参考資料 3

国内の PFAS 関連研究について

PFAS を対象とした研究事例について、令和 4 年度食品安全確保総合調査「パーフルオロ化合物に係る国際機関等の評価及び科学的知見の情報収集並びに整理成果報告書」（令和 5 年 3 月、一般財団法人化学物質評価研究機構）[1]の別添 3「調査事業報告項目の情報抽出結果」における 257 報（主な評価書に収載された Reference リストから選定された 203 報（評価書文献）及び文献 DB 文献から選定された 54 報（文献 DB 文献））について、国内の研究機関が関わっていると考えられる文献数を独自に集計した。

なお、当該資料において示されている文献は、「日本における PFOS、PFOA、PFHxS のリスク評価の根幹として最重要と考えられる」という観点から選定されているため、PFAS 全体を対象としたものではないことや環境動態に関する文献は海外事例を含んでいないことに留意が必要である。

選定文献数	257 (33)
[研究内容の内訳]	
環境動態（環境中濃度、バイオモニタリング）	14 (14)
毒性（動物実験、*in vitro*）	82 (8)
毒性（疫学調査）	130 (7)
生体内動態（半減期等の ADME）	22 (2)
物理化学的性質	6 (2)
リスク評価	3 (0)

※括弧（）内の数字は国内の研究機関が関わっていると考えられた文献の独自の集計数

参考までに、上記の国内の研究機関が関わっていると考えられた文献 33 報について、以下、タイトルとアブストラクトを一覧にして示す（発表年の順に列記）。

[1] https://www.fsc.go.jp/fsciis/survey/show/cho20230050001

表　食品安全委員会の調査事業報告書より独自に抽出した国内の PFAS 関連研究

No.	Title	Abstract
1	Krafft points, critical micelle concentrations, surface tension, and solubilizing power of aqueous solutions of fluorinated surfactants (Kunieda, H.; Shinoda, K., J. Phys. Chem. 1976, 80, 22, 2468–2470)	The Krafft points, critical micelle Concentrations (cmc), surface tension above the cmc, and solubilizing power in aqueous solutions of perfluoroalkane carboxylates as functions of fluorocarbon chain length and the types of gegenions have been studied. The Krafft point, surface tension above the cmc, and solubilizing power differ markedly with the types of gegenions, but the cmc is mainly dependent on the fluorocarbon chain length and not on the types of gegenions of same valency.
2	Characterization of hepatic responses of rat to administration of perfluorooctanoic and perfluorodecanoic acids at low levels (Kawashima, Y; Kobayashi, H; Miura, H; Kozuka, H, Toxicology. 1995 May 23;99(3):169-78. doi: 10.1016/0300-483x(95)03027-d.)	Male rats were fed a diet that contained perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) at concentrations ranging from 0.0025-0.04% (w/w) and from 0.00125-0.01% (w/w), respectively, for 1 week. The hepatic responses of the rats to PFOA and PFDA were examined. Upon the administration of PFOA and PFDA, three peroxisome proliferator-responsive parameters, peroxisomal beta-oxidation, microsomal 1-acylglycerophosphocholine (1-acyl-GPC) acyltransferase and cytosolic long-chain acyl-CoA hydrolase, were induced in a dose-dependent manner. A multiple regression analysis of the three parameters revealed that the data from rats treated with PFOA and PFDA shared one common line, indicating a marked correlation among the inductions of the three parameters. The activities of glutathione (GSH) S-transferases towards 1-chloro-2,4-dinitrobenzene (CDNB) and 1,2-dichloro-4-nitrobenzene (DCNB) were depressed by PFOA and PFDA. Significant inverse correlations were found between activities of GSH S-transferases and peroxisomal beta-oxidation. The administration of PFOA and PFDA significantly increased hepatic concentration of triacylglycerol. The perfluorocarboxylic acids at relatively high doses caused accumulation of cholesterol in liver. Electron microscopic studies showed that the administration of PFOA and PFDA caused an increase in cell size and proliferations of peroxisomes, and that the treatment of rats with PFDA at dietary concentration of 0.01% caused a marked increase in small lipid droplet in hepatocytes, indicative of hepatotoxic manifestations. The present results suggest that when PFOA and PFDA are administered at low levels, there are no differences between the properties of the perfluorocarboxylic acids as peroxisome proliferators, although the administration of PFDA at the doses exceeding a certain level becomes markedly toxic to hepatocytes.
3	The influence of time, sex and geographic factors on levels of perfluorooctane sulfonate and perfluorooctanoate in human serum over the last 25 years (Harada, Kouji; Saito, Norimitsu; Inoue, Kayoko; Yoshinaga, Takeo; Watanabe, Takao; Sasaki, Shiro; Kamiyama, Shigetoshi; Koizumi, Akio, J Occup Health. 2004 Mar;46(2):141-7. doi: 10.1539/joh.46.141.)	Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are important perfluorochemicals (PFCs) in various applications. Recently, it has been shown that these chemicals are widespread in the environment, wildlife and humans. But the kinds of factors that affect their levels in serum are unclear, and it is also not clear whether exposure to them is increasing or not. To investigate the impacts of time, geographical location and sex on the levels of these chemicals, we measured PFOS and PFOA concentrations in human sera samples collected both historically and recently in Miyagi, Akita and Kyoto Prefectures in Japan. The PFOS and PFOA levels in sera [Geometric Mean (Geometric Standard Deviation)] (microg/L) in 2003 ranged from 3.5 (2.9) in Miyagi to 28.1 (1.5) in Kyoto for PFOS and from 2.8 (1.5) to 12.4 (1.4) for PFOA. Historical samples collected from females demonstrated that PFOS and PFOA concentrations have increased by factors of 3 and 14, respectively, over the past 25 yr. There are large sex differences in PFOS and PFOA concentrations in serum at all locations. Furthermore, there are predominant regional differences for both PFOS and PFOA concentrations. In Kyoto the concentrations of PFOA in dwellers who had lived in the Kinki area for more than 2 yr were significantly higher than in people who had recently moved into the area, in both sexes. This finding suggests that there are sources of PFOA in the Kinki area that have raised the PFOA serum levels of its inhabitants. Further studies are needed to elucidate these sources in the Kinki area of Japan.
4	Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion (Harada, Kouji; Inoue, Kayoko; Morikawa, Akiko; Yoshinaga, Takeo; Saito, Norimitsu;	Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are detected in the environment, as well as more specifically in wildlife and humans. However, the toxicokinetic aspects of perfluorochemicals in humans are unclear. In this study, we measured concentrations of PFOA and PFOS in subjects who had lived in Kyoto city for more than 10 years. The serum concentrations of PFOA and PFOS were higher in females who menstruated than those who did not menstruation ($P<0.01$), but in males this did not change by age; the levels in females reached those in males at an age of 60 years. We then determined the renal clearances of PFOA and PFOS in young (20-40 years old, N=5 for each sex) and old

No.	Title	Abstract
	Koizumi, Akio, Environ Res. 2005 Oct;99(2):253-61. doi: 10.1016/j.envres.2004.12.003. Epub 2005 Jan 18.)	(60 years old, N=5 for each sex) subjects of both sexes. All young females were menstruating, while all old females were not. The renal clearances were 10(-5)-fold smaller than the glomerular filtration rate in humans, suggesting the absence of active excretion in human kidneys. The renal clearances of PFOA and PFOS were approximately one-fifth of the total clearance based on their serum half-lives, assuming a one-compartment model. The sex differences in renal clearance that have been reported in rats and Japanese macaques were not found in our human subjects. We tried to build a one-compartment pharmacokinetic model using the reported half-lives in human. The model was simple but could predict the serum concentrations in both males and females fairly well. We therefore suggest that an internal dose approach using a pharmacokinetic model should be taken because of the large species differences in kinetics that exist for PFOA and PFOS.
5	P1073 難分解性化学物質に対する生体試料バンクの有用性検証と曝露評価 (吉永 侃夫, 原田 浩二, 井上 佳代子, 難分解性物質研究グループ, 小泉 昭夫, 産業衛生学雑誌, 2005 年 47 巻 Special 号 688-)	環境中に放出されて多種多様の化学物質による環境汚染や人体への影響を監視しするために､私達は難分解性化学物質を対象とし”生体試料バンク”を設立した。今回このバンクの試料を用いて、バンクの有用性の証明と、新規物質の曝露評価を行った。【方法】約 30 年前から収集された生体試料（血液と陰膳方式の食事）と新規に全国で 10 箇所で集め出した試料（血液、母乳と購入方式の食事）を基に血液 24,500、母乳 1,080、食事 3,800 検体から成るバンクを創設した。これらの試料から 1980 年代、1995 年代を中心とした、同一人物からセットで提供された血液と食事検体を用いて、GC/MS 法（有機溶剤抽出法）で#74、#118、#99、#138、#146、#153、#163&164、#156、#170、#180、#182&187 のコンジェナーの PCB を、原子吸光法（還元気化法）でメチル水銀を測定して既報のデータと比較てバンクの有用性を検討した。また新規化合物として、PBDEs を GC/MS 法（有機溶剤抽出法）で低-中臭化の、#47、#100、#99、#153 のコンジェナーを、PFOS、PFOA を固相抽出して LC/MS 法で測定してヒトの曝露評価を行った。
6	Gene expression profiles in rat liver treated with perfluorooctanoic acid (PFOA) (Guruge, Keerthi S; Yeung, Leo W Y; Yamanaka, Noriko; Miyazaki, Shigeru; Lam, Paul K S; Giesy, John P; Jones, Paul D; Yamashita, Nobuyoshi, Toxicol Sci. 2006 Jan;89(1):93-107. doi: 10.1093/toxsci/kfj011. Epub 2005 Oct 12.)	Perfluorooctanoic acid (PFOA; Pentadecafluorooctanoic acid) is widely used in various industrial applications. It is persistent in the environment and does not appear to undergo further degradation or transformation. PFOA is found in tissues including blood of wildlife and humans; however, the environmental fate and biological effects of PFOA remain unclear. Microarray techniques of gene expression have become a powerful approach for exploring the biological effects of chemicals. Here, the Affymetrix, Inc. rat genome 230 2.0 GeneChip was used to identify alterations in gene regulation in Sprague-Dawley rats treated with five different concentrations of PFOA. Male rats were exposed by daily gavage to 1, 3, 5, 10, or 15 mg PFOA/kg, body weight (bw)/day for 21 days and at the end of the exposure, liver was isolated and total liver RNA were used for the gene chip analysis. Over 500 genes, whose expression was significantly ($p < 0.0025$) altered by PFOA at two-fold changes compared to control, were examined. The effects were dose-dependent with exposure to 10 mg PFOA/kg, bw/day, causing alteration in expression of the greatest number of genes (over 800). Approximately 106 genes and 38 genes were consistently up- or down-regulated, respectively, in all treatment groups. The largest categories of induced genes were those involved in transport and metabolism of lipids, particularly fatty acids. Other induced genes were involved in cell communication, adhesion, growth, apoptosis, hormone regulatory pathways, proteolysis and peptidolysis and signal transduction. The genes expression of which was suppressed were related to transport of lipids, inflammation and immunity, and especially cell adhesion. Several other genes involved in apoptosis; regulation of hormones; metabolism; and G-protein coupled receptor protein signaling pathways were significantly suppressed.
7	Biliary excretion and cerebrospinal fluid partition of perfluorooctanoate and perfluorooctane sulfonate in humans (Harada, K. H.; Hashida, S.; Kaneko, T.; Takenaka, K.; Minata, M.; Inoue, K.; Saito, N.; Koizumi, A., Environ Toxicol Pharmacol. 2007 Sep;24(2):134-9. doi: 10.1016/j.etap.2007.04.003. Epub 2007 May 4.)	Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are detected in the environment and, more specifically, in wildlife and humans. The large variation in the reported biological half-lives for PFOA and PFOS has remained unexplored. In this study, we aimed to evaluate their partition from serum to bile and cerebrospinal fluid (CSF) in humans. Four pairs of serum and bile, and 7 pairs of serum and CSF were donated by patients. In considering biliary excretion, the median concentrations of PFOA and PFOS in serum samples were 3.8 and 23.2ng/mL, respectively, whereas those in bile samples were 1 and 27.9ng/mL, respectively. The median ratio of PFOS concentrations (bile/serum: 0.60) was significantly higher than that for PFOA, 0.21 (p<0.01). Biliary excretion rates for PFOA and PFOS in the present study subjects were estimated as 1.06 and 2.98mL/kg/day, respectively, which is significantly higher than serum clearances via urine in humans and might represent a major excretion route. Biliary reabsorption rates of PFOA and PFOS were estimated to be 0.89 and 0.97, respectively. In considering partition into the cerebrospinal fluid, the median concentrations of PFOA and PFOS in serum samples were 2.6 and 18.4ng/mL, respectively, whereas those in CSF

