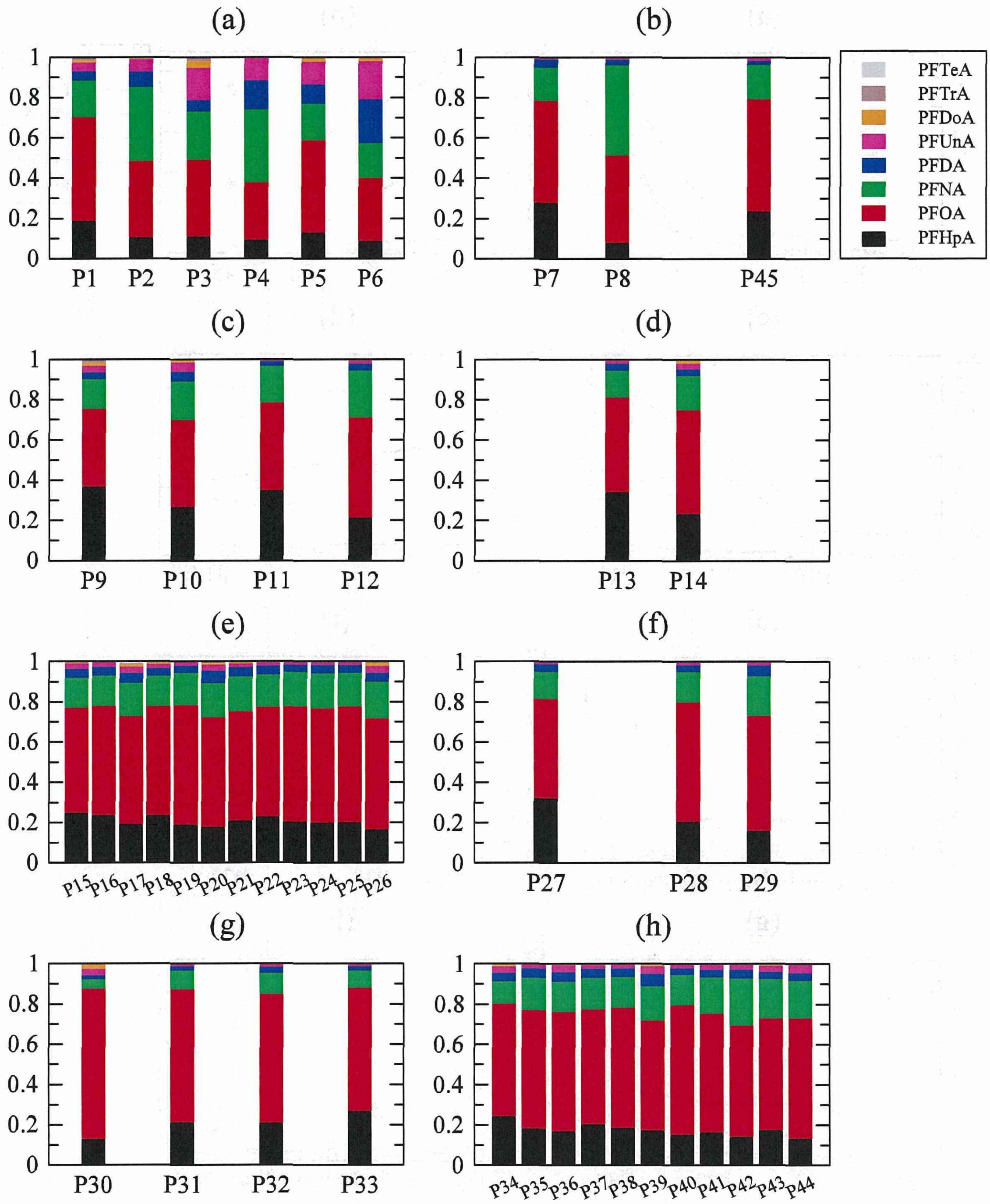

図５．河川水中PFCAsの組成。黒、赤、緑、青、桃色、橙色、茶色、灰色はそれぞれPFHpA、PFOA、PFNA、PFDA、PFUnA、PFDoA、PFTrA、PFTeAを表す。横軸の左方向が上流側、右方向が下流側の測定点。(a) 桂川、(b) 西高瀬川（P7–8）および安威川（P45）、(c) 鴨川、(d) 高野川、(e) 宇治川、(f) 琵琶湖疏水（P27）および山科川（P28–29）、(g) 木津川、(h) 淀川。

