資料1

打合せ会（体内動態）資料
令和5年6月15日（木）

[redacted]

選定資料

1	PK
2	PK
3	PK
4	PBPK
5	PBPK
6	血液動態 Alb
7	半減期
8	半減期

9	母子移行
10	肝
11	母子移行
12	半減期
13	尿・PK
14	胆汁・中枢
15	血液動態　血漿/全血
16	PK

17	母子移行
18	母子移行
19	母子移行
20	母子移行
21	半減期
22	PBPK
23	PBPK

全血→血漿

US EPA（2023）PFOS

Poothong et al. (2017, 4239163) found that median PFOS concentrations in plasma, serum, and whole blood were 5.24, 4.77, and 2.85 ng/mL, respectively. These findings suggest that the common practice of multiplying by a factor of 2 to convert the concentrations in whole blood to serum {Ehresman, 2007, 1429928} will not provide accurate estimates for PFOS.

US EPA（2023）PFOA

Poothong et al. (2017, 4239163) found that median PFOA concentrations in plasma, serum, and whole blood were 1.90, 1.60, and 0.93 ng/mL, respectively. These findings suggest that the common practice of multiplying by a factor of 2 to convert the concentrations in whole blood to serum {Ehresman, 2007, 1429928} will not provide accurate estimates for PFOA.

EFSA (2020)

Partitioning behaviours of PFASs between human plasma and blood cells were investigated by several authors (Ehresman et al., 2007; Hanssen et al., 2013; Jin et al., 2016; K€arrman et al., 2006;Poothong et al., 2017). Median serum (or plasma) to whole blood ratio of PFOS, PFOA, PFHxS, PFNA and PFUnDA was approximately 2.

Studies on whole blood have also been conducted, with the advantage that whole blood represents the entire circulating fluid. it has been common to multiply the whole blood concentration with a factor of 2 to be comparable with concentrations in serum and plasma (Ehresman et al., 2007).

＃15　PFOS、PFOA、PFHxS、PFHxAの血漿/全血濃度比は、9.8/6.4（1.25）、1.2/1.0（1.2）、1.1/0.63（1.7）、0.46/1.4 ng/mLであった。

資料4_PFAS選定文献概要表　ヒト　全血を用いた知見

通し番号		
11	メタアナリシス	臍帯血一部全血
12	前向き出生コホート研究	全血
31	前向き出生コホート研究	乾燥血
37	出生コホート研究	一部全血
44	前向き出生コホート研究	一部全血
58	メタアナリシス	一部全血
59	メタアナリシス	補正
60	メタアナリシス	一部全血
60	メタアナリシス	一部全血

Table S1. The adjustment factors for gender and various biomarkers.

	PFOS	PFHxS	PFOA	PFHpA	PFNA	PFDA	PFUnDA
Serum: milk	0.00971 [6]	0.0114 [7]	0.0336 [7]	NA	NA	NA	NA
Blood: Serum [a]	0.4	0.4	0:4	0.4	0.4	0.4	0.4
Blood: Plasma [b]	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Male: female [c]	1.49 [d]	1.61 [d]	1.23 [d]	0.89 [e]	1.17 [d]	1.07 [e]	1.03 [d]
Mean: Median	1.35 [d]	1.44 [d]	1.19 [d]	1.25 [e]	1.34 [d]	1.16 [e]	1.99 [d]

Note: a, b, based on the volume of serum and plasma accounted for approximate 40% and 55% of human blood, respectively;

PKとPBPK

Verner etal.　2016　#2

Subject-specific characteristics		PFOS	PFOA	PFHXS
Maternal age at delivery (years)	30			
Pre-pregnancy maternal body weight (kg)	70			
Child's birth weight (kg)	3.4			
Child 's weight (kg) at Age　C	12.1			
At age child weight measurement (years)	2			
Total duration of breastfeeding (years)	0.5			
Age at maternal blood sample (years)	29.8			
Maternal oral dose (ug/kg/d)	0.001			
Volume of distribution (l/kg) constant		0.23	0.17	0.213
Plasma:milk level ratio constant		0.0138	0.0577	0.014
Cord:maternal plasma level ratio constant		0.454	0.783	0.556
Half-lives (years) constant		5.4	3.8	8.5