No.	Title	Abstract
		samples were 0.06 and 0.10ng/mL, respectively. The median ratio of PFOS concentrations (CSF/serum: 9.1 (×10(-3))) was comparable to that of PFOA, 17.6 (×10(-3)), suggesting that PFOA and PFOS cannot pass through the blood-brain barrier freely. In conclusion, the biliary excretion of these compounds was comparable in both rats and humans and the long half-lives in humans might be attributable to low levels of excretion in urine and high biliary reabsorption rates.
8	The ubiquitous environmental pollutant perfluorooctanoicacid inhibits feeding behavior via peroxisome proliferator-activated receptor-alpha (Asakawa, Akihiro; Toyoshima, Megumi; Harada, Kouji H; Fujimiya, Mineko; Inoue, Kayoko; Koizumi, Akio, Int J Mol Med. 2008 Apr;21(4):439-45.)	Perfluorinated compounds (PFCs) have been employed as surface treatment agents in a variety of products. Perfluorooctanoic acid (PFOA), a PFC that is found globally in the environment and in human tissues, has been increasing significantly in serum levels over the past 50 years. Here, we demonstrated that PFOA inhibits feeding behavior as potently as the endogenous peroxisome proliferator-activated receptor (PPAR)-alpha ligand, oleoylethanolamide (OEA), via the activation of PPAR-alpha, the vagal nerve and hypothalamic neuropeptides. Peripherally administered PFOA decreased food intake as potently as OEA. PFOA decreased gastric emptying and increased the expression level of the gene encoding urocortin 1 in the hypothalamus and the immunoreaction for urocortin 1 in the paraventricular nucleus. Vagotomy attenuated the inhibitory effects of PFOA on feeding. The inhibition of food intake and body-weight gain by PFOA was completely mitigated in PPAR-alpha-/-mice. Our studies demonstrated that the ubiquitous environmental pollutant PFOA works as an imitator of OEA mimicking its action in the feeding regulatory system, providing a new mode of action as represented by environmental 'anorexigens'.
9	Neonatal death of mice treated with perfluorooctane sulfonate (Yahia, D.; Tsukuba, C.; Yoshida, M.; Sato, I.; Tsuda, S., J Toxicol Sci. 2008 May;33(2):219-26. doi: 10.2131/jts.33.219.)	Pregnant mice exposure to perfluorooctane sulfonate (PFOS) causes neonatal death. Ten pregnant ICR mice per group were given 1, 10 or 20 mg/kg PFOS daily by gavage from gestational day (GD) 0 to the end of the study. Five dams per group were sacrificed on GD 18 for prenatal evaluation, the others were left to give birth. Additional studies were conducted for histopathological examination of lungs and heads of fetuses and neonates at birth. PFOS treatment (20 mg/kg) reduced the maternal weight gain and feed intake but increased the water intake. The liver weight increased in a dose-dependent manner accompanied by hepatic hypertrophy at 20 mg/kg. PFOS reduced the fetal body weight in a dose-dependent manner and caused a bilateral enlargement in the neck region in all fetuses at 20 mg/kg and mild enlargement in some fetuses at 10 mg/kg, in addition to skeletal malformations. Almost all fetuses at 20 mg/kg were alive on GD18 and showed normal lung structure; but at parturition, all neonates were inactive and weak, showed severe lung atelectasis and severe dilatation of intracranial blood vessel, and died within a few hours. At 10 mg/kg, all neonates were born alive, 0.27 showed slight lung atelectasis, all of them had mild to severe dilatation of the intracranial blood vessel, and 0.45 of neonates died within 24 hr. The cause of neonatal death in mice exposed to PFOS may be attributed either to the intracranial blood vessel dilatation or to respiratory dysfunction. The former might be a cause of the latter.
10	Effect of perfluorooctane sulfonate (PFOS) on influenza A virus-induced mortality in female B6C3F1 mice (Guruge, Keerthi S; Hikono, Hirokazu; Shimada, Nobuaki; Murakami, Kenji; Hasegawa, Jun; Yeung, Leo W Y; Yamanaka, Noriko; Yamashita, Nobuyoshi, J Toxicol Sci. 2009 Dec;34(6):687-91. doi: 10.2131/jts.34.687.)	Recent studies showed that perfluorooctane sulfonate (PFOS) affects the mammalian immune system at levels reportedly found in the general human population. It has been demonstrated that exposure to immunotoxic chemicals may diminish the host resistance of animals to various pathogenic challenges and enhance mortality. Therefore, the current study was carried out to characterize the effect of a 21 day pre-administration of zero, 5, or 25 microg PFOS/kg bw/day in female B6C3F1 mice on host resistance to influenza A virus infection. At the end of PFOS exposure, body/organ weights did not significantly change whereas PFOS distribution in blood plasma, spleen, thymus and lung was dose-dependently increased. PFOS exposure in mice resulted a significant increase in emaciation and mortality in response to influenza A virus. The effective plasma concentrations in female mice were at least several fold lower than reported mean blood PFOS levels from occupationally exposed humans, and fell in the upper range of blood concentrations of PFOS in the normal human population and in a wide range of wild animals. Hence, it should be important to clarify the precise mechanism(s) for excess mortality observed in the high dose group.
11	乳汁中ペルフルオロ化合物の定量及び母体血からの移行性 (中田 彩子, 斉藤 貢一, 岩崎 雄介, 伊藤 里恵, 岸 玲子, 中澤 裕之, 分析化学, 2009 年 58 巻 8 号 653-659)	本研究では，ペルフルオロ化合物（PFCs）の子どもへの暴露源として乳汁に着目し，高速液体クロマトグラフィー/タンデム質量分析法（LC/MS/MS）による高感度分析法を構築した．前処理には Oasis WAX による固相抽出法を採用した．添加回収試験では，平均回収率 94.3～109.0%（RSD＜10.3%）と良好な結果が得られ，本法による定量限界は，ペルフルオロオクタン酸（PFOA）に関しては 0.012 ng/mL，ペルフルオロオクタンスルホン酸（PFOS），ペルフルオロヘキサンスルホン酸（PFHxS）及びペルフルオロノナン酸（PFNA）では 0.004 ng/mL であった．本法を用いてヒト母乳，育児用粉ミルク及び牛乳の分析を行ったところ，ヒト母乳中か

No.	Title	Abstract
		ら比較的高濃度の PFCs が検出され，その濃度範囲は PFOS で 0.046～0.098 ng/mL，PFOA では 0.016～0.270 ng/mL であった．更に，ヒト母体血から母乳への PFCs 移行性を調べるために，母乳と同一個人から採取した母体血中の PFCs 濃度を測定したところ，母体血と母乳の間には有意な相関性が示された．
12	都市大気中ペルフルオロオクタンスルホン酸 (PFOS) 濃度の週間変化 (小谷野 道子, 杉田 和俊, 稲葉 洋平, 山口 一郎, 谷保 佐知, 山下 信義, 遠藤 治, 大気環境学会誌, 2010 年 45 巻 6 号 279-282)	都市大気中の perfluorooctane sulfanate (PFOS) の測定を行った。東京に隣接する和光市で、大気中浮遊粒子 (TSP) を 2006 年 7 月 3-29 日 (夏期) と 12 月 1-27 日 (冬期) の毎日捕集した。捕集した試料はメタノールで超音波抽出し、LC/MS/MS で分析した。この方法による PFOS の回収率は 90%、繰り返し精度は 13% (c.v.)であった。TSP 濃度の幾何平均値は 7 月が 48 μg/m3、12 月が 43 μg/m3 とほぼ同等であった。これに対し PFOS 濃度の幾何平均値は 7 月が 6.8 pg/m3、12 月が 3.5 pg/m3 と夏期の方が冬期よりも高かった。大気中の PFOS 濃度は、平日に対して、土曜と日曜の週末に低い週間変化を示していた。
13	Ultrasonic-induced tonic convulsion in rats after subchronic exposure to perfluorooctane sulfonate (PFOS) (Kawamoto, Kosuke; Sato, Itaru; Tsuda, Shuji; Yoshida, Midori; Yaegashi, Kaori; Saito, Norimitsu; Liu, Wei; Jin, Yihe, J Toxicol Sci. 2011 Jan;36(1):55-62. doi: 10.2131/jts.36.55.)	Perfluorooctane sulfonate (PFOS) is one of the persistent organic pollutants distributed widely in the global environment. We have found that a single oral administration of PFOS induced tonic convulsion in mice and rats when a brief ultrasonic stimulus was applied to the animals. The aim of this study is to examine whether the neurotoxicity is caused by subchronic dietary exposure to PFOS. Rats were treated with dietary PFOS at 0, 2, 8, 32 and 128 ppm for 13 weeks. Animals were carefully observed for pharmacotoxic signs and responses to the ultrasonic stimulus applied biweekly. PFOS increased liver weight and decreased food consumption and body weight. PFOS concentrations in the serum, brain, liver and kidney were increased almost proportional to its total dose, although the ratios of PFOS concentrations in tissues to total doses in the group treated with the highest concentration were a little lower. The ranges of relative concentrations in the brain, liver and kidney to serum concentration were 0.13 to 0.24, 2.7 to 6.3 and 0.82 to 1.6, respectively. PFOS alone did not cause any neurotoxic symptoms; however, 5 rats out of 6 showed tonic convulsion in the 6th week when ultrasonic stimulus was applied to the 128 ppm rats with the total PFOS dose of 338 mg/kg. The ultrasonic stimulus did not cause convulsion in the other groups. Histopathological examination including electron microscopic examination could not detect any abnormality in the brain. Because the acute oral dose of PFOS causing the convulsion was 250 mg/kg (Sato et al., 2009), the convulsion induced by PFOS seemed to depend on its total dose regardless of treatment schedule.
14	Levels and profiles of long-chain perfluorinated carboxylic acids in human breast milk and infant formulas in East Asia (Fujii, Yukiko; Yan, Junxia; Harada, Kouji H; Hitomi, Toshiaki; Yang, Hyeran; Wang, Peiyu; Koizumi, Akio, Chemosphere. 2012 Jan;86(3):315-21. doi: 10.1016/j.chemosphere.2011.10.035. Epub 2011 Nov 21.)	In this study, 90 human breast milk samples collected from Japan, Korea, and China were analyzed for perfluorooctanoic acid (PFOA) (C8), perfluorononanoic acid (PFNA) (C9), perfluorodecanoic acid (PFDA) (C10), perfluoroundecanoic acid (PFUnDA) (C11), perfluorododecanoic acid (PFDoDA) (C12), and perfluorotridecanoic acid (PFTrDA) (C13). In addition, infant formulas (n = 9) obtained from retail stores in China and Japan were analyzed. PFOA was the predominant compound and was detected in more than 60% of samples in all three countries. The PFOA, PFNA, PFDA, and PFUnDA levels in Japan were significantly higher than those in Korea and China ($p<0.05$). The PFTrDA level was highest in Korea ($p<0.05$). The median PFOA concentrations were 89 pg mL(-1) (48% of total perfluorinated carboxylic acids (PFCAs) (C8-C13)) in Japan, 62 pg mL(-1) (54%) in Korea, and 51 pg mL(-1) (61%) in China. The remaining ∑PFCAs (C9-C13) were 95 pg mL(-1) in Japan, 52 pg mL(-1) in Korea, and 33 pg mL(-1) in China. Among the long-chain PFCAs, odd-numbered PFCAs were more frequently detected than even-numbered PFCAs, except for PFDA in Japan. There were no evident correlations between the mother's demographic factors and the PFCA concentrations. PFOA, PFNA, and PFDA were frequently detected in both Japan and China, but there were no significant differences between the two countries. The total PFCA concentrations in the infant formulas were lower than those in the breast milk samples in Japan ($p<0.05$), but not in China ($p>0.05$). In conclusion, various PFCAs were detected in human breast milk samples from East Asian countries.
15	Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants (Okada, Emiko; Sasaki, Seiko; Saijo, Yasuaki; Washino, Noriaki; Miyashita, Chihiro; Kobayashi, Sumitaka; Konishi, Kanae; Ito, Yoichi M; Ito, Rie;	BACKGROUND: Recent studies have shown effects of prenatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) on infants in the general environmental levels. Laboratory animal studies have shown that exposure to PFOS and PFOA is associated with immunotoxic effects. OBJECTIVES: To investigate the relationship between maternal PFOS and PFOA levels and infant allergies and infectious diseases during the first 18 months of life. Cord blood immunoglobulin (Ig) E levels were also evaluated. METHODS: We conducted a prospective cohort study of pregnant women from 2002 to 2005 in Sapporo, Japan. Maternal PFOS and PFOA levels were measured in relation to cord blood IgE concentrations (n=231) and infant allergies and infectious diseases (n=343). Characteristics of mothers and their infants were obtained from

No.	Title	Abstract
	Nakata, Ayako; Iwasaki, Yusuke; Saito, Koichi; Nakazawa, Hiroyuki; Kishi, Reiko, Environ Res. 2012 Jan;112:118-25. doi: 10.1016/j.envres.2011.10.003. Epub 2011 Oct 24.)	self-administered questionnaires and medical records. Development of infant allergies and infectious diseases was determined from self-administered questionnaires at 18 months of age. Concentrations of PFOS and PFOA in maternal serum and concentrations of IgE in umbilical cord serum at birth were measured. RESULTS: Cord blood IgE levels decreased significantly with high maternal PFOA concentration among female infants. However, there were no significant associations among maternal PFOS and PFOA levels and food allergy, eczema, wheezing, or otitis media in the 18 month-old infants (adjusted for confounders). CONCLUSIONS: Although cord blood IgE level decreased significantly with high maternal PFOA levels among female infants, no relationship was found betweenmaternal PFOS and PFOA levels and infant allergies and infectious diseases at age in 18 months.
16	東京都内の水道水中の有機フッ素化合物濃度および組成分布 (水環境学会誌, 2012 年 35 巻 3 号 57-64)	東京都内の水道水について，有機フッ素化合物（PFCs）である 11 種のペルフルオロアルキルカルボン酸類および 5 種のペルフルオロアルキルスルホン酸類を測定した。40 地点の PFCs の総濃度は 0.72～95 ng・L-1 の範囲で，平均値は 19 ng・L-1 であった。最多検出地点では 12 種の PFCs が検出され，PFCs 組成比を用いたクラスター分析の結果，都内の水道水は多摩地域と区部の二種類にほぼ大別できた。区部の水道水の PFCs 組成比および濃度は類似しているのに対して，多摩地域の水道水の組成比および濃度にはばらつきがみられた。これは区部の水道水が表流水を原水としているのに対して，多摩地域では各浄水所において表流水に地下水を混合して原水としていることによるものと考えられた。諸外国の PFCs の指針値等と測定値を比較した結果，都内の水道水中の個々の PFC 濃度は指針値等を下回った。
17	Temporal trends of perfluoroalkyl acids in plasma samples of pregnant women in Hokkaido, Japan, 2003-2011 (Okada, Emiko; Kashino, Ikuko; Matsuura, Hideyuki; Sasaki, Seiko; Miyashita, Chihiro; Yamamoto, Jun; Ikeno, Tamiko; Ito, Yoichi M; Matsumura, Toru; Tamakoshi, Akiko; Kishi, Reiko, Environ Int. 2013 Oct;60:89-96. doi: 10.1016/j.envint.2013.07.013. Epub 2013 Sep 6.)	Perfluoroalkyl acids (PFAAs) are persistent organic pollutants that are used in a wide range of consumer products. Recent epidemiological studies have shown that prenatal exposure to toxic levels of PFAAs in the environment may adversely affect fetal growth and humoral immune response in infants and children. Here we have characterized levels of prenatal exposure to PFAA between 2003 and 2011 in Hokkaido, Japan, by measuring PFAA concentrations in plasma samples from pregnant women. The study population comprised 150 women who enrolled in a prospective birth cohort study conducted in Hokkaido. Eleven PFAAs were measured in maternal plasma samples using simultaneous analysis by ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. At the end of the study, in 2011, age- and parity-adjusted mean concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS) were 1.35ng/mL, 1.26ng/mL, 0.66ng/mL, 1.29ng/mL, 0.25ng/mL, 0.33ng/mL, 0.28ng/mL, and 3.86ng/mL, respectively. Whereas PFOS and PFOA concentrations declined 8.4%/y and 3.1%/y, respectively, PFNA and PFDA levels increased 4.7%/y and 2.4%/y, respectively, between 2003 and 2011. PFUnDA, PFDoDA, and PFTrDA were detected in the vast majority of maternal samples, but no significant temporal trend was apparent. Future studies must involve a larger population of pregnant women and their children to determine the effects of prenatal exposure to PFAA on health outcomes in infants and children.
18	Perfluoroalkyl substances in the blood of wild rats and mice from 47 prefectures in Japan: use of samples from nationwide specimen bank (Taniyasu, Sachi; Senthilkumar, Kurunthachalam; Yamazaki, Eriko; Yeung, Leo W Y; Guruge, Keerthi S; Kannan, Kurunthachalam; Yamashita, Nobuyoshi, Arch Environ Contam Toxicol. 2013 Jul;65(1):149-70. doi: 10.1007/s00244-013-9878-4. Epub 2013 Mar 14.)	Numerous studies have reported on the global distribution, persistence, fate, and toxicity of perfluoroalkyl and polyfluoroalkyl substances (PFASs). However, studies on PFASs in terrestrial mammals are scarce. Rats can be good sentinels of human exposure to toxicants because of their habitat, which is in close proximity to humans. Furthermore, exposure data measured for rats can be directly applied for risk assessment because many toxicological studies use rodent models. In this study, a nationwide survey of PFASs in the blood of wild rats as well as surface water samples collected from rats' habitats from 47 prefectures in Japan was conducted. In addition to known PFASs, combustion ion chromatography technique was used for analysis of total fluorine concentrations in the blood of rats. In total, 216 blood samples representing three species of wild rats (house rat, Norway rats, and field mice) were analyzed for 23 PFASs. Perfluorooctanesulfonate (PFOS; concentration range <0.05-148 ng/mL), perfluorooctane sulfonamide (PFOSA; <0.1-157), perfluorododecanoate (<0.05-5.8), perfluoroundecanoate (PFUnDA; <0.05-51), perfluorodecanoate (PFDA; <0.05-9.7), perfluorononanoate (PFNA; <0.05-249), and perfluorooctanoate (PFOA) (<0.05-60) were detected >80 % of the blood samples. Concentrations of several PFASs in rat blood were similar to those reported for humans. PFSAs (mainly PFOS) accounted for 45 % of total PFASs, whereas perfluoroalkyl carboxylates (PFCAs), especially PFUnDA and PFNA, accounted for 20 and

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		10 % of total PFASs, respectively. In water samples, PFCAs were the predominant compounds with PFOA and PFNA found in >90 % of the samples. There were strong correlations ($p < 0.001$ to $p < 0.05$) between human population density and levels of PFOS, PFNA, PFOA, and PFOSA in wild rat blood.
19	日本人集団における魚介類摂取量、血清肝酵素、PFOS、PFOA の血中濃度(Consumption of Seafood, Serum Liver Enzymes, and Blood Levels of PFOS and PFOA in the Japanese Population)(英語)(Yamaguchi Miwa(Department of Preventive Medicine, Institute of Health Biosciences, the University of Tokushima Graduate School), Arisawa Kokichi, Uemura Hirokazu, Katsuura-Kamano Sakurako, Takami Hidenobu, Sawachika Fusakazu, Nakamoto Mariko, Juta Tomoya, Toda Eisaku, Mori Kei, Hasegawa Manabu, Tanto Masaharu, Shima Masayuki, Sumiyoshi Yoshio, Morinaga Kenji, Kodama Kazunori, Suzuki Takaichiro, Nagai Masaki, Satoh Hiroshi, Journal of Occupational Health(1341-9145)55 巻 3 号 Page184-194(2013.05))	Perfluoroctanesulfonate(PFOS)と perfluorooctanoate(PFOA)の血中濃度と関連する因子について横断的研究により検討した。日本の 15 都道府県に居住する男性 307 例と女性 301 例(16-76 歳)を対象とした。PFOS と PFOA の血中濃度は、液体クロマトグラフィ質量分析で測定した。肝酵素(γ-GTP、GOT、GPT)と ω-3 多価不飽和脂肪酸(DHA と EPA)の血清濃度も測定した。PFOS と PFOA の血中濃度と、41 種類の料理、食物、飲料の摂取頻度および肝酵素と ω-3 多価不飽和脂肪酸の血清濃度との関連性を、順位相関を用いて検討した。煮魚、刺身、近海魚の摂取頻度は、潜在的交絡因子について調整すると、PFOS の血中濃度と有意な正の相関を示した。GOT、GPT、DHA、EPA の血清濃度は、血中 PFOS および PFOA と有意な正の相関を示した。PFOS と PFOA の血中濃度には有意な地域差もあり、その中央値は東海/北陸/近畿地方で最も高かった。日本人集団では、PFOS の血中濃度が主に魚の摂取量と関連していたことや、PFOS と PFOA の濃度は肝酵素の血清濃度と関連していたことが示唆された。
20	日本の淡水域に生息するギンブナ（Carassius auratus (gibelio) langsdorfii) 中の有機フッ素化合物蓄積量調査 (白坂 華子, 門上 希和夫, 環境化学, 2014 年 24 巻 3 号 67-76)	Perfluorinated compounds (PFCs) that are widely used as surfactants and coatings were determined in muscles of crucian carp (Carassius auratus (gibelio) langsdorfii) taken from 14 freshwater areas throughout Japan during 2003-2005.The sampling sites comprised 10 rivers and 4 ponds and were categorized into 4 groups based on local circumstances: large cities, small cities, agricultural areas and remote areas. PFCs were detected in all samples analyzed, and total PFCs concentrations ranged from 1.60 to 30.1 (average: 9.54, median: 8.80) ng/g wet wt. and 167 to 3496 (average: 914, median:645) ng/g lipid wt. The highest concentrations of PFCs were found in fish caught at sites in large cities. Fish in the remote area's had low PFCs concentrations. Branched chain PFC isomers were also detected, although the relative ratios of the straight chains to the branch isomers were different between sampling sites. To obtain maternal transfer rates for the PFCs, female fish were collected from the Murasaki River during the spawning season and their muscles and eggs were analyzed. The maternal transfer rate of PFCs was 9.1%, which is lower than those of hydrophobic substances such as dioxins, organochlorine pesticides and hexabromocyclododecanes. As a result, sexual differences between male and female fish were not found.
21	Bioconcentration of perfluorinated compounds in wild medaka is related to octanol/water partition coefficient (Katsumi Iwabuchi, Norimasa Senzaki, Shuji Tsuda, Haruna Watanabe, Ikumi Tamura, Hitomi Takanobu, Norihisa Tatarazako, Fundamental	Perfluorinated compounds (PFCs) have been used widely, detected worldwide in the environment, and have accumulated highly in animals. As far as we know, there have been no reports which relate the PFC concentration in wild animals to the physicochemical properties. Therefore, we measured the concentrations of 15 currently available PFCs (perfluorocarboxylic acids with x carbons: Cx, perfluorosulfonic acids with x carbons: CxS) in medaka and the environmental water where medaka live. Samples were obtained from 7 points in Japan (Iwate, Ibaraki, Niigata, Hyogo, Yamaguchi, Ehime, and Nagasaki) from July to September in 2013. Twenty to forty medaka were collected from each point, as well as 2 L of water in a clean PET bottle. PFCs were extracted and concentrated using a solid-phase cartridge, and were measured by LC/MS/MS. The medaka samples were treated individually. C5-C9 and C8S were detected mainly in the water, C11-C13 and C8S were detected mainly in medaka. C8S

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	Toxicological Sciences, 2015 年, 2 巻 5 号 201-208)	was always detected in high concentrations in the water and medaka. The bioconcentration factors (BCFs) of PFCs were calculated from PFC concentrations of the water and the medaka. The BCFs of C8-C11 were increased exponentially with the length of carbon chain. The BCF of C8S (approx. 5,500) was far greater than C8 (approx. 330) or C9 (approx. 480). However, the BCFs of C8-C11 and C8S tended to increase in proportion with octanol/water partition coefficient (log Kow).
22	Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats (Klaunig, James E; Shinohara, Motoki; Iwai, Hiroyuki; Chengelis, Christopher P; Kirkpatrick, Jeannie B; Wang, Zemin; Bruner, Richard H, Toxicol Pathol. 2015 Feb;43(2):209-20. doi: 10.1177/0192623314530532. Epub 2014 May 28.)	Perfluorohexanoic acid (PFHxA), a 6-carbon perfluoroalkyl (C6; CAS # 307-24-4), has been proposed as a replacement for the commonly used 8-carbon perfluoroalkyls: perfluorooctanoic acid and perfluorooctane sulfonate. PFHxA is not currently a commercial product but rather the ultimate degradation product of C6 fluorotelomer used to make C6 fluorotelomer acrylate polymers. It can be expected that, to a greater or lesser extent, the environmental loading of PFHxA will increase, as C6 fluorotelomer acrylate treatments are used and waste is generated. This article reports on a chronic study (duration 104 weeks) that was performed to evaluate the possible toxicologic and carcinogenic effects of PFHxA in gavage (daily gavage, 7 days per week) treated male and female Sprague-Dawley (SD) rats. In the current study, dosage levels of 0, 2.5, 15, and 100 mg/kg/day of PFHxA (males) and 5, 30, and 200 mg/kg/day of PFHxA (females) were selected based on a previous subchronic investigation. No effects on body weights, food consumption, a functional observational battery, or motor activity were observed after exposure to PFHxA. While no difference in survival rates in males was seen, a dose-dependent decrease in survival in PFHxA-treated female rats was observed. Hematology and serum chemistry were unaffected by PFHxA. PFHxA-related histologic changes were noted in the kidneys of the 200-mg/kg/day group females. Finally, there was no evidence that PFHxA was tumorigenic in male or female SD rats at any of the dosage levels examined.
23	Association of perfluorinated chemical exposure in utero with maternal and infant thyroid hormone levels in the Sapporo cohort of Hokkaido Study on the Environment and Children's Health (Kato, S.; Itoh, S.; Yuasa, M.; Baba, T.; Miyashita, C.; Sasaki, S.; Nakajima, S.; Uno, A.; Nakazawa, H.; Iwasaki, Y.; Okada, E.; Kishi, R., Environ Health Prev Med. 2016 Sep;21(5):334-344. doi: 10.1007/s12199-016-0534-2. Epub 2016 Apr 30.)	OBJECTIVES: Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) have been widely used as industrial products, and are persistent organic pollutants due to their chemical stability. Previous studies suggested that PFOS and PFOA might disrupt thyroid hormone (TH) status. Although TH plays an important role in fetal growth during pregnancy, little attention has been paid to the relationships between maternal exposure to perfluorocarbons and TH statuses of mothers and fetuses. We investigated the effects of low levels of environmental PFOS and PFOA on thyroid function of mothers and infants.METHODS: Of the eligible subjects in a prospective cohort, 392 mother-infant pairs were selected. Concentration of maternal serum PFOS and PFOA was measured in samples taken during the second and third trimesters or within 1 week of delivery. Blood samples for measuring thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels were obtained from mothers at early gestational stage (median 11.1 weeks), and from infants between 4 and 7 days of age, respectively.RESULTS: Median concentrations of PFOS and PFOA were 5.2 [95 % confidence interval (CI) 1.6-12.3] and 1.2 (95 % CI limitation of detection-3.4) ng/mL, respectively. Maternal PFOS levels were inversely correlated with maternal serum TSH and positively associated with infant serum TSH, whereas maternal PFOA showed no significant relationship with TSH or FT4 among mothers and infants.CONCLUSIONS: These findings suggest that PFOS may independently affect the secretion and balances of maternal and infant TSH even at low levels of environmental exposure.
24	Peroxisome proliferator activated receptor-mediated genotoxicity of perfluoroalkyl acids using human lymphoblastoid cells (Maki Nakamura, Tomomi Takahashi, Takuya Izumi, Masanori Miura, Satomi Kawaguchi, Ayumi Yamamoto, Shuji Tsuda, Takanori Nakamura, Shuhei Tanaka, Naoto Shimizu, Yu F. Sasaki, Fundamental Toxicological Sciences, 2016 年 3 巻 4 号 143-150)	Perfluoroalkyl acids (PFAAs) have been widely used since 1950s. The long chained-PFAAs, such as perfluorooctanoic acid (PFOA) are persistent and bio-accumulative, and are detected in humans. PFOA, which is a peroxisome proliferator activated receptor (PPAR) α agonist, has been suggested to be a carcinogen in epidemiological and animal studies. In some studies PFOA is shown to be non-mutagenic in Ames and micronucleus tests, but in other studies it caused oxidative DNA damage and micronucleus formation. However, there has been no report that has examined whether PFOA-induced genotoxicity is mediated by PPARα. In order to relate genotoxicity of PFAAs to PPARα, we conducted two kinds of comet assays (cellular and acellular), a micronucleus (MN) test, and a TK mutation assay with and without PPARαantagonists by using human lymphoblastoid cells. PFAAs at 125-1000 μg/mL showed positive responses in the cellular comet assay but not in the MN test and TK mutation assay. A PPARα antagonist GW6471 (2 μg/mL) only partly reduced PFOA-induced DNA damage (in the cellular comet assay), but abolished PFOA-induced intracellular ROS formation. PFAAs with 8-12 carbons also showed positive responses in the acellular comet assay where there is no cellular function such as PPAR. Therefore, PFOA-induced DNA damage was partly related to the oxidative stress via PPARα, without manifestation of chromosome aberration and point mutation in this cell line.

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25	Particle size specific distribution of perfluoro alkyl substances in atmospheric particulate matter in Asian cities (Ge, H; Yamazaki, E; Yamashita, N; Taniyasu, S; Ogata, A; Furuuchi, M, Environ Sci Process Impacts. 2017 Apr 19;19(4):549-560. doi: 10.1039/c6em00564k.)	Seasonal and local characteristics of perfluorinated alkylated substances (PFASs) were examined using size-segregated particles including an ultrafine range. The examination included sampling and analysis of ambient particles collected at four sites located in different environments in three different countries, Japan (Kanazawa and Okinawa), Hong Kong and India. To minimize the evaporation artefacts derived from PFASs during the sampling, an air sampler that permitted particles smaller than 0.1 μm (PM(0.1)) to be separated at a moderate pressure drop (<5-15 kPa), was used for all of the air sampling procedures. In the case of Kanazawa, a local city in Japan, the concentration of PFASs was found to be dominated by carboxylates, especially PFOA, PFNA and PFDA regardless of the particle size and sampling period. Ultrafine particles were found to be the largest contributor to the mass fraction of PFCAs, while the maximum PFOS mass fractions were determined to be in the coarse-sized fractions. The seasonal difference in the total PFAS concentration can be largely attributed to precipitation. The results were basically similar for all sites that were examined. The type of land use may be a more influencing factor on the mass fraction of the PFASs than the country of origin. The dependency of PFAS mass fraction on the specific surface of the particle suggests that ultrafine PFAS particles are segregated, not only by gas deposition but could also be segregated by a mechanism involving compositional dependence or the primary source of the particles. Other possible sources of PFASs, other than from traffic are also possible.
26	Prenatal exposure to perfluoroalkyl acids and prevalence of infectious diseases up to 4 years of age (Goudarzi, H.; Miyashita, C.; Okada, E.; Kashino, I.; Chen, C. J.; Ito, S.; Araki, A.; Kobayashi, S.; Matsuura, H.; Kishi, R., Environ Int. 2017 Jul;104:132-138. doi: 10.1016/j.envint.2017.01.024. Epub 2017 Apr 7.)	Perfluoroalkyl acids (PFAAs) are synthetic chemicals with ability to repel oils and water, and have been widely used in many industrial and household applications such as adhesives and water- and stain-repellent surfaces to nonstick coatings. Animal studies have shown that PFAAs have immunotoxic effects. However, few epidemiological studies have investigated the effects of PFAAs on infectious diseases occurrence. We examined the relationship between prenatal exposure to PFAAs and prevalence of infectious diseases up to 4years of life. A total of 1558 mother-child pairs, who were enrolled in the Hokkaido Study on Environment and Children's Health, were included in this data analysis. Eleven PFAAs were measured in maternal plasma taken at 28-32weeks of gestation using ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. Participant characteristics were obtained from medical birth records and self-administered questionnaires during pregnancy and after delivery. Physicians' diagnosis of common infectious diseases including otitis media, pneumonia, respiratory syncytial virus infection, and varicella up to 4years were extracted from the mother-reported questionnaires. The number of children who developed infectious diseases up to 4years of age was as follows: otitis media, 649 (41.4%); pneumonia, 287 (18.4%); respiratory syncytial virus infection, 197 (12.6%); varicella 589 (37.8%). A total of 1046 -0.671 children had at least one of the diseases defined as total infectious diseases. After adjusting for appropriate confounders, PFOS levels in the highest quartile were associated with increased odds ratios (ORs) of total infectious diseases (Q4 vs. Q1 OR: 1.61; 0.95 CI: 1.18, 2.21; p for trend=0.008) in all children. In addition, perfluorohexane sulfonate (PFHxS) was associated with a higher risk of total infectious diseases only among girls (Q4 vs. Q1 OR: 1.55, 0.95 CI: 0.976, 2.45; p for trend=0.045). We found no association between infectious diseases and other examined PFAAs. Our findings suggest that prenatal exposure to PFOS and PFHxS may associated with infectious diseases occurrence in early life. Therefore, prenatal exposure to PFAAs may be immunotoxic for the immune system in offspring.
27	メダカ及びその生息地点の環境水，底質中の有機フッ素化合物の存在状況と生物濃縮の関係 (岩渕 勝己, 鑪迫 典久, 水環境学会誌, 2018 年 41 巻 4 号 61-71)	有機フッ素化合物 (PFAA) は，環境残留性や蓄積性が世界的に問題となっている。本研究では，メダカ (Olyzias latipes) ，その生息地点の環境水，底質を採取して 15 種の PFAA 濃度を分析し，環境中の存在状況と生物濃縮を明らかにすることを目的とした。各サンプルから検出される PFAA 濃度は採取地点により異なるが，組成比はほぼ一定していた。メダカへの生物濃縮係数 (BCF) と，PFAA のオクタノール/水分配係数 (Log Kow) との間には相関が見られた。環境水と底質の PFAA 濃度は，底質の乾燥重量あたりよりも強熱減量 (IL) あたりの濃度で比較した方が良好に相関しており，底質とメダカでも同様であった。底質の IL あたりの PFAA 濃度，性別，体長からメダカへの蓄積量を重回帰分析により推定したところ，底質の IL あたりの PFAA 濃度がメダカへの蓄積に有意に関連していた。
28	Association between perfluoroalkyl substance exposure and thyroid hormone/thyroid antibody levels in maternal and cord blood:	BACKGROUND: Thyroid antibodies (TAs) are the most common cause of hypothyroidism during gestation. Although previous studies found that prenatal exposure to perfluoroalkyl substances (PFASs) disrupts thyroid hormones (THs) in humans, their effects on TAs during the perinatal period have not been investigated.OBJECTIVE: To explore the associations between prenatal exposure to eleven different PFASs from two

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	The Hokkaido Study (Itoh, S.; Araki, A.; Miyashita, C.; Yamazaki, K.; Goudarzi, H.; Minatoya, M.; Ait Bamai, Y.; Kobayashi, S.; Okada, E.; Kashino, I.; Yuasa, M.; Baba, T.; Kishi, R., Environ Int. 2019 Dec;133(Pt A):105139. doi: 10.1016/j.envint.2019.105139. Epub 2019 Sep 10.)	different groups (carboxylates and sulfonates) and the expression of THs and TAs in maternal and cord blood while considering maternal TA status.METHODS: In a prospective birth cohort (the Hokkaido Study), we included 701 mother-neonate pairs recruited in 2002-2005 for whom both prenatal maternal and cord blood samples were available. Eleven PFASs were measured in maternal plasma obtained at 28-32 weeks of gestation using ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry. THs and TAs including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured in maternal blood during early pregnancy (median 11 gestational weeks), and in cord blood at birth.RESULTS: The median levels of TgAb and TPOAb in maternal serum were 15 and 6.0 IU/mL, respectively. The median TgAb level in neonates was 38.0 IU/mL, and TPOAb were detected in only 0.123 of samples. Maternal FT3 level was positively associated with PFAS levels in both TA-positive and TA-negative mothers. Maternal perfluorooctanoate was inversely associated with maternal TPOAb. Among boys, some maternal PFASs were associated with higher TSH and lower FT3 levels in maternal TA-negative group, while perfluorodecanoic acid was associated with lower TSH in maternal TA-positive group. Among girls, some PFAS of mothers showed associations with lower TSH and higher FT3 in maternal TA-negative group, while perfluorododecanoic acid was associated with lower FT4 in maternal TA-positive. Maternal PFASs showed associations with boy's TgAb inversely in maternal TA-negative group and with girl's TgAb positively in maternal TA-positive group.CONCLUSIONS: Our results suggest thyroid disrupting effects of PFAS exposure and susceptibility vary depending on maternal TA levels.
29	Fluorous Property of a Short Perfluoroalkyl-Containing Compound Realized by Self-Assembled Monolayer Technique on a Silicon Substrate (Ryuma Kise, Aki Fukumi, Nobutaka Shioya, Takafumi Shimoaka, Masashi Sonoyama, Hideki Amii, Toshiyuki Takagi, Toshiyuki Kanamori, Kazuo Eda, Takeshi Hasegawa, Bulletin of the Chemical Society of Japan, 2019 年 92 巻 4 号 785-789)	Fluorous properties represented by water-and-oil repellency are perfluoroalkyl (Rf) compound-specific characteristics, which are widely used for surface coating of glass, electronic devices and textiles for preventing water and grease fouling. According to the stratified dipole-arrays (SDA) theory, the minimum Rf length of (CF2)7 is theoretically necessary for realizing fluorous properties. Unfortunately, however, production of compounds involving this chemical unit is strictly banned because of concerns of environmental pollution, which is a big dilemma. Here, we show that the fluorous properties can be realized by self-assembled monolayer (SAM) even with a short Rf-containing compound, since the SAM technique makes the best use of the self-aggregation property of the Rf groups, and it readily makes the molecules immobile.
30	Effect of prenatal exposure to per- and polyfluoroalkyl substances on childhood allergies and common infectious diseases in children up to age 7 years: The Hokkaido study on environment and children's health (Ait Bamai, Y.; Goudarzi, H.; Araki, A.; Okada, E.; Kashino, I.; Miyashita, C.; Kishi, R., Environ Int. 2020 Oct;143:105979. doi: 10.1016/j.envint.2020.105979. Epub 2020 Jul 24.)	Per- and polyfluoroalkyl substances (PFAS) are widely used bio-accumulative chemicals in many industrial and household products. Experimental studies reported that exposure to PFAS results in immunotoxicity. We have previously reported that prenatal exposure to PFAS decreased the risk of allergies, while it increased the risk of infectious diseases at ages 2 and 4 years. However, it remains unclear whether the adverse effects of PFAS on allergies and infectious diseases continue until a reliable age of diagnosing allergies. This study aimed at investigating the effects of prenatal exposure to PFAS on the prevalence of allergies and infectious diseases in children up to age 7, from the Hokkaido Study. Among mother-child pairs enrolled in the Hokkaido study and followed up until the age of 7 years, 2689 participants with maternal PFAS, 1st trimester of pregnancy and 7-year-old questionnaire survey data were included in this study. Eleven PFAS in the 3rd-trimester plasma were measured using ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. Wheeze, rhino-conjunctivitis, and eczema were defined using the International Study of Asthma and Allergies on Childhood (ISAAC) questionnaire. History childhood infectious diseases diagnosed by a doctor was assessed by a mother-reported questionnaire at child's age 7 The relative risk of childhood allergies was calculated by generalized estimating equation models. The odds ratio of an episode of infectious diseases was calculated by logistic regression analysis, adjusted for potential confounders. The prevalence of various allergies and infectious diseases was: wheeze, 11.9%; rhino-conjunctivitis, 11.3%; eczema, 21.0%; chickenpox, 61.5%; otitis media, 55.7%; pneumonia, 30.6%; and respiratory syncytial virus infection, 16.8%. Prenatal exposure to perfluorooctanoic acid, perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) was inversely associated with rhino-

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		conjunctivitis, while that for perfluorooctanoate (PFOA), perfluorooctane sulfonate, PFUnDA, perfluorododecanoic acid (PFDoDA), and perfluorotridecanoic acid was inversely associated with eczema. For infectious diseases, PFDA and PFDoDA were associated with increased risk of pneumonia and PFOA was associated with increased risk of RSV infection among children not having any siblings (only-one-child). Our results corroborate the hypothesis on immunosuppressive and immunomodulating effects of PFAS on allergies and infectious diseases in children. These effects observed previously at 2 and 4 years continued until the age of 7 years. However, additional studies assessing inflammatory biomarkers along with ISAAC questionnaires, doctor-diagnosed allergies, and longer follow-ups are necessary to better assess the effects of exposure to chemicals on human immune outcomes.
31	A profile analysis with suspect screening of per- and polyfluoroalkyl substances (PFASs) in firefighting foam impacted waters in Okinawa, Japan (Yukioka, Satoru; Tanaka, Shuhei; Suzuki, Yuji; Echigo, Shinya; Kärrman, Anna; Fujii, Shigeo, Water Res. 2020 Oct 1;184:116207. doi: 10.1016/j.watres.2020.116207. Epub 2020 Jul 20.)	Per- and polyfluoroalkyl substances (PFASs) are a group of persistent contaminants detected in firefighting foam impacted waters. Previous studies have performed suspect and non-target screening by high-resolution mass spectrometry (HRMS) to determine the composition of PFAS contamination and to discover unknown PFASs. Here, we performed a profile analysis with suspect screening against two lists in the NORMAN Suspect List Exchange in firefighting foam impacted environmental and drinking water (n = 18) collected in Okinawa, Japan, in April 2019. Samples were analyzed by liquid chromatography (LC) quadrupole time-of-flight (QTOF) MS in electron spray ionization mode. Suspect screening returned 116 candidate PFASs with their molecular weights, functional groups, and perfluoroalkyl chain lengths. Long-chain perfluoroalkyl acids (PFAAs) and some of their precursors were specifically found around the firefighting training area. Short-chain PFAAs were assumed to be formed from precursors by environmental processes. Perfluoroalkyl sulfonamide precursors were found to be transformed to perfluoroalkyl sulfonic acids (PFSAs) in the drinking water treatment process. In contrast, biological activated carbon filtration formed perfluoroalkyl carboxylic acids (PFCAs). The PFAS profile showed that a large number of different substances needs to be considered.
32	The association between prenatal perfluoroalkyl substance exposure and symptoms of attention-deficit/hyperactivity disorder in 8-year-old children and the mediating role of thyroid hormones in the Hokkaido study (Itoh, Sachiko; Yamazaki, Keiko; Suyama, Satoshi; Ikeda-Araki, Atsuko; Miyashita, Chihiro; Ait Bamai, Yu; Kobayashi, Sumitaka; Masuda, Hideyuki; Yamaguchi, Takeshi; Goudarzi, Houman; Okada, Emiko; Kashino, Ikuko; Saito, Takuya; Kishi, Reiko, Environ Int. 2022 Jan 15;159:107026. doi: 10.1016/j.envint.2021.107026. Epub 2021 Dec 7.)	BACKGROUND: Disruption of thyroid hormone (TH) levels during pregnancy contributes to attention deficit hyperactivity disorder (ADHD). Exposure to perfluoroalkyl substances (PFAS) during gestation may affect levels of maternal and neonatal TH; however, little is known about the effect of PFAS on ADHD mediated by TH. OBJECTIVES: We investigated the impact of maternal PFAS exposure on children's ADHD symptoms with the mediating effect of TH. METHODS: In a prospective birth cohort (the Hokkaido study), we included 770 mother-child pairs recruited between 2002 and 2005 for whom both prenatal maternal and cord blood samples were available. Eleven PFAS were measured in maternal serum obtained at 28-32 weeks of gestation using ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry. TH and thyroid antibody, including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured in maternal blood during early pregnancy (median 11 gestational weeks) and in cord blood at birth. ADHD symptoms in the children at 8 years of age were rated by their parents using the ADHD-Rating Scale (ADHD-RS). The cut-off value was set at the 80th percentile for each sex. RESULTS: Significant inverse associations were found between some PFAS in maternal serum and ADHD symptoms among first-born children. Assuming causality, we found only one significant association: maternal FT4 mediated 17.6% of the estimated effect of perfluoroundecanoic acid exposure on hyperactivity-impulsivity among first-born children. DISCUSSION: Higher PFAS levels in maternal serum during pregnancy were associated with lower risks of ADHD symptoms at 8 years of age. The association was stronger among first-born children in relation to hyperactivity-impulsivity than with regard to inattention. There was little mediating role of TH during pregnancy in the association between maternal exposure to PFAS and reduced ADHD symptoms at 8 years of age.
33	Association of exposure to prenatal perfluoroalkyl substances and estrogen receptor 1 polymorphisms with the second to fourth digit ratio in school-aged children: The Hokkaido study (Nishimura, Yoko; Moriya, Kimihiko; Kobayashi, Sumitaka; Ikeda-Araki,	Per- and Polyfluoroalkyl substances (PFAS) have endocrine-disrupting effects. The ratio of the lengths of the second and fourth digits (2D:4D) is a noninvasive retrospective index of prenatal exposure to sex hormones, and estrogen receptor 1 (ESR1) polymorphisms may contribute to 2D:4D determination. We investigated whether ESR1 polymorphisms modify the effects of prenatal PFAS exposure on 2D:4D. Participants (n = 1024) with complete data in a prospective birth cohort study (the Hokkaido Study) were included, and maternal plasma in the third trimester was used to examine PFAS concentrations. 2D:4D was determined from photocopies of palms of children using Vernier calipers. ESR1 polymorphisms (rs2234693, rs9340799, and rs2077647) were genotyped by TaqMan polymerase chain reaction. PFAS and 2D:4D association with ESR1

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	Atsuko; Sata, Fumihiro; Mitsui, Takahiko; Itoh, Sachiko; Miyashita, Chihiro; Cho, Kazutoshi; Kon, Masafumi; Nakamura, Michiko; Kitta, Takeya; Murai, Sachiyo; Kishi, Reiko; Shinohara, Nobuo, Reprod Toxicol. 2022 Apr;109:10-18. doi: 10.1016/j.reprotox.2022.02.002. Epub 2022 Feb 22.)	polymorphisms was assessed by multiple linear regression adjusted for potential confounding factors. A 10-fold increase in maternal perfluorooctanoic acid (PFOA) concentration was associated with a 1.54% [95% confidence interval (CI): 0.40, 2.68] increase in mean 2D:4D in children with an AA genotype at rs9340799 and a 2.24% (95% CI: 0.57, 3.92) increase in children with an AA genotype at rs2077647. A 10-fold increase in perfluorododecanoic acid (PFDoDA) was associated with a significant increase in 2D:4D in children with the AA genotype [rs9340799, 1.18% (95% CI: 0.02, 2.34); and rs2077647, 1.67% (95% CI: 0.05, 3.28)]. These associations were apparent among males. A significant gene-environment interaction between PFOA or PFDoDA and ESR1 polymorphism was detected. These findings suggest that ESR1 polymorphisms modify the effects of prenatal exposure to PFAS on sex differentiation.