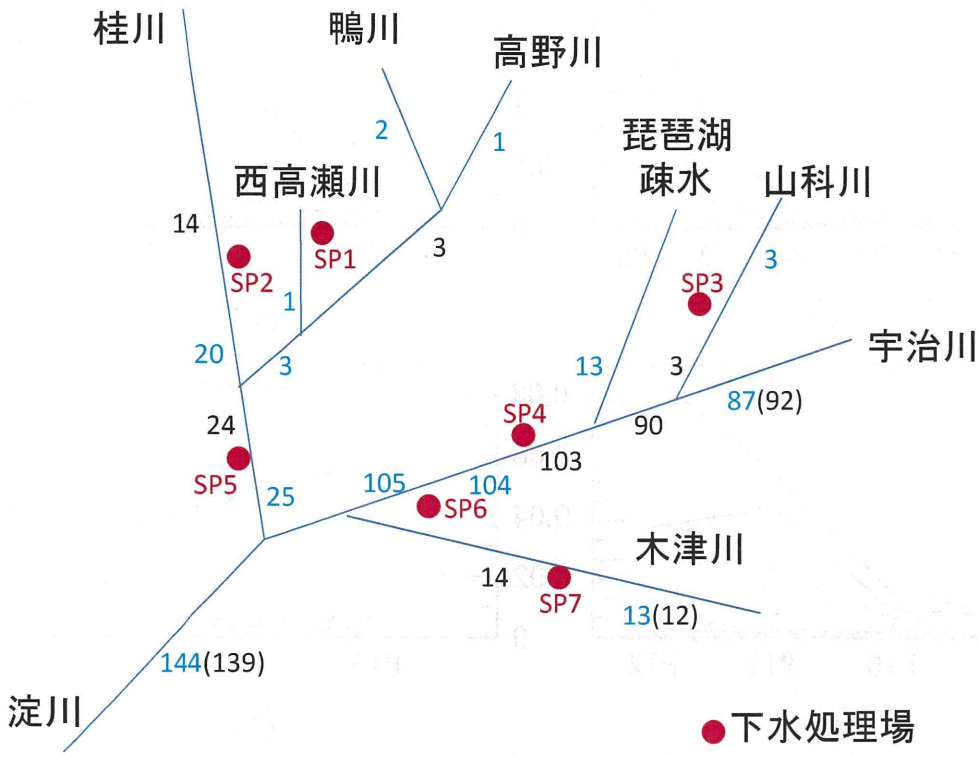

図６．淀川水系の流量（$m^3\ s^{-1}$）の推定値（青字）と国土交通省による2004年5月3日の測定値（黒字）。カッコ内は推定に使用しなかった測定値。

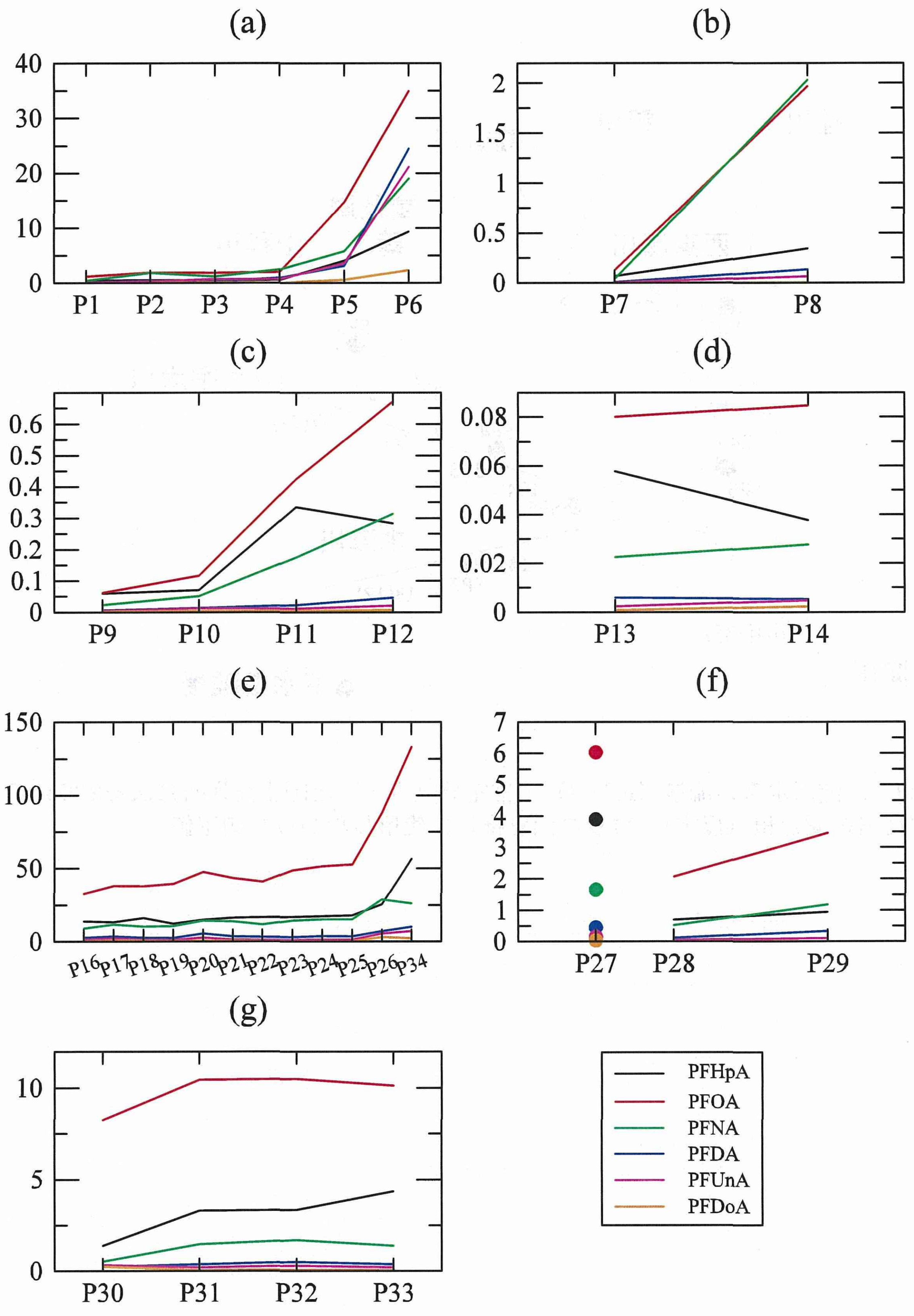

図７．淀川水系によるPFCAs輸送量（g day^{-1}）。黒、赤、緑、青、桃色、橙色線はそれぞれPFHpA、PFOA、PFNA、PFDA、PFUnA、PFDoAを表す。PFTrAおよびPFTeAについては微量のため省略した。横軸の左方向が上流側、右方向が下流側の測定点。(a) 桂川、(b) 西高瀬川、(c) 鴨川、(d) 高野川、(e) 宇治川、(f) 琵琶湖疏水（P27）および山科川（P28–29）、(g) 木津川。P34は宇治川、桂川、木津川合流部の下流側の採取地点。

