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Highly elevated levels, infant dietary exposure and health risks of medium-chain chlorinated paraffins in breast milk from China: Comparison with short-chain chlorinated paraffins☆

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ABSTRACT

Short-chain chlorinated paraffins (SCCPs) are persistent organic pollutants which are toxic to human. Median-chain chlorinated paraffins (MCCPs) have similar toxicity to SCCPs. The productions of chlorinated paraffins (CPs) in China were 1 million tons in 2013 and remained high after that, which may lead to high risks for human exposure to CPs. To investigate temporal trends and health risks of SCCPs and MCCPs in breast milk in China, samples ($n = 2020$) were collected from urban and rural areas of 11 Chinese provinces in 2017 and mixed into 42 pooled samples. SCCPs and MCCPs were analyzed by two-dimensional gas chromatography with electron-capture negative-ionization mass spectrometry (GC × GC-ECNI-MS). The MCCP concentrations (median (range)) were 472 (94–1714) and 567 (211–1089) ng g^{-1} lipid in urban and rural areas, respectively, which showed continuously rapidly increasing during 2007–2017. The SCCP concentrations (median (range)) were 393 (131–808) and 525 (139–1543) ng g^{-1} lipid in urban and rural areas, respectively. The results showed SCCP levels decreased in urban areas between 2007 and 2017. Significant increases in MCCP/SCCP ratios might arise from extensive manufacturing and use of MCCPs. The median estimated dietary intake via breast milk in urban and rural samples were 1230 and 2510 ng kg^{-1} d^{-1}, respectively, for SCCPs and 2150 and 1890 ng kg^{-1} d^{-1}, respectively, for MCCPs. Preliminarily risk assessment showed that SCCPs posed a significant health risk to infants via breastfeeding. The high MCCP levels should also be of concern because of continuous growth and negative effect on infants. Correspondence analysis indicated congeners with higher carbon and chlorine numbers in dietary tend to accumulate in breast milk.

1. Introduction

Chlorinated paraffins (CPs), with the formula $C_xH_{(2x+2)-y}Cl_y$, are synthetic mixtures of polychlorinated n-alkanes (Feo et al., 2009) which are extensively utilized as flame retardants, metal-cutting fluids, plasticizers and as additives in lubricants (Bayen et al., 2006). Commercial CP products are subclassified according to carbon chain lengths into short-chain CPs (C_{10-13}, SCCPs), medium-chain CPs (C_{14-17}, MCCPs), and long-chain CPs (C_{18-30}, LCCPs). SCCPs were classified as possible human carcinogenic (group 2B) in 1990 by the International Agency for Research on Cancer (IARC 1990). In 2015, SCCPs were regarded as endocrine disrupters by the European Union (EU 2015). SCCPs have the potential of long-range transport, persistence, bioaccumulation and biological toxicity so that they were added to the Stockholm Convention as persistent organic pollutants (POPs) in 2017 (POPRC 2017). The

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production and use of SCCPs are banned or restricted in the United States, Japan, the European Union, and Canada (van Mourik et al., 2016). This has led to manufacturing and use of MCCPs as alternatives to SCCPs at considerably higher levels (Gluge et al., 2016). The environmental occurrences of MCCPs have even exceeded those of SCCPs (van Mourik et al., 2016). MCCPs exhibit similar cytotoxicity and perturbation of metabolism to SCCPs (Ren et al., 2019), and can bioaccumulate and be biomagnified in food chains (Du et al., 2020; Houde et al., 2008). However, there is still limited data on human exposure of MCCPs.

Breast milk is rich in fat and easy to collect in a non-invasive manner, so it is regarded as a favorable biological matrix to investigate human exposure levels to POPs for both evaluating the maternal body load and infant exposure risks (Raab et al., 2013). In addition, infants are more vulnerable than adults to hazardous chemicals because their metabolic pathways and immune system are immature and they weigh less than adults (Landrigan et al., 1999). CPs can be transferred from the mother to an infant via placental transfer during gestation (Qiao et al., 2018) and breastfeeding transfer during lactation (Xia et al., 2017b). A recent study showed that breastfeeding resulted in significantly higher infant exposure to CPs than placental transfer (Liu et al., 2020b).