US EPA 2023 PFOS

Table 4-6. Updated and Original Chemical-Specific Parameters for PFOS in Humans

Parameter	Updated Value	Original Value[a] # 2
Volume of Distribution (mL/kg)	230[b]	230
Half-life (yr)	3.4[c]	5.5
Clearance (mL/kg/d)	0.128[d]	0.079
Cord Serum:Maternal Serum Ratio	0.40[e]	0.42
Milk:Serum Partition Coefficient	0.016[f]	0.014

[a] Verner et al. (2016, 3299692).
[b] Thompson et al. (2010, 2919278). # 16
[c] Li et al. (2018, 4238434). # 8
[d] Calculated from half-life ($t_{1/2}$) and volume of distribution (V_d). Clearance (Cl) = V_d * ln(2)/$t_{1/2}$.
[e] Average values for total PFOA Cord Serum:Maternal Serum ratios (see PFOS Appendix). This is a similar approach to that used by Verner et al. (2016, 3299692), but also includes studies made available after the publication of that model.
[f] Average value of studies as reported in Table 4-7. This is a similar approach to that used by Verner et al. (2016, 3299692), but also includes studies made available after the publication of that model.

Table 4-7. Summary of Studies Reporting the Ratio of PFOS Levels in Breastmilk and Maternal Serum or Plasma

Source	HERO ID	Milk:Maternal Plasma Ratio	Included in Verner et al. (2016, 3299692) Analysis
Haug et al. (2011, 2577501)	2577501	0.014	No
Seung-Kyu Kim et al. (2011, 2919258)	2919258	0.011	No
Liu et al. (2011, 2919240)	2919240	0.020	No
Kärrman et al. (2007, 1290903)	1290903	0.010	No
Cariou et al. (2015, 3859840)[a]	3859840	0.011	Yes
Sunmi Kim et al. (2011, 1424975)[b] # 14	1424975	0.030	Yes
Verner et al. (2016, 3299692) # 2	3299692	0.014[c]	–
Additional Studies	–	0.016[d]	–

Whether studies were included in the analysis of Verner et al. (2016, 3299692) is noted. The reported values were based on the mean of ratios in the study populations except when noted otherwise.

[a] Median result based on the report of Pizzurro et al. (2019, 5387175).

[b] Median result as reported by the authors.

[c] Average value of milk:maternal plasma ratio used by Verner et al. (2016, 3299692).

[d] Average value of milk:maternal plasma ratio with the inclusion of additional studies not in the original analysis. This value was used in the human PK model.

ほとんど選定資料は算出根拠になっていない。

Table 4-6. Updated and Original Chemical-Specific Parameters for PFOA in Humans

Parameter	Updated Value	Original Value[a] # 2
Volume of Distribution (mL/kg)	170[b]	170
Half-life (yr)	2.7[c]	3.8
Clearance (mL/kg/d)	0.120[d]	0.085
Cord Serum:Maternal Serum Ratio	0.83[e]	0.79
Milk:Serum Partition Coefficient	0.049[f]	0.058

Notes:

[a] Verner et al. (2016, 3299692).

[b] Thompson et al. (2010, 2919278). # 16

[c] Li et al. (2017, 9641333). # 8

[d] Calculated from half-life and volume of distribution. $Cl = Vd * \ln(2)/t_{1/2}$.

[e] Average values for total PFOA Cord Serum:Maternal Serum ratios (see PFOA Appendix). This is a similar approach to that used by Verner et al. (2016, 3299692), but also includes studies made available after the publication of that model.

[f] Average value of studies as reported in Table 4-7. This is a similar approach to that used by Verner et al. (2016, 3299692), but also includes studies made available after the publication of that model.

Table 4-7. Summary of Studies Reporting the Ratio of PFOA Levels in Breastmilk and Maternal Serum or Plasma

Source		HERO ID	Milk:Maternal Plasma Ratio	Included in Verner et al. (2016, 3299692) Analysis
Haug et al. (2011. 2577501)		2577501	0.038	No
Seung-Kyu Kim et al. (2011. 2919258)		2919258	0.025	No
Liu et al. (2011. 2919240)		2919240	0.11	No
Cariou et al. (2015. 3859840)[a]		3859840	0.034	Yes
Sunmi Kim et al. (2011. 1424975)[b]	# 14	1424975	0.04	Yes
Verner et al. (2016. 3299692)	# 2	3299692	0.058[c]	–
Additional Studies		–	0.049[d]	–

Notes: Whether studies were included in the analysis of Verner et al. (2016. 3299692) is noted. The reported values were based on the mean of ratios in the study populations except when noted otherwise.

[a] Median result based on the report of Pizzurro et al. (2019. 5387175).

[b] Median result as reported by the authors.

[c] Average value of milk:maternal plasma ratio used by Verner et al. (2016. 3299692).

[d] Average value of milk:maternal plasma ratio with the inclusion of additional studies not in the original analysis. This value was used in the human PK model.

Loccisano et al 2011 #5

Table 1
Chemical parameters for PBPK models for PFOA and PFOS in monkeys and humans.

PFOA	Definition and units	Value	Source
Tmc	Resorption maximum (mg/h/kg$^{0.75}$)[a]	0.15 (monkey); 10 (human; 3.8 yrs); 6 (human (2.3 yrs)	Fit to plasma concn. in monkey; estimated to give desired half-life in human (3.8 or 2.3 yrs)
Kt	Affinity constant (mg/L)	0.055	Fit plasma and urine concn. in monkey
Free	Free fraction of chemical in plasma	0.02	Fit to plasma concn. in monkey
PL	Liver:plasma partition coefficient	2.2	Rat tissue data (Kudo et al., 2007)
PF	Fat:plasma partition coefficient	0.04	Rat tissue data (Kudo et al., 2007)
PK	Kidney:plasma partition coefficient	1.05	Rat tissue data (Kudo et al., 2007)
PSk	Skin:plasma partition coefficient	0.1	Rat tissue data (Kudo et al., 2007)
PR	Rest of body:plasma partition coefficient	0.12	Rat tissue data (Kudo et al., 2007)
PG	Gut:plasma partition coefficient	0.05	Rat tissue data (Kudo et al., 2007)
Kurine	Urinary elimination rate (/h/kg$^{-0.25}$)	50 (monkey); 3e^{-4} (human)	Fit to urine concn. in monkey and human

限外濾過性？

(Olsen et al., 2007). 職業的ばく露の退職後
PFOA半減期 3.8年
PFOS半減期 5.4年.
Bartell et al. (2010) 飲用水ばく露停止後
PFOA 半減期2.3 年

PFOS			
Tmc	Resorption maximum (mg/h/kg$^{0.75}$)[a]	1.3 (monkey); 3.5 (human)	Fit to plasma concn. data in monkey; estimated to give desired half-life in human (5.4 yrs)
Kt	Affinity constant (mg/L)	0.023	Fit to plasma concn. data in monkey
Free	Free fraction of chemical in plasma	0.025	Fit to plasma concn. in monkey
PL	Liver:plasma partition coefficient	3.72	Mouse tissue data (DePierre)
PF	Fat:plasma partition coefficient	0.14	Mouse tissue data (DePierre)
PK	Kidney:plasma partition coefficient	0.8	Mouse tissue data (DePierre)
PSk	Skin:plasma partition coefficient	0.29	Mouse tissue data (DePierre)
PR	Rest of body:plasma partition coefficient	0.2	Mouse tissue data (DePierre)
PG	Gut:plasma partition coefficient	0.57	Mouse tissue data (DePierre)
Kurine	Urinary elimination rate (/h/kg$^{-0.25}$)	0.003 (monkey); 0.001 (human)	Fit to urine concn. in monkey and human

大半の臓器移行のデータは実験動物の知見を利用
選定資料は根拠になっていない。

Loccisano et al 2013 #4

Table 3

Chemical parameters for PBPK models for PFOA and PFOS in pregnant and lactating women, fetus, and infant.