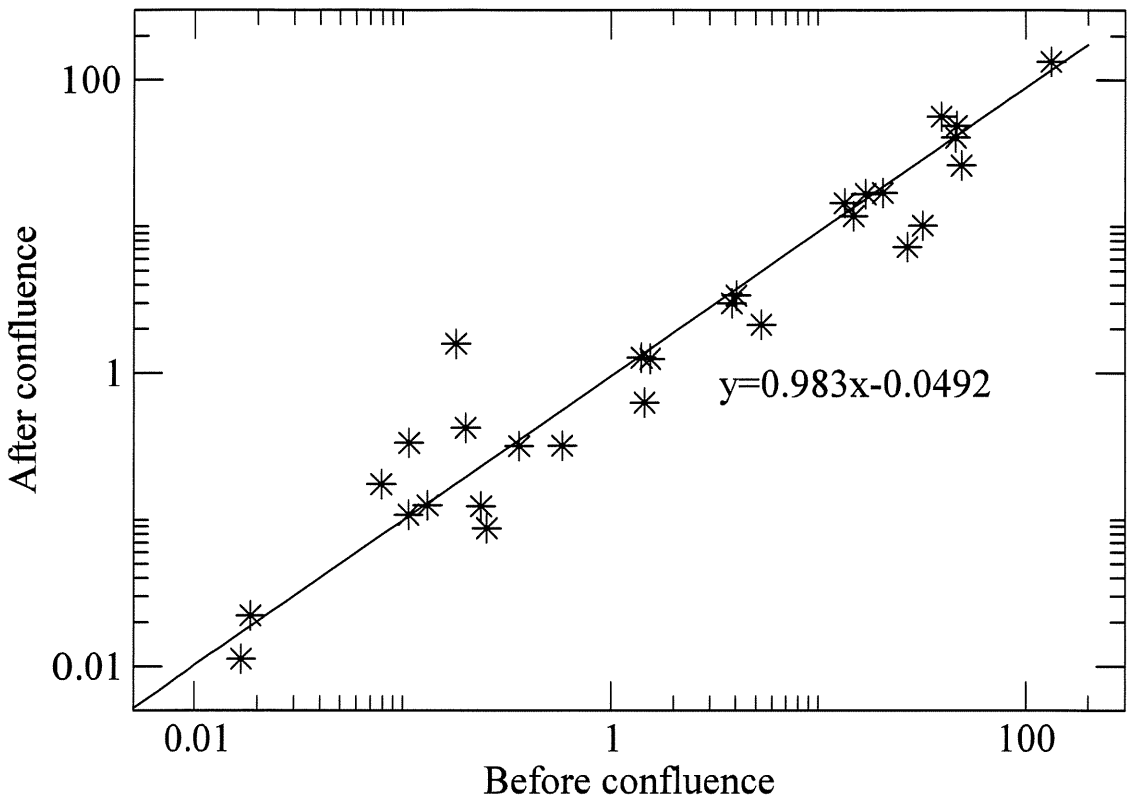

図８．PFCAs輸送量の河川合流点の上流側の和（横軸）と下流側（縦軸）との比較（g day^{-1}）。直線は対数スケールでの回帰直線（R^2=0.95, p<<0.05）。

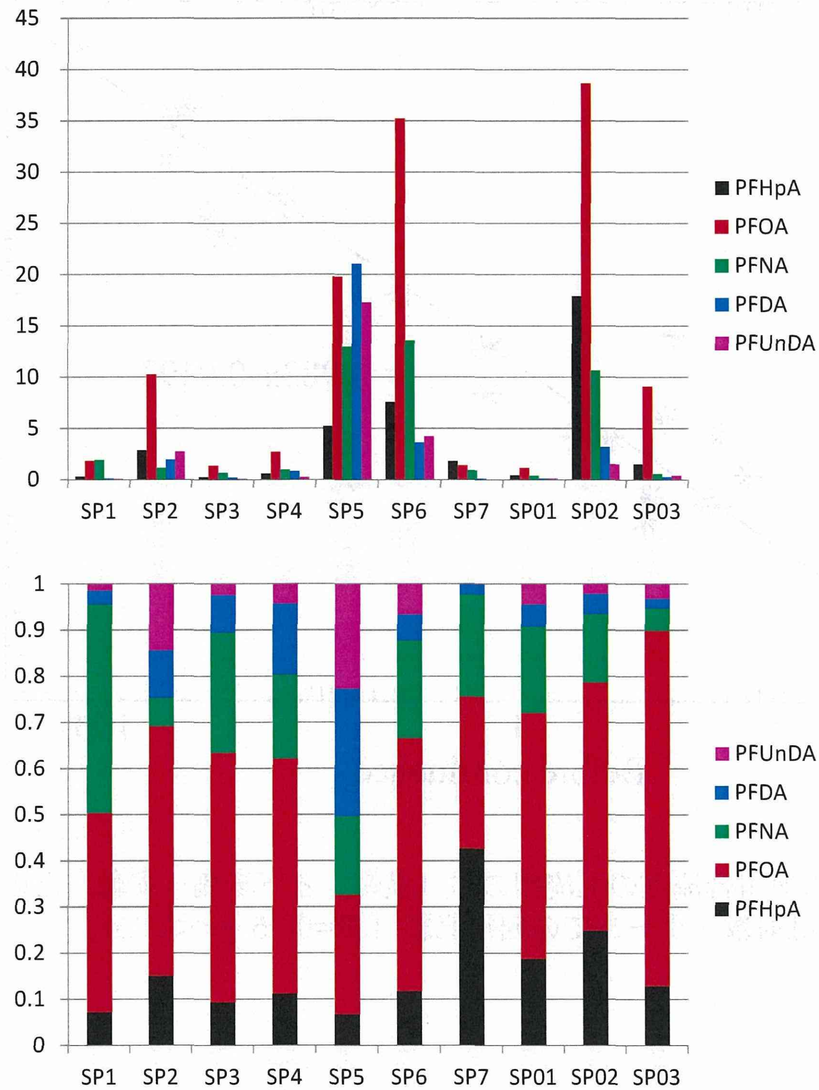

図９．下水処理場からのPFCAs排出量（上段、g day^{-1}）と組成（下段）。

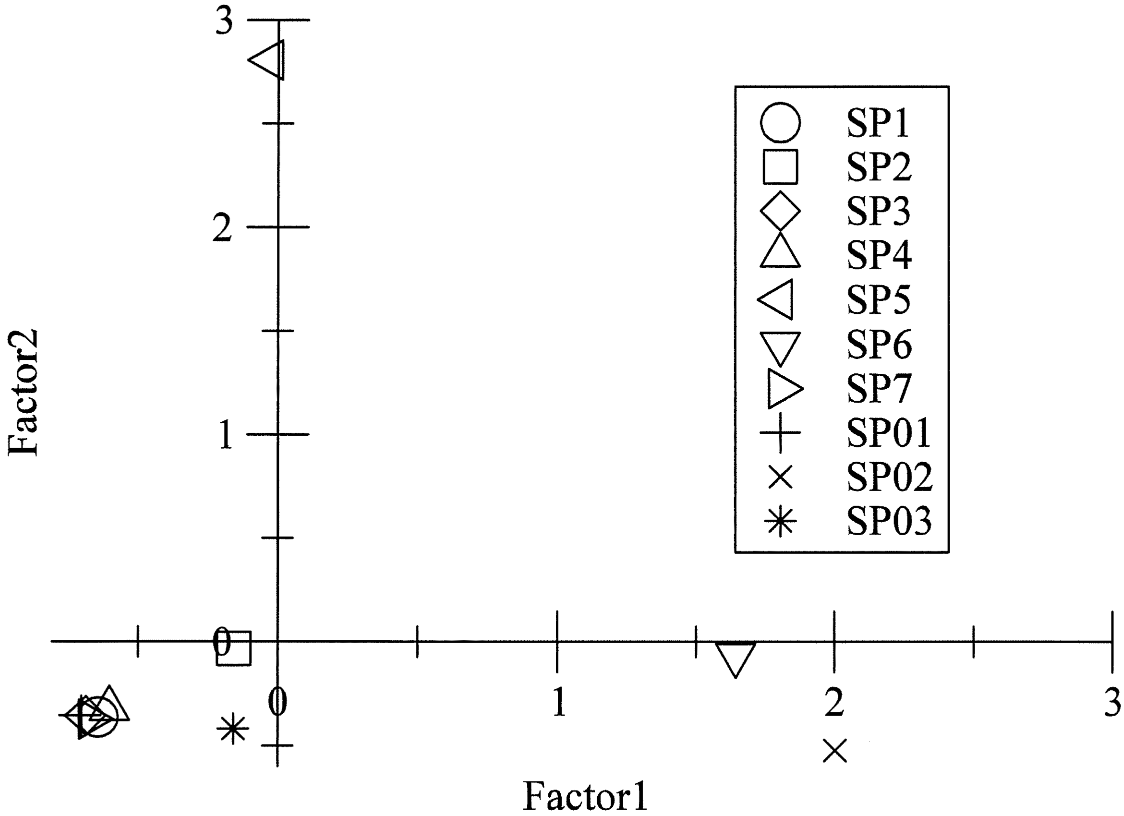

図１０．下水処理場からのPFCAs排出量に対する因子分析による因子得点の散布図。

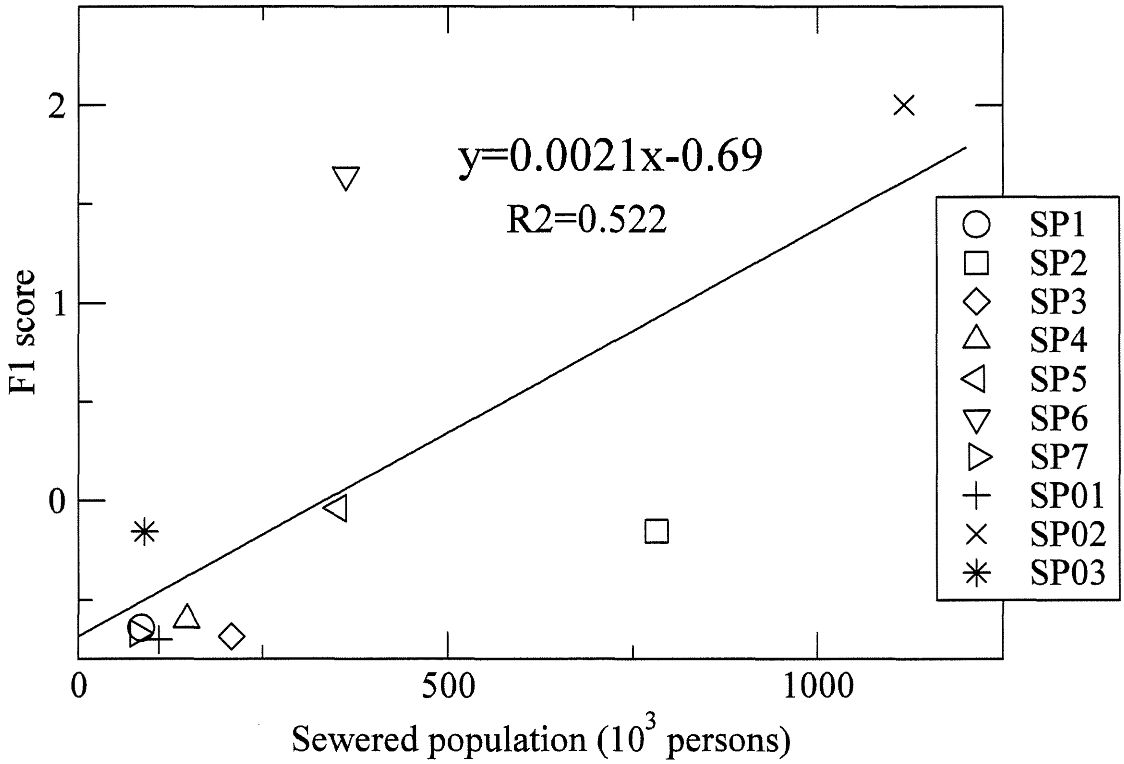

図１１．下水処理場の第1因子得点と処理人口（千人）との比較。

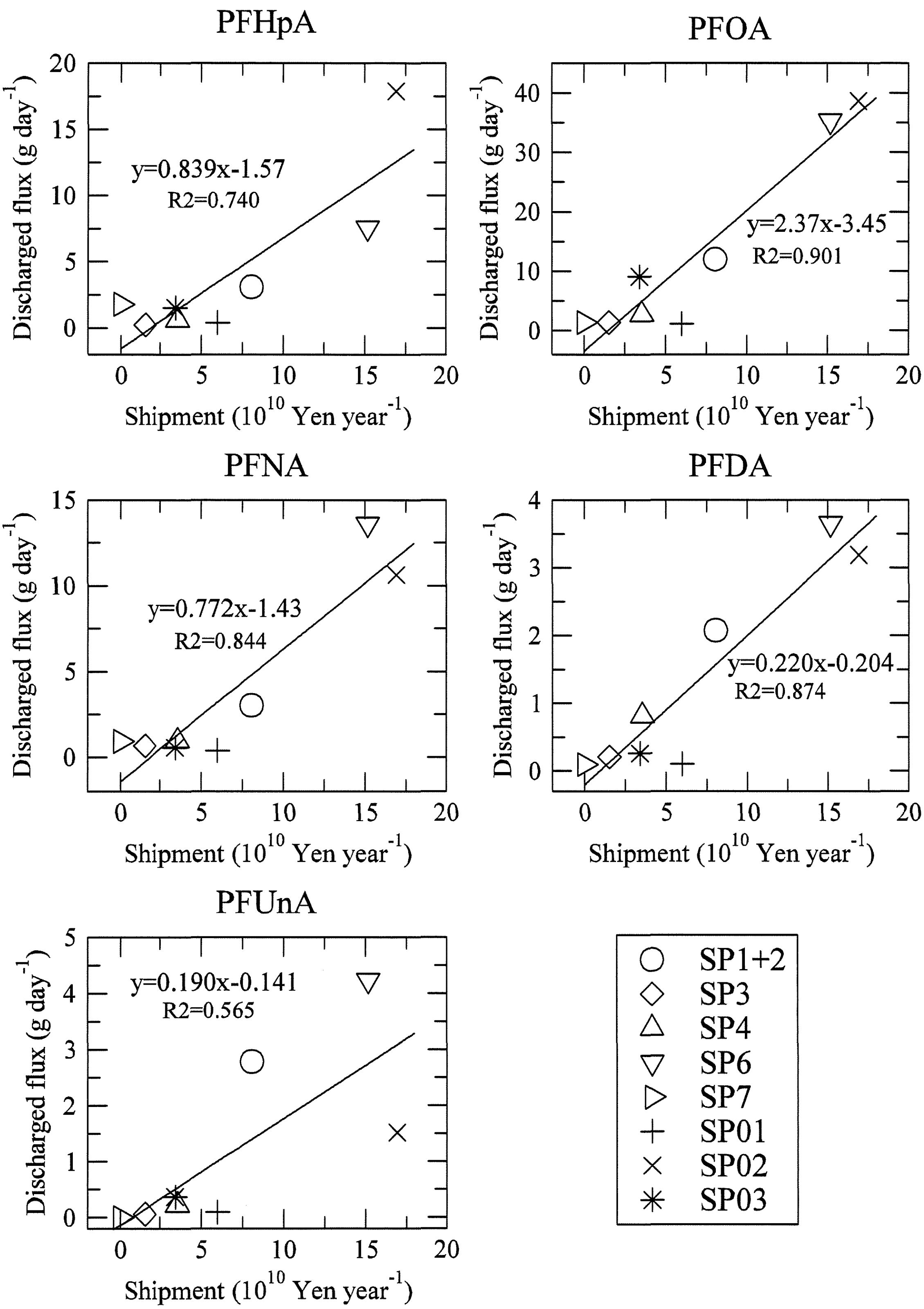

図１２．SP5を除く下水処理場からのPFCAs排出量（g day^{-1}）と管轄地域における食料品製造業の2012年度製造品出荷高（100億円）の比較。

III. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Akio Koizumi, Kouji Harada, Yukiko Fujii.	Comparing pesticides in human breast milk from China, Korea and Japan.	Sherma Zibadi, Ronald Ross Watson and Victor R. Preedy	Handbook of dietary and nutritional aspects of human breast milk: Prevention, treatment and toxicity.	Wageningen Academic Publishers	オランダ	2013	743-758

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yan JX, Inoue K, Asakawa A, Harada KH, Watanabe T, Hachiya N, Koizumi A.	Methylmercury Monitoring Study in Karakuwacho, a Peninsula Area in Japan	Bull. Environ. Contam. Toxicol.	In press	In press	In press
Harada KH, Niisoe T, Imanaka M, Fujii Y, Ishikawa H, Koizumi A, et al.	Radiation dose rates now and in the future for residents neighboring restricted areas of Fukushima Daiichi Nuclear Power Plant	Proc Natl Acad Sci USA.	111(10)	E914-923	2014
Matsubara F, Sagara Y, Kato Y, Harada K, Koizumi A, Haraguchi K.	Detection of Antibodies to Human T-Cell Leukemia Virus Types 1 and 2 in Breast Milk from East Asian Women	Biol. Pharm. Bull.	37(2)	311-314	2014
Fujii Y, Harada KH, Hitomi T, Kobayashi H, Koizumi A, Haraguchi K.	Temporal trend and age-dependent serum concentration of phenolic organohalogen contaminants in Japanese men during 1989-2010	Environ. Poll.	185	228-233	2014
Fujii Y, Nishimura E, Kato Y, Harada KH, Koizumi A, Haraguchi K.	Dietary exposure to phenolic and methoxylated organohalogen contaminants in relation to their concentrations in breast milk and serum in Japan	Environ. Int.	63(1)	19-25	2014

Nanayakkara S, Senevirathna STMLD, Abeysekera T, Harada KH, Kobayashi H, KoizumiA, et al.	An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central Region of Sri Lanka	J. Occup. Health.	56(1)	28-38	2014
Koizumi A, Niisoe T, Harada KH, Fujii Y, Adachi A, Hitomi T, Ishikawa H.	^{137}Cs trapped by biomass within 20 km of the Fukushima Daiichi Nuclear Power Plant	Environ Sci Technol.	47(17)	9612-9618	2013