China is the world's largest producer and consumer of CPs (Xu et al., 2014). Industrial production of CPs in China began in 1978 with an output of 3.4 kt and rapidly reached 1 million t/year in 2013 (Gluge et al., 2016; Xu et al., 2014). Although no official data are available, CP production has remained high since 2013. High levels of CP production and use in China have inevitably resulted in high levels of CPs in the environment, which could enter the human body. Relatively high concentrations of SCCPs and MCCPs have been found in breast milk samples collected in China and the levels of SCCPs exhibited higher than MCCPs between 2007 and 2011 (Xia et al., 2017a; 2017b). However, the recent study found that concentrations of MCCPs were higher than SCCPs in breast milk from the Yangtze River Delta (YRD) in China in 2015–2016 (Zhou et al., 2020). No large-scale studies have been conducted to investigate the occurrences of SCCPs and MCCPs in breast milk in China since 2011. Studies on temporal trends of SCCPs and MCCPs in breast milk are not available in China. Continuous investigation of CPs in breast milk in Chinese general population will allow for exploration of the temporal distributions of CPs, especially MCCPs, and evaluation of human health risks. In addition, various external exposure pathways can lead to human body burden of CPs, and dietary intake is the main exposure route (Gao et al., 2018). Consequently, to further understand the potential relationship between external and internal human exposure to CPs, it is vital to explore the human body burden of CPs (i.e., human breast milk) resulting from dietary exposure.

The objective of this study was to investigate the concentrations and congener profiles of SCCPs and MCCPs in breast milk samples in China and study the temporal trends between 2007 and 2017. Dietary intakes for infants via breastfeeding were estimated, and the potential health risks posed to infants were also assessed. In addition, the bioaccumulation of SCCPs and MCCPs for mothers through dietary intake was initially assessed. This study provides important data for health risk assessments of CPs, especially MCCPs.

2. Materials and methods

2.1. Sample collection

Samples were collected following the "Fourth WHO-Coordinated Survey of Human Milk for Persistent Organic Pollutants in Cooperation with UNEP" (WHO 2007), under guidance from the China National Center for Food Safety Risk Assessment (Beijing, China). Individual breast milk samples ($n = 2020$) were collected from 29 urban areas and 13 rural areas in 11 provinces in 2017. More than 30 donors were selected at each rural sampling site, and at least 50 donors at each of the urban sites. Sample details are given in Table S1. For the rural samples, individual samples from the same area were mixed to form one pooled sample, and for the urban samples, all samples from the same city were mixed together. This gave 29 urban pooled samples and 13 rural pooled samples. All samples were stored at −20 °C before analysis.

2.2. Sample preparation

Before analysis, approximately 25 mL of each breast milk sample was freeze-dried and ground into a powder. 2.5 ng of $^{13}C_{10}$-*trans*-chlordane was spiked before extraction. Next, each sample was extracted by an accelerated solvent extractor (ASE350, Dionex, Sunnyvale, CA, USA) with a mixture of *n*-hexane and dichloromethane (1:1, v/v). The extract was evaporated to dryness to gravimetrically determine the lipid content. Gel permeation chromatography was used to remove lipids from the extract. Then, the extract was purified using a multilayer chromatography column. The eluate was concentrated, solvent exchanged into cyclohexane, then 2.5 ng of ε-hexachlorocyclohexane (Dr. Ehrenstorfer, Augsburg, Germany) was added, and the extract was evaporated to approximately 50 μL.

2.3. Instrumental analysis

In total, 48 SCCP ($C_{10-13}Cl_{5-10}$) and MCCP ($C_{14-17}Cl_{5-10}$) congener groups were analyzed by two-dimensional gas chromatography with electron-capture negative-ionization mass spectrometry (GC × GC-ECNI-MS) fitted with a ZX2004 loop cryogenic modulator (Zoex Corporation, Houston, TX, USA). The instrument parameters and quantification method are described in previous studies (Reth et al., 2005; Xu et al., 2019).