	PFOA			PFOS		
Parameter	**mother**	**fetus**	**infant**	**mother**	**fetus**	**infant**
Free fraction of chemical in plasma (Free)	0.02	0.02	0.02	0.025	0.025	0.025
Volume of distribution (Vdc; infant only, scaled to BWKid)	-	-	0.17		-	0.22
Renal resorption Parameters						
transporter maximum, Tmc (ug/h/kg$^{0.75}$)	10	-	-	3.5	-	-
affinity constant, Kt (ug/L)	0.055	-	-	0.023	-	-
Partition Coefficients						
Gut:plasma (Pgut)	0.05	-	-	0.57	-	-
Liver:plasma (Pliv)	2.2	-	-	3.72	-	-
Kidney: plasma (Pkid)	1.05	-	-	0.8	-	-
Fat: plasma (Pfat)	0.04	-	-	0.13	-	-
Mammary Tissue: plasma (Pmam; gestation only)	0.13	-	-	0.16	-	-
Rest of body tissues: plasma (Ptis)	0.12	0.12	-	0.20	0.20	-
Placenta:Plasma (Ppla)	0.28	-	-	0.41	-	-
Skin: plasma (PSk)	0.1	-	-	0.29	-	-
Mammary tissue:plasma (PMam; gestation only)	0.13	-		0.16	-	-
Milk: plasma (PMilk; lactation only)	0.038	-	-	0.0122	-	-
Uptake/Elimination Rate Constants						
urinary elimination rate constant, kurinec (/h/kg-0.25); keliml for infant (/h)	0.1	-	0.005	0.005	-	0.001

PFOA-specific parameters; PFOS parameters are in Table 1 of the manuscript.

tissue:plasma partition coefficients (from rat)

constant PMam = 0.13 mammary:blood partition coeff. (from mouse)

constant PPla = 0.28 placenta:blood partition coeff. (from rat)

The placental transfer rate constants were adjusted (calibrated) to yield the maternal:fetal ratios observed in several of the datasets that reported maternal or cord blood PFC levels (Apelberg et al. 2007; Fei et al. 2007; Midasch et al. 2007（#20で引用）; Washino et al. 2009).

乳腺・胎盤移行データは実験動物の知見を利用
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EFSA 2020

Table M.1a: Ratios of concentrations in breast milk and maternal serum of PFOA, PFNA, PFHxS and PFOS, calculated based on mean or median values reported by various authors

Reference	Milk/serum ratio							
	Based on mean values				Based on median values			
	PFHxS	PFOS	PFOA	PFNA	PFHxS	PFOS	PFOA	PFNA
Kärrman et al. (2007)	0.018	0.0097	NA	NA	0.018	0.0089	NA	NA
Haug et al. (2011a,b)	NA	0.014	0.038	NA	NA	0.013	0.018	NA
Kim et al. (2011a) #14	0.006	0.009	0.018	NA	0.018	0.011	0.025	NA
Liu et al. (2011)	NA	0.018	0.11	0.047	NA	0.014	0.096	0.039
Median	0.012	**0.012**	**0.038**	0.047	0.018	**0.012**	**0.025**	0.039

NA: not applicable.

Note: Median ratios were the basis for the values used in the PBPK modelling, being 0.015 for PFHxS/PFOS and 0.03 for PFOA/PFNA.

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$$k_{human} = k_{rat} \times (Bw_{human}/BW_{rat})^{-0.25}$$

BWbirth=3.68 ;Body weight at birth in Kg, new add opinion 2020
PT= 0.74 ;placenta transfer, new add opinion 2020
Ratio= 0.03 ;maternal/Milk concentration during breastfeeding, new add opinion 2020
DECLINE = 0.077 ;decline of PFOA in milk was 7.7% per month, new add opinion 2020

The CONTAM Panel (2018)
Tmc of 6,000 µg/h/kg$^{-0.75}$→half-life of 2.3 years for PFOA

; Chemical-specific parameters (PFOA)
Tmc = 6,000 ;Maximum resorption rate
Kt = 55 ;Resorption affinity; same as monkey

Free = 0.02 ;Free fraction of PFOA in plasma; same as monkey
PL = 2.2 ;Liver/plasma partition coefficient ラット
PF = 0.04 ;Fat/plasma partition coefficient ラット
PK = 1.05 ;Kidney/plasma partition coefficient ラット
PSk = 0.1 ;Skin/plasma partition coefficient ラット
PR = 0.12 ;Rest of the body/plasma partition coefficient ラット
PG = 0.05 ;Gut/blood plasma coefficient ラット
kurinec = 0.0003 ;urinary elimination rate constant (/h/kg^-0.25); estimated from Harada et al. (2005) #13

大半の臓器分布のデータは実験動物の知見を利用
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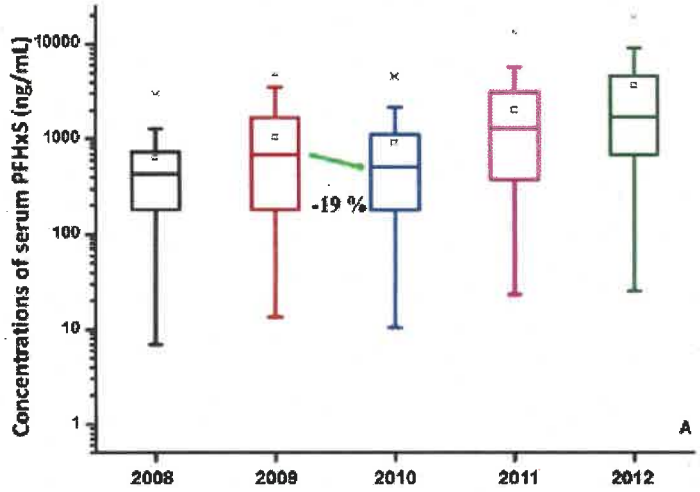
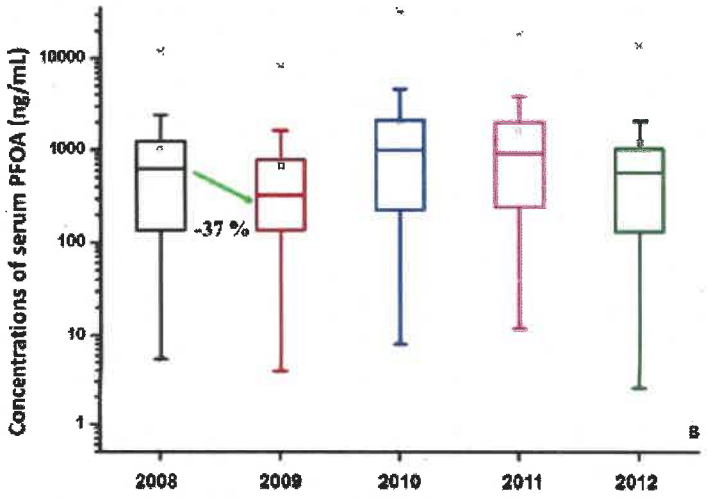
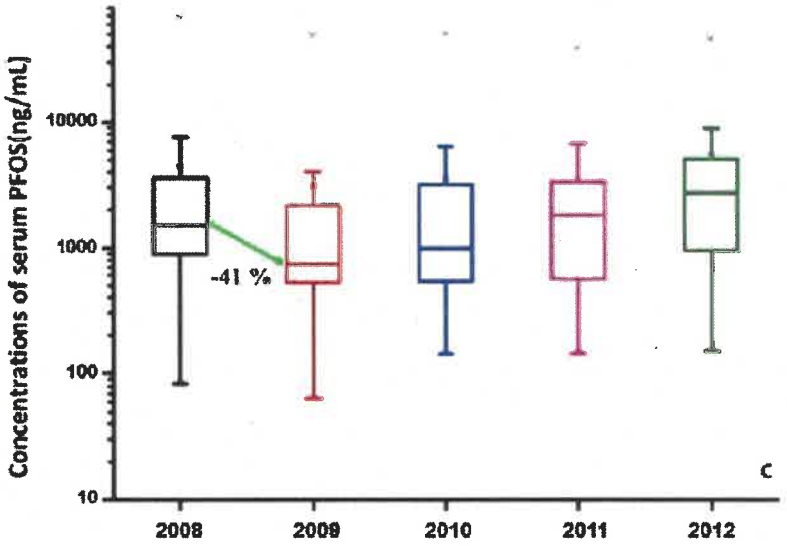
#12 Fu et al 2016







The 3 M Company was the main PFOS producer in history and manufactured approximately 3600 tonnes per year of POSF before 2002
The annual productions of PFOS and PFHxS in the plant were approximately 60 and 0 tonnes in 2008, respectively.
The annual production volumes of PFOS from 2009 to 2011 were 30, 10, and 10 tonnes, respectively, whereas those of PFHxS were 10, 10 and 30 tonnes, respectively