Fujii Y, Harada KH, Koizumi A.	Occurrence of perfluorinated carboxylic acids (PFCAs) in personal care products and compounding agents	Chemosphere.	93(3)	538-544	2013
Liu W, Yin T, Okuda H, Harada KH, Li Y, Xu B, Yang J, Wang H, Fan X, Koizumi A, Miyata T.	Protein S K196E mutation, a genetic risk factor for venous thromboembolism, is limited to Japanese	Thromb Res.	132(2)	314-315	2013
Kato Y, Haraguchi K, Onishi M, Ikushiro S, Endo T, Ohta C, Koga N, Yamada S, Degawa M.	3,3′,4,4′-Tetrachlorobiphenyl-mediated decrease of serum thyroxine level in C57BL/6 and DBA/2 mice occurs mainly through enhanced accumulation of thyroxine in the liver	Biol Pharm Bull	37	504-509	2014
Kimura O, Ohta C, Koga N, Haraguchi K, Kato Y, Endo T.	Carrier-mediated uptake of nobiletin, a citrus polymethoxyflavonoid, in human intestinal Caco-2 cells	Food Chem	154	145-150	2014
Kato Y, Onishi M, Haraguchi K, Ikushiro S, Ohta C, Koga N, Endo T, Yamada S, Degawa M.	A possible mechanism for 2,3',4,4',5'-pentachlorobiphenyl-mediated decrease in serum thyroxine level in mice	Biol. Pharm. Bull.	36	1594-1601	2013

IV. 研究成果の刊行物・別刷

44. Comparing pesticides in human breast milk from China, Korea and Japan

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Abstract

Persistent organic pollutants (POPs) are ubiquitous and persistent environmental contaminants that bioaccumulate in biota. The screening of POP contamination in milk is important to assess current exposure in infants. Since POPs are lipophilic and small molecules, they tend to be transported from blood vessels to breast milk via passive transport pathways. Human breast milk in East Asian countries showed unique POP profiles. Concentrations of DDT and hexachlorobenzene are very high in breast milk of Chinese mothers while chlordanes, polychlorobiphenyls and perfluorooctanoic acid are high in breast milk of Japanese mothers and polybrominated diphenyl ethers in breast milk of Korean mothers. Those salient differences in profile are associated with the past and current exposure profiles of chemicals in the three countries. Levels of classical POPs, which have been regulated, are decreasing in human breast milk and a health risk in infants is unlikely. However, emerging POPs have been detected in recent studies, which warrants continuous monitoring of chemicals in human breast milk for child health.

Keywords: breast milk, persistent organic pollutants, monitoring, East Asia, human specimen bank

S. Zibadi, R.R. Watson and V.R. Preedy (eds.) **Handbook of** dietary and nutritional aspects of human breast milk
Human Health Handbooks no. 5 - DOI 10.3920/978-90-8686-764-6_44,

A. Koizumi, K.H. Harada and Y. Fujii

Key facts

- Persistent Organic Pollutants (POPs) are ubiquitous and persistent environmental contaminants that bioaccumulate in biota.
- Humans may be exposed to these chemicals through various pathways, but milk serves for all chlorinated and probably most brominated POPs as the primary route of exposure for infants.
- Due to the lipophilicity, persistency and bioaccumulativeness, classic and new POPs are easily transferred from mother to infants via breast milk.
- Human breast milk in East Asian countries showed unique POP profiles.

Summary points

- POPs are ubiquitous and persistent environmental contaminants that bioaccumulate in biota.
- The screening of POP contamination in milk is important to assess current exposure in infants.
- Since POPs are lipophilic and small molecules, they tend to be transported from blood vessels to breast milk via passive transport pathways.
- Concentrations of dichloro-diphenyl-trichloroethane (DDT) and hexachlorobenzene are very high in breast milk of Chinese mothers while chlordanes, polychlorobiphenyls and perfluorooctanoic acid are high in breast milk of Japanese mothers and polybrominated diphenyl ethers in breast milk of Korean mothers.
- POP profiles in human breast milk in East Asian countries revealed historical aspects of their uses, production processes of POPs and sources of POPs.
- Emerging POPs have been detected in recent studies, which warrants continuous monitoring of chemicals in human breast milk for child health.

Abbreviations

BBM	Blood-breast milk
BDE	Brominated diphenyl ether
CHL	Chlordane
DDT	Dichloro-diphenyl-trichloroethane
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
MOE	Margin of exposure
NOAEL	No observed adverse effect level
p,p'-DDD	p,p'-dichlorodiphenyldichloroethane
p,p'-DDE	p,p'-dichlorodiphenyldichloroethylene
PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyls
PFCAs	Perfluorinated carboxylic acids
PFCs	Perfluorinated compounds
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonate
PFTrDA	Perfluorotridecanoic acid
PFUnDA	Perfluoroundecanoic acid
POPs	Persistent organic pollutants
TDI	Tolerable daily intake

44.1 Introduction

POPs are ubiquitous and persistent environmental contaminants that bioaccumulate in biota. Since 2004 POPs have been globally addressed by the Stockholm Convention (UNEP, 2004). This class of compounds is frequently measured and detected in the tissues of birds, fish, and mammals, including human adipose tissue and milk. While humans may be exposed to these chemicals through various pathways, milk serves for all chlorinated and probably most brominated POPs as the primary route of exposure for the infants. Therefore, the screening of POP contamination in milk is important to assess current exposure in infants. Additionally, the assessment of time trends of POP contamination is important to understand the effects of regulatory actions on chemicals and to decide what regulatory actions might be needed. Of particular importance here is the screening of POPs currently in use and the screening of upcoming persistent toxic substances. Specifically it is important to monitor all POPs, POP candidates and other persistent toxic substances with high production volumes. In this section, we will consider relatively new POPs other than dioxins.

44.2 Transfer of xenobiotics in mother's blood to breast milk

Small molecular nutrients such as fatty acids and trace elements are mainly transported from blood vessels to breast milk through two pathways. Those are passive transport pathways and active transport pathways (Figure 44.1). The former pathways do not need any energy, i.e. ATP, and and transport is by concentration gradient. Transport rates are, however, dependent on physiochemical properties. Generally, as molecules are more lipophilic and smaller, they tend to have higher rates. In the second pathway transfer is mediated by molecule-specific transporters. Such transporters are known to mediate transfers of chemicals from blood to breast milk in mammary glands.

44.2.1 Active and passive transport of xenobiotics as blood-breast milk barrier

It is known that there is a BBM barrier for immunological defense (Guidry *et al.*, 1998). BBM is also suggested to be a barrier for many small molecules such as chemicals (Shennan and Peaker, 2000) and heavy metals (Abadin *et al.*, 1997). There is a hallmark as to whether or not the transport of a given chemical across BBM is limited. When concentrations of molecules in the plasma reach an equilibrium, the ratio of concentrations of molecules in breast milk to that in plasma is known as the milk/plasma ratio, being the most reliable hallmark for BBM for a given chemical. When the active transport systems are involved in the transfer processes, rates of the transportation are usually saturable; while in the passive transport process, they are independent of plasma concentrations. These two processes show discernible behavior only when concentrations are high but essentially the same when the concentrations are small.

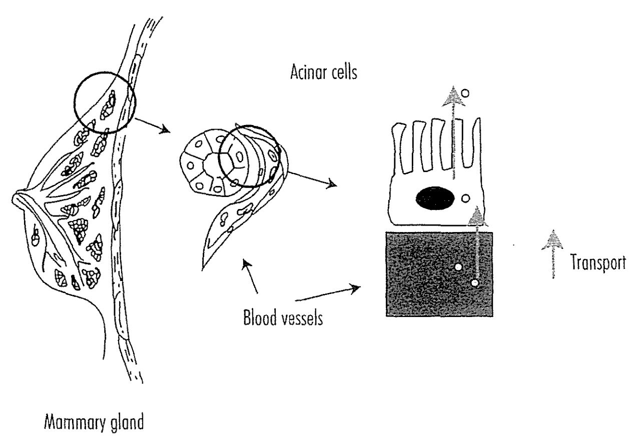

Figure 44.1. Substance transport in the mammary gland.

Transporters in BBM barrier

It has been reported that several transporters are located on the mammary epithelium. There is a good and comprehensive review paper on the transporter (Dabeka *et al.*, 1986). Although those data suggest the presence of transporters, it is almost entirely unknown what kinds of environmental chemicals are actively transported by transporters to discernible amounts. There are technical difficulties to evaluate the transporter activities. Gene ablated mice (i.e. knock-out mice) have been widely used to investigate physiological roles of transporters but physiological compensatory mechanisms (Smit *et al.*, 1993) in knock-out mice often hampered the analysis.

Passive transportation in BBM

Physico-chemical properties have a profound impact on the transport activities from serum to breast milk. We have demonstrated a typical example. PBDEs and PCBs, which are typical POPs, have many congeners. Those congeners are considered to be similar compounds: the former chemicals contain bromides while the latter chemicals contain chlorines on the similar carbon structures. However, differences in numbers of halogenated compounds result in differences in molecular sizes, numbers of functional groups and lipophilicity. In Figure 44.2, both serum and breast milk profiles (weight %) for these two chemicals are compared. In the PBDEs, larger congeners are detected in breast milk than lower molecular weight ones. In contrast, there is no such trend for PCBs. To further investigate such a clear contrast between PBDEs and PCBs, quantitative structure-activity relationship analysis was conducted (Inoue *et al.*, 2006). We obtained the following equation to explain variations of milk/serum partitions for PBDEs and PCBs:

Log p =1.664-0.1871 ClogP -0.2092 HBA

Where log p indicates the logarithm of the milk/serum partition coefficient, ClogP is a descriptor for hydrophobicity similar to Log Kw (water octanol partition coefficient) and HBA indicates

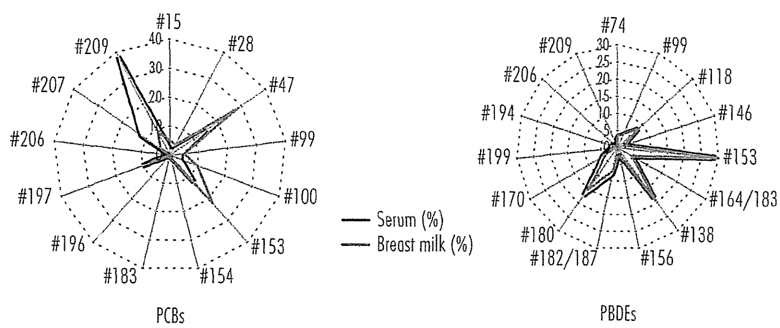

Figure 44.2. Relative abundances of congeners of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in serum and breast milk in the early breast-feeding period up to 10 weeks after delivery.

the number of hydrogen-bond acceptors. This equation implies that smaller and more lipophilic compounds are more likely partitioned into breast milk than larger and hydrophilic compounds.

In summary, the above equation strongly suggests that POPs in general are a very strong candidate for passive transport from mothers to infants.

44.3 Profiles of POPs in breast milk in three countries

44.3.1 POPs

POPs are very stable and difficult to degrade in the natural environment. POPs are characterized as having bioaccumulation potential in the human body and as being a substance toxic to humans and ecosystems. POPs constitute 21 chemicals. They are classified in terms of pesticides, industrial materials, and unintentionally-generated chemicals (Table 44.1). This time we covered 5 predominant contaminations (DDT, CHL, HCH, HCB and PCB) in human breast milk from China, Japan and Korea.

44.3.2 Overall trend in three countries

The human breast milk from China, Japan and Korea contains detectable amounts of 5 classic POPs and related isomers (DDTs, CHLs, HCHs, HCB, PCBs), which suggests that the mothers living in East Asia have been widely exposed to these contaminants. The average levels in three countries are in the order of DDTs > HCHs > PCBs > HCB > CHLs. The mean concentrations of 5 POPs are shown in Figure 44.3. All the analytes investigated were DDTs (p,p'-DDE, p,p'-DDD, o,p'-DDT, p,p'-DDT), CHLs (oxychlordane, trans-nonachlor, cis-nonachlor), HCHs (α-, β- and γ-HCH), and HCB and 15 PCBs (#74, #99, #101, #105, #118, #138, #146, #149, #153, #156, #163, #170, #180, #183, #187). In this survey, human breast milk was obtained from the Kyoto University Human Specimen Bank (Koizumi *et al.*, 2005, 2009). The samples were collected in 2007 and 2008 from volunteers living in China (n=25, Beijing in Dec. 2007), Japan (n=20, Kyoto from Dec. 2007 to Apr. 200) and Korea (n=29, Seoul in Oct. 2007). The main data from this section (Profiles of POPs in breast milk in three countries) is compiled in a published research paper (Haraguchi *et al.*, 2009).

China: The most predominant contaminants in human breast milk were DDTs (1,300 (430-3,000) ng/g lipid). The second most frequent contaminants were HCHs (570 (67-3,000) ng/g lipid), followed by HCB (86 (48-150) ng/g lipid). The contamination of PCBs (56 (26-130) ng/g lipid) and CHLs (3.8 (1.4-11) ng/g lipid) were low in relation to those in Japan and Korea.

Japan: DDTs (160 (49-550) ng/g lipid), PCBs (110 (14-210) ng/g lipid), HCHs (77 (31-270) ng/g lipid), CHLs (31 (11-58) ng/g lipid) and HCB (13 (4.5-25) ng/g lipid) were detected in the human breast milk. Characteristically, PCBs and CHLs were found at higher levels than those from China and Korea.

Table 44.1. 21 chemicals designated as persistent organic pollutions.

Pesticides	
dichloro-diphenyl-trichloroethane (DDT)	insecticide, pesticide intermediate
toxaphene	insecticide, miticide
chlordane (CHL)	termite control agent
heptachlor	insecticide, termite control agent
endrin	insecticide, rodenticide
aldrin	insecticide
dieldrin	insecticide, insecticide for termite, mothproof agent
mirex	insecticide, termite control agent. flame retardant
hexachlorobenzene (HCB)	seed disinfectant
pentachlorobenzene	pesticide intermediate, flame retardant, mildew-proofing agent
γ-Hexachlorocyclohexane (γ- HCH)	insecticide, drug medicine
Industrial materials	
polychlorinated biphenyl (PCB)	insulating oil, heat medium
perfluorooctanesulfonic acid (PFOS)	fire extinguishing agent, surface-activating agent
perfluorooctane sulfonylfluoride (PFOSF)	water repellent material
tetra-bromodiphenyl ether	plastic flame retardant
penta-bromodiphenyl ether	plastic flame retardant
hexa-bromodiphenyl ether	plastic flame retardant
hepta-bromodiphenyl ether	plastic flame retardant
hexa-bromobiphenyl	plastic flame retardant
Unintentionally-generated materials	
polychlorinated biphenyl	impure substance of aromatic organochlorine compounds
polychlorinated dibenzo-p-dioxins	refuse combustion, chlorinated pesticide byproduct
polychlorinated dibenzo furan	refuse combustion, chlorinated pesticide byproduct
hexachlorobenzene (HCB)	pesticide byproduct
pentachlorobenzene	refuse combustion, pesticide byproduct
α-hexachlorocyclohexane (α-HCH)	γ-hexachlorocyclohexane byproduct
β-hexachlorocyclohexane (β-HCH)	γ-hexachlorocyclohexane byproduct

Korea: The levels of DDTs (180 (49-580) ng/g-lipid), PCBs (61 (20-128) ng/g lipid), HCHs (110 (17-830) ng/g lipid), CHLs (14 (6.4-31) ng/g lipid), and HCB (13 (8.1-21) ng/g lipid) in Korean breast milk are similar to those levels in the Japanese.

44.3.3 DDT

DDT is an insecticide and a pesticide intermediate that was used worldwide. In our survey of 2007-2008, mean concentrations of DDTs were 1,300 ng/g lipid in human breast milk from Chinese mothers, which was about 7 times higher than values in those of Korean (180 ng/g lipid)

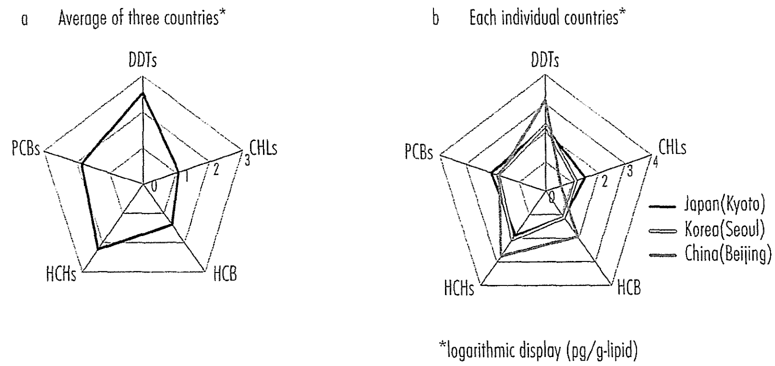

Figure 44.3. Profiles of 5 persistent organic pollutants (dichloro-diphenyl-trichloroethane; DDT, chlordane; CHL, hexachlorocyclohexane; HCH, hexachlorobenzene; HCB, polychlorinated biphenyl; PCB) in three countries.

and Japanese (170 ng/g lipid). DDT composition was dominated by p,p'-DDE (92-96%), followed by p,p'-DDT (3-5%), and p,p'-DDD (0.4-1%). In China, DDT concentrations in human breast milk substantially decreased from 7,700 to 2,000 ng/g-lipid during 1983-1998 (Yu *et al.*, 2006). Nevertheless, the concentrations of total DDTs in China were still more than 7 times higher than those in Korea and Japan in 2007-2008. Generically, the concentration ratio of p,p'-DDE/p,p'-DDT indicates the exposure residual time of p,p'-DDT in the environment. For that reason, lower ratios suggest more recent exposure to p,p'-DDT (Wong *et al.*, 2005). In Beijing, China, the ratio was 5.6 in 1993 (Yu *et al.*, 2006), but 32.9 in 2007. These facts also support our conclusion that the exposure to p,p'-DDT in Beijing, China, has been declining.

Recently dicofol (trade name, Kelthane) was detected at 1/100 levels of DDTs in human breast milk from Chinese, Korean and Japanese mothers (Fujii *et al.*, 2011). Dicofol is a pesticide used worldwide as a DDT substitute. Dicofol is manufactured from technical-grade DDT. Therefore, commercial Dicofol has DDT as an impurity. Since the concentrations of dicofol in the human breast milk were relatively low in relation to the concentrations of DDTs (1/100 levels), the current levels of dicofol do not indicate that dicofol is a major source of the total DDT concentrations in the three East Asian countries.

44.3.4 CHL

CHLs are insecticides that were mainly used for agricultural applications. A potential exposure route of CHLs in human breast milk might be the dietary source. Another source may be the living environment, since CHLs have often been used as a termite pest control insecticide which is sprayed on to wooden houses in Japan (Konishi *et al.*, 2001; Taguchi and Yakushiji, 1988). CHLs were most abundant (31 ng/g lipid) in Japanese human breast milk compared with breast milk from Korea and China, where the levels were 14 ng/g lipid in Seoul and 3.8 ng/g lipid in Beijing. Oxychlordane and trans-nonachlor were predominant compounds in all three countries. Since oxychlordane is a degrader from the other CHLs, this result indicates that the exposure came from past usage of it. *Trans*-nonachlor is presumed to be hardly metabolised and to disappear slowly from the human body (Tashiro and Matsumura, 1977). In Japan, the use of CHLs increased during the 1980s, and then its use was prohibited in 1986. A survey during 1986-1998 shows that CHL levels in human breast milk slightly declined from 110 to 85 ng/g lipid in the Osaka (a city near Kyoto) area (Konishi *et al.*, 2001). The present data also supports a decreasing trend in CHLs in Japan.

44.3.5 HCH

γ-HCH is used as an insecticide and drug medicine. α-HCH and β-HCH are the by-products of γ-HCH. HCHs in human breast milk were dominated by β-HCH. We could not detect any other isomers of HCHs in all samples. Apart from lindane production which is approximately 99% of γ-HCH, the distribution percentage of HCH isomers (65-70% of α-HCH and 5-6% of β-HCH) in commercial HCHs can be converted to exclusively β-HCH in the human body. The higher ratios of β-HCH indicated no new exposure of people to commercial HCHs in East Asia. HCH levels were the highest in China (570 ng/g lipid), followed by Korea (110 ng/g lipid) and the lowest in Japan (77 ng/g lipid). In the 1998 survey (Yu *et al.*, 2006), HCH levels were 1,200 ng/g lipid in Beijing. The current study suggested that the levels in Beijing, China declined by half during the past 10 years. The contamination levels of HCHs in China are in a similar range to those in Russia, and still around 5 times higher than those levels in Japan and Korea.

44.3.6 HCB

HCB is a seed disinfectant and an unintentionally generated pesticide by-product. The mean concentrations of HCB in human breast milk from China (86 ng/g lipid) were about one order of magnitude higher than those from Japan and Korea. HCB has never been registered in China as a pesticide, but is generated unintentionally by industrial activities (Wong *et al.*, 2005). Since HCB was detected in Chinese agricultural products such as tea leaves (Nakata *et al.*, 2005), HCB was possibly used as a pesticide or widely contaminated the environment as an impurity. HCB is still being used in Russia for the production of pyrotechnic and ordinance materials for the military (Barber *et al.*, 2005). The levels of HCB in Chinese breast milk are similar to those from Russia in 2003/2004 (100 ng/g lipid) (Tsydenova *et al.*, 2007). In Japan and Korea, lower levels of HCB were observed in human breast milk (both of 13 ng/g lipid). This indicates that there is no usage and/or a lack of strong exposure source of HCB in these two countries.

44.3.7 PCBs

PCBs were used as an insulating oil and heat medium, which were produced from 1930 to the 1970s. PCB concentrations in human beings are assumed to be related to historical industrial activities in the surrounding environment and dietary exposure via seafood. The mean concentrations of PCBs in human breast milk were higher in Japan (110 ng/g lipid) than in the other two countries (Korea: 61 ng/g lipid, China: 56 ng/g lipid). Major components were #153