to 4 years in PFDA and PFUnDA for young females, and
- from 0.8 years in PFHpA, 1.2 years in PFOA, 3.2 years in PFNA to 7.1 years in PFDA and 7.4 years PFUnDA for males and older females as presented in Zhang *et al.* (2013) (ECHA, 2017b).

Table 6: Elimination T1/2 values from different authors, for different species and PFCAs

Species	**Substance**	**Elimination T1/2**	**Reference**
Pigs	PFHxA	4.1 days	Numata *et al.* (2014)
	PFHpA	74 days	
	PFOA	236 days	
Humans	PFBA	1.7 days	Chang *et al.* (2008)
Occupational workers	PFOA	3.4 years (median)	Olsen *et al.* (2007)
Fire fighters	PFHpA	62 days (median)	Xu 2020
Young females	PFHpA	1 year	Zhang *et al.* (2013) (geometric mean)
	PFOA	1.5 years	
	PFNA	1.7 years	
	PFDA and PFUnDA	4 years	
Man and older females	PFHpA	0.82 years	
	PFOA	1.2 years	
	PFNA	3.2 years	

	PFDA	7.1 years	
	PFUnDA	7.4 years	
Humans	PFOA	2.7 years (mean)	Li *et al.* (2018)
Humans	PFOA	2.5 years	Thompson *et al.* (2010) (contaminated drinking water)
Humans	PFOA	2-4 years	ECHA (2019b)
Humans	PFHpA	1.14 year	Table 5
Rat	PFHxA	M: 1-2.5h[a] F: 0.42 – 2.6 h	Chengelis *et al.* (2009)
Rat	PFHpA	M: 0.10d (=2.4h), F: 0.05d (=1.2h) at 17.7 mg/kg	Ohmori *et al.* (2003)
	PFOA	M: 5.63 d, F: 0.08 d (=19u)	
	PFNA	M: 29.5 d, F: 2.44 d	

[a] increases with increasing dose (10, 50, 150, 300 mg/kg)

Elimination T1/2s have been used as a metric to estimate the bioaccumulation potential in air-breathing organisms. For example, the elimination T1/2 for PFOA in humans was important in the identification of PFOA (T1/2 2 – 4 years) as a substance fulfilling the B criteria in Annex XIII (ECHA, 2013).

Conclusion: Elimination T1/2s of PFHpA in humans are 62 – 99 – <288 – <584 days (median), meaning a quantitative range of 70-100 days. The elimination T1/2 of PFHpA is shorter than the elimination half-life of PFOA for the same species. Since PFOA is identified as B-substance and not vB-substance (ECHA, 2013), PFHpA cannot be regarded as vB.

4.4 Volume of distribution

The volume of distribution (V) used by Zhang et al. (2013) was the Vd of PFOA calculated by Thompson *et al.* (2010). Hereto, the latter used an elimination rate of 0.0008 day^{-1} calculated from an elimination T1/2 of PFOA of 2.5 years, longer than the 1.14 years for PFHpA calculated with the median concentration of Zhang *et al.* (2013) (elimination rate 0.0017 day^{-1}) (Table 5). Calculation of the V with an elimination rate of 0.0017 day^{-1} (and keeping the other parameters unchanged) gives a V of 78 and a T1/2 of 192 days.
Ohmori *et al.* (2003) measured steady state V values (Vss) in male and female rats. Zhang *et al.* (2013) defend their use of the Vd of PFOA for PFHpA by stating that "*Ohmori et al. reported that V was not much different between PFCAs, or between sexes in rats, although the V value of PFDA was larger than those of other PFCAs*". However, Ohmori *et al.* (2003) wrote that "*The difference in Vss between PFCAs, was not so significant as the difference in T1/2, although Vss of PFDA was larger than those of other PFCAs*".

The difference between Vss in male rats for PFHpA (196 ml/kg) and PFOA (338 ml/kg) was regarded as significant by the authors (Table 1 in Ohmori *et al.* (2003)). The difference between both values is a factor 1.73. A V of 170 for PFOA divided by 1.73 is a V of 98 for PFHpA, and a corresponding T1/2 of 241 days.

Conclusion: the V of PFOA used for PFHpA by Zhang *et al.* (2013) can be regarded as worst case for T1/2 calculation of PFHpA.

4.5 Bioaccumulation potential

BMF values can provide an indication of a biomagnification potential. BMF can on its own be considered as a basis to conclude that a substance meets the B or vB criteria, if the BMF is ≥ 1 (PBT guidance). The BMF of PFHpA in pigs is 2.7, although lower than the BMF of PFOA (up to 125 for prey-predator relationship). For PFOA the value of BMF ≥ 1 was applied as indication of potential biomagnification (ECHA, 2013).

The kinetic BSAF of PFHxA for earthworms was 0.122 g_{oc} g_{dw}^{-1}). The BSAF values (based on wet weight) increased from 0.008 to 0.040, at decreasing soil concentrations. *For a substance exceeding log Kow of 4.5, a BSAF value in the order of 2 is an indication of a BCF of 2000 and higher, based on pore water concentration; however, lower BSAF values should not be used to the contrary (PBT guidance)*. The estimated log Kow of PFHpA is 4.15 for the acid and 0.33 for the anion (KowWin), making interpretation of the BSAF in view of B-assessment difficult. Increasing BSAF values with decreasing exposure might be an element of concern at low, environmentally relevant concentrations.

The human BMF can be calculated from measured concentrations in human blood (Zhang *et al.,* 2013) and in drinking water (Xu *et al.,* 2020) with the following formula:

$$BMF = \frac{Corganism}{Cdiet}$$

The concentration in the human body ($C_{organism}$) is calculated from the concentration in blood. However, the concentration in the whole body is expected to be lower than the concentration in the blood. This was demonstrated in the Numata (2014) study, where the difference between the fraction of ingested PFHpA measured in the whole pig and in the blood was a factor of 2,4. This rate is used to calculate the human body concentration from the blood concentration (Annex 2). If we additionally consider drinking water as the main intake source (C_{diet} = $C_{drinking\ water}$), a body weight of 70 kg and a daily drinking water consumption of 2l, the resulting BMF is 1.9 (see Annex 2).

Conclusion: Based on the biomagnification in pigs (2.7) and the calculated human BMF (1.9) which are both >1, PFHpA seems to fulfill the (v)B criterion and should be considered as bioaccumulative. To decide on B or vB, the BMF and elimination T1/2 of PFHpA can be compared with the BMF and elimination T1/2 of PFOA which is B. Since both parameters are lower for PFHpA than for PFOA, PFHpA should be classified as B and not vB.

4.6 B or not B

PFHxA shows properties of concern such as strong binding potential to proteins and an effective distribution within organisms. However, it does not fulfil the bioaccumulation criteria of Annex XIII to REACH (ECHA, 2019a).

PFOA is identified as PBT (ECHA, 2013). The B was, amongst other arguments, based on evidence that PFOA biomagnifies in air-breathing mammals (BMFs range from 1.3 – 125 for selected predator prey relationships) and PFOA accumulates in humans (a. PFOA is present in human blood of the general population, b.T1/2 in blood range from 2 - 4 years in humans).

PFHpA:

B:

- BMF can on its own be considered as a basis to conclude that a substance meets the (v)B criterion, if the BMF is ≥ 1 (PBT guidance). PFHpA accumulates in pigs (BMF_{liver} = 7, $BMF_{whole\ pig}$ = 2.7) and earthworms; bioaccumulation in earthworms increases with decreasing exposure which might be an element of concern at low, environmentally relevant concentrations. The calculated BMF in humans is 1.9. For PFOA the BMF ≥ 1 was applied as indication of potential biomagnification in the conclusion on the classification as B (ECHA, 2013).

Not vB

- The BMFs of PFHpA (2.7 in pigs, 1.9 in humans) are lower than most BMFs of PFOA. PFOA was identified as B, so PFHxA cannot be identified as vB.

5 Conclusion

PFHpA fulfills the B-criterion for bioaccumulation and should be identified as such because the BMF in pigs and humans are ≥ 1. Other parameters contributing to the weight of evidence for the bioaccumulation potential are the human elimination T1/2s of 70-100 days and the bioaccumulation in earthworms which increases with decreasing soil concentrations, which might be an issue of environmental concern.

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Annex 1

alternative method									
PFHpA, median	BLOOD	l blood/kg bw	kg bw	serum/blood rate	ng/l serum (Zhang, 2013)	URINE	ng/l urine (Zhang, 2013)	l urine/day	ln 2
		0.077	60	0.57	58		0.82	1.3	0.693147
		4.62	l blood			elimination	1.07	ng/d	
		2.63	l serum						
		152.74	ng						
	T1/2	99.31	days						
	k2	0.0070	d-1						

Annex 2

BMF human					
	Corganisme / C diet				
	Corganisme / C drinking water (main intake source)				
	Corganisme	152,74	ng in 5 l blood	Zhang *et al* . 2013	
		366,57	ng in adult	factor 2.4 (amount whole body/amount in blood)	
		5,24	ng/kg bw	70 kg bw	
	Cdrinking water	97	ng/l	Xu et al., 2020, contaminated	
		194	ng/2l	intake	
		2,77	ng/kg bw	intake	
	BMF	1,89			