2.4. Quality assurance and quality control

Before use, all glassware was rinsed three times with anhydrous methanol, acetone, and dichloromethane in sequence to eliminate background interferences. Spiking experiments were performed to validate the analytical method. The mean recoveries for the spiked samples were 92.7% and 86.3% for SCCPs and MCCPs, respectively. One blank sample was added to each batch of seven samples to monitor background SCCP and MCCP concentrations. The results showed that the SCCP and MCCP concentrations in the blank samples were less than 10% of those in the breast milk samples. Therefore, the concentrations in the samples were not blank corrected. The method detection limit was defined as three times the standard deviation of the average values in the blank samples. The method detection limits for the SCCPs and MCCPs were 7 and 12 ng g^{-1} lipid weight (lw), respectively. The recoveries were in range of 78.6%–109.1%, whose coefficients of variation were below 15%.

2.5. Statistical analysis

Statistical analysis was performed with SPSS Statistics 21.0 software, OriginPro 9.1. and Excel 2010. Pearson correlation analyses were performed to evaluate the correlation between the concentrations of SCCPs and MCCPs. Paired-sample t-tests were executed to compare the SCCP and MCCP concentrations between the urban and rural samples. Statistical significance was accepted at p-Values <0.05. The regression analysis was used to evaluate the temporal trend. Bivariate correlation analyses were carried out to assess the relationships of CP congener group patterns among dietary and breast milk samples. The statistical significance was accepted at the level of 0.01 (2-tailed). Correspondence analysis was performed to compare the differences in CP congeners of foods and breast milks to explore possible metabolic pathways.

2.6. Estimated daily intake and risk assessment

The dietary intake of CPs via breast milk for infants needs to be estimated to evaluate their total exposure to CPs. The estimated dietary intake (EDI) was calculated using Eq. (1). To assess the health risks of exposure to CPs, the margin of exposure (MOE) was calculated using Eq. (2).

$$\mathrm{EDI} = C \times M \times R \times \Phi \quad (1)$$

$$MOE = (\mathrm{NOAEL\ or\ } BMDL_{10})/EDI \quad (2)$$

where C is the SCCP or MCCP concentration in breast milk (ng g^{-1} lw), M is the daily intake from breast milk (g kg BW^{-1} d^{-1}), and R is the lipid content of the milk (%). The estimated daily intake from breast milk was 125 g kg BW^{-1} d^{-1} for an average milk intake of about 750 mL d^{-1} for an infant weighing 6 kg (CNS, 2013). The median lipid contents of the milk samples used for the calculations were 3.1% for the urban samples and 3.3% for the rural samples.ϕ is the infant absorption efficiency percent of CPs, which is assumed to be 100% (USEPA 2002).

3. Results and discussion

3.1. Concentrations and congener group profiles of SCCPs and MCCPs in breast milk from urban and rural China in 2017

The SCCP and MCCP concentrations in breast milk samples from urban and rural areas in 11 provinces around China are shown in Table 1. SCCPs and MCCPs were detected in all 42 pooled samples. For provinces where there was more than one urban or rural sample site, the results for all sites of the same type (i.e., urban or rural) in that province are averaged. The SCCP concentrations were in range of 131–808 ng g^{-1} lw for urban samples and 139–1543 ng g^{-1} lw for rural samples, while the MCCP concentration ranges were 94–1714 ng g^{-1} lw and 211–1089 ng g^{-1} lw in the urban and rural samples, respectively. The CP concentrations in breast milk from China of this study were very high compared with those in other studies (Table S2). The ratios of MCCPs/SCCPs (M/S) in the urban and rural samples were 1.6 ± 1.1 and 1.4 ± 1.1, respectively, indicating that MCCPs were predominant in breast milk samples collected in 2017. A comparison with other POPs in breast milk samples from China showed the CP concentrations in this study were significantly higher than those of ∑PBDEs (0.3–4.0 ng g^{-1} lw) (Zhang et al., 2017b), ∑PCDD/Fs (0.03–0.5 ng g^{-1} lw and 0.03–0.4 ng g^{-1} lw in urban and rural areas, respectively), and ∑dl-PCBs (0.75–8.45 ng g^{-1} lw and 0.66–5.65 ng g^{-1} lw in urban and rural regions, respectively) (Zhang et al., 2016). The extensive production and use of CPs in China might result in a high environmental load. Humans can be both directly and indirectly exposed to CPs after their release into the environment, which could contribute to higher concentrations of CPs than other POPs in breast milk in China.

Table 1
SCCP and MCCP concentrations (ng g^{-1} lw) in 42 pooled breast milk samples collected from urban and rural areas in 11 Chinese provinces in 2017.

Province	Urban		Rural	
	∑SCCPs	∑MCCPs	∑SCCPs	∑MCCPs
Gansu	131	149	513	421
Inner Mongolia	417	1714	536	642
Henan	808	251	1543	963
Jiangsu	211	430	–	–
Shanghai	626	569	353	572
Jiangxi	633	750	139	561
Guangxi	138	94	635	237
Guangdong	406	467	189	211
Zhejiang	321	905	–	–
Hunan	380	476	–	–
Guizhou	–	–	988	1089

The spatial distributions of SCCPs and MCCPs in breast milk are shown in Figure S1. Among the urban and rural samples, the highest SCCP concentrations were found in Henan Province. Henan Province is one of the largest producers of CPs in China, so the results could be attributed to local CP yields, consumption, and emission (Zhang et al., 2017a). The highest MCCP concentrations for the urban and rural samples were found in Inner Mongolia and Guizhou Province, respectively. CP concentrations in sediment samples from Hongfeng Lake in 2017/2019 were markedly elevated compared with 2013/2014, indicating a recent rapid increase in the production and use of CPs in Guizhou Province (Zhang et al., 2019). The spatial variations observed for breast milk might be strongly related to the production and use of CPs in different provinces (Liu et al., 2020a).

CPs in breast milk samples were analyzed in both urban and rural areas in seven provinces (Gansu, Inner Mongolia, Henan, Shanghai, Jiangxi, Guangxi, and Guangdong) (Table 1). Paired-sample *t*-tests showed that there were no significant differences in the SCCP and MCCP concentrations between the urban and rural samples ($P > 0.05$). The ratio of the ∑CP (∑MCCPs + ∑SCCPs) concentrations in urban samples to rural samples ranged from 0.3 to 2.2. This differed from a previous study where almost all ∑CP concentrations in urban areas were higher than those in rural areas because of industrial activities using CPs in urban areas (Xia et al., 2017b). Consumer behavior might also affect CP exposure in urban and rural populations. High concentrations of CPs have been found in food packaging, which could be widely used in rural areas without effective supervision and result in CP leakage into the environment and exposure for rural residents (Wang et al., 2018, 2019) The widespread use of mulching film and plastic wrap in agriculture may also contribute to high CP concentrations in food consumed by humans. Our results suggest that CP concentrations in rural areas should be continuously investigated and the reasons for elevated CP concentrations should be further determined.

The SCCP and MCCP congener group profiles in the breast milk samples from urban and rural areas in 11 provinces around China were analyzed. Overall, the SCCP and MCCP congener compositions in all of the samples were generally similar among urban and rural areas and different provinces (Figure S2). C_{10}-CPs were the most abundant SCCP congener groups, accounting for 53.0% of ∑SCCPs, following by C_{11}-CPs. The predominant SCCP chlorine congeners were Cl_6-and Cl_7-CPs, accounting for 31.3% and 35.4% of the ∑SCCPs, respectively. The SCCP congener patterns in breast milk in this study were similar to those found in the YRD (Zhou et al., 2020) but different from those in the UK (Thomas et al., 2006) where C_{11}-CPs were the predominant SCCP carbon congeners. This difference was likely related to the different congener compositions of CP technical mixtures, with C_{11}- and C_{12}-CPs predominant in CP mixtures in the UK. The predominant MCCP carbon congeners were C_{14}-CPs, which contributed 60.5% of the ∑MCCPs. For the chlorine congener groups of the MCCPs, Cl_7-and Cl_8-CPs were the most abundant, contributing to 26.5% and 31.2% of the total MCCPs, respectively. The MCCP congener group profiles in breast milk samples in this study were similar to those found in breast milk samples from the YRD but slightly different from those in Scandinavia, where $C_{14}Cl_{5-6}$ were predominant (Zhou et al., 2020).

3.2. Temporal trends in SCCPs and MCCPs in breast milk between 2007 and 2017

SCCP and MCCP concentrations in breast milk samples collected from urban and rural areas in China between 2007 and 2017 are shown in Fig. 1. The unitary linear recursive analysis was performed to further explore the temporal trends of SCCPs and MCCPs in breast milk from urban and rural China between 2007 and 2017 (Figure S3). In urban areas, the SCCP concentrations increased slightly between 2007 (median: 681 ng g^{-1} lw) and 2011 (median: 733 ng g^{-1} lw). By contrast, between 2011 and 2017, the median SCCP concentrations decreased greatly in urban areas (393 ng g^{-1} lw), with a rate of decrease of 46.4%. On the whole, the SCCP levels in urban areas decreased during 2007–2017 because the slope of the equation was less than zero (Figure S3a). Meanwhile, in rural areas, the SCCP median concentrations increased slightly between 2007 (303 ng g^{-1} lw) and 2011 (360 ng g^{-1} lw), and increased significantly between 2011 and 2017 (525 ng g^{-1} lw), with a growth rate of 45.8%. The rate of decrease in SCCP concentrations in urban samples was almost equal to the growth rate in rural samples from 2011 to 2017. In general, the SCCP levels in rural areas increased from 2007 to 2017 as the slope greater than zero (Figure S3c). In the urban samples, the median MCCP concentrations increased slightly from 2007 (60.4 ng g^{-1} lw) to 2011 (64.3 ng g^{-1} lw), and greatly (with about six times) between 2011 and 2017 (472 ng g^{-1} lw). In the rural samples, MCCPs increased slightly from 2007 (35.7 ng g^{-1} lw) to 2011 (45.4 ng g^{-1} lw), and significantly (with approximately eleven folds) between 2011 and 2017 (567 ng g^{-1} lw). The significant high slopes (49 for urban samples, 58 for rural samples) of the regression equations indicated the highly elevated MCCPs levels in China between 2007 and 2017 (Figure S3b and S3d). The increasing trend of MCCPs in breast milk was in accordance with the elevated MCCP levels in sediment cores from the Pearl River Delta (Chen et al., 2011), marine mammals from the South China Sea (Zeng et al., 2015), and sediment cores from nine lakes in China (Zhang et al., 2019). Increases in the M/S ratios in breast milk showed that the proportion of MCCPs increased greatly between 2007 and 2017 (Figure S4), suggesting that MCCPs were predominant in breast milk in recent years. A similar increasing temporal trend for the M/S ratio was observed in another study of human samples in China (van Mourik et al., 2020).

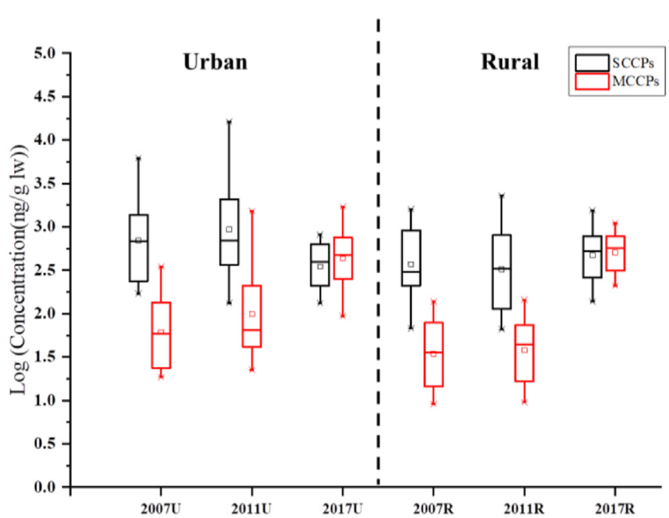

Fig. 1. SCCP and MCCP concentrations in breast milk samples collected from urban and rural areas in China between 2007 and 2017.

It is extremely likely that the large increases in the M/S ratios in breast milk are related to the elevated production and consumption of MCCPs in recent years in China. CP commercial mixtures are gradually being replaced with mixtures with lower SCCP contents as SCCPs are phased out in China (Gluge et al., 2018; Liu et al., 2020a; MEEPRC 2017). In China, CP commercial mixtures are classified as CP-42, CP-52, and CP-70 according to their chlorine contents rather than carbon chain length, which does not differentiate among SCCPs, MCCPs, and LCCPs. CP-52, which has a chlorine content of 52%, is the main CP mixture, with a contribution of 90% to the total CP mixtures produced in China (van Mourik et al., 2016). A previous study found the mean value of MCCPs in CP-52 obtained from China in 2017 was 57%, which indicates that MCCPs are likely to be predominant in current Chinese CP commercial products (Gluge et al., 2018). In addition, MCCPs have relatively high octanol–water partition coefficients (K_{ow}) compared with SCCPs. A previous study indicated that the bioaccumulation factors of MCCPs were higher than those of SCCPs in food webs in Lake Ontario (Houde et al., 2008). As a result, MCCPs are more likely than SCCPs to accumulate through trophic levels to humans, leading to high M/S ratios in breast milk. The high MCCP yields and increasing M/S ratios indicate that MCCP concentrations in breast milk are extremely likely to keep increasing in coming years. Furthermore, MCCPs, rather than SCCPs, are classed as harmful to breastfed infants according to the European Chemicals Agency (ECHA 2008). Consequently, the manufacture, use, and emission of MCCPs should attract increasing attention.

The SCCP and MCCP congener profiles in breast milk samples collected in urban and rural China between 2007 and 2017 are shown in Fig. 2. In all of the breast milk samples, C_{10}- and C_{11}-CPs were the predominant SCCP congeners. Increased relative abundance of C_{13}-CPs was observed in both urban and rural samples between 2007 and 2017. For MCCPs, C_{14}-CPs were the most abundant MCCP congeners during the whole study period, followed by C_{15}-CPs. The MCCP congener patterns showed a temporal trend from shorter to longer chains in both urban and rural samples. In urban samples, the relative abundance of C_{14}-CPs decreased with an average annual change rate of 2.5%, while those of C_{16}-CPs and C_{17}-CPs increased with average annual change rates of 16.1% and 24.5%, respectively. For the rural samples, the average annual decrease in the C_{14}-CP congener relative abundance was 2.7%, while the rates of increase for C_{16}-CPs and C_{17}-CPs were 19.4% and 63.2%, respectively. The significant increase in the relative abundance of MCCPs with longer carbon chains might indicate the emergence of LCCPs in breast milk because some LCCP congeners have similar physicochemical properties to MCCPs (Feo et al., 2009; Zhou et al., 2020). These results suggest that, at the same times as standardizing the management of SCCPs, management measures should be taken for MCCPs and LCCPs.

3.3. Estimated dietary intakes for infants and risk assessment of SCCPs and MCCPs via breastfeeding

The EDIs (Eq. (1)) of SCCPs and MCCPs in breast milk samples collected in urban and rural areas between 2007 and 2017 were calculated using the 5th, 50th, and 95th percentiles of the CP concentrations (Table 2). The median EDIs for CPs via breast milk in 2017 were 1230 ng kg^{-1} d^{-1} for urban samples (range 508–5630 ng kg^{-1} d^{-1}) and 2510 ng kg^{-1} d^{-1} for rural samples (range 573–5650 ng kg^{-1} d^{-1}) for SCCPs, and 2150 ng kg^{-1} d^{-1} for urban samples (range 366–6640 ng kg^{-1} d^{-1}) and 1890 ng kg^{-1} d^{-1} for rural samples (range 840–7040 ng kg^{-1} d^{-1}) for MCCPs. The

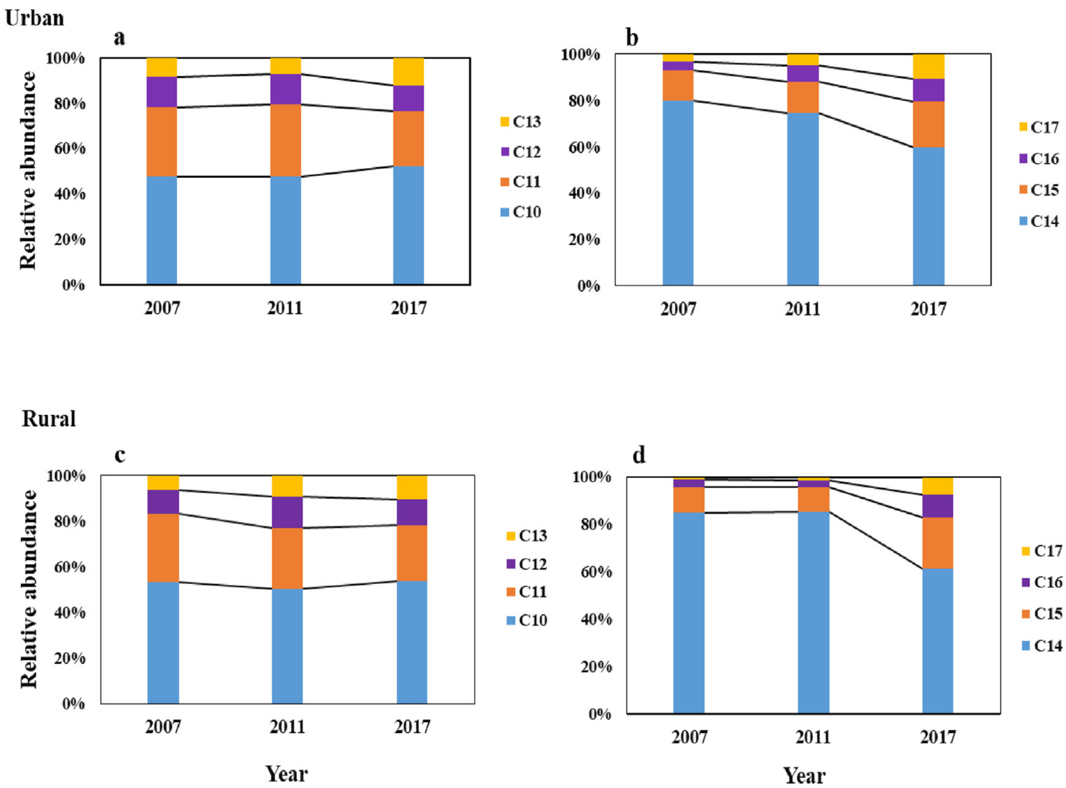

Fig. 2. Relative abundances of carbon congener groups profiles of SCCPs (a and c) and MCCPs (b and d) in breast milk samples from urban (a and b) and rural (c and d) regions in China between 2007 and 2017.

Table 2
EDIs (ng kg^{-1} d^{-1}) of SCCPs and MCCPs via breastfeeding for Chinese infants (given as percentiles) between 2007 and 2017 and MOEs calculated using EDIs and the no observed adverse effect level (NOAEL) or the benchmark dose lower confidence limit (BMDL) in animals.

		Urban			Rural		
		2007	2011	2017	2007	2011	2017
EDI(ng kg−1 d−1)							
SCCPs	5th	766	939	508	357	344	573
	50th	2980	3390	1230	1310	1520	2510
	95th	13,200	32,700	5630	6320	8650	5650
MCCPs	5th	85.3	132	366	43.0	45.1	840
	50th	264	297	2150	152	212	1890
	95th	1060	3400	6640	554	450	7040
MOE(ECB)							
SCCPs	95th	7580	3060	17,800	15,800	11,600	17,700
MCCPs	95th	21,700	6770	3460	41,500	51,000	3270
MOE(EFSA)							
SCCPs	95th	174	70	409	364	266	407
MCCPs	95th	34,000	10,600	5420	65,000	80,000	5110

Note: SCCP and MCCP concentrations in breast milk samples from urban and rural areas collected in 2007 and 2011 from previous studies (Xia et al., 2017a; 2017b). The NOAEL values for SCCPs and MCCPs from the ECB are 100 (ECB 2000) and 23 mg kg^{-1} d^{-1} (ECB 2007), respectively. The $BMDL_{10}$ value for SCCPs and MCCPs from the EFSA are 2.3 and 36 mg kg^{-1} d^{-1} (ESFA 2019), respectively.

EDIs in this study were much higher than those reported in samples from Sweden (median: 65 ng kg^{-1} d^{-1} for SCCPs and 170 ng kg^{-1} d^{-1} for MCCPs) and Norway (median: 60 ng kg^{-1} d^{-1} for SCCPs and 253 ng kg^{-1} d^{-1} for MCCPs) (Zhou et al., 2020), but lower than those reported in samples from Mianyang, China (mean: 17,400 ng kg^{-1} d^{-1} for SCCPs and 6000 ng kg^{-1} d^{-1} for MCCPs) (Liu et al., 2020b). The EDI temporal trends for SCCPs and MCCPs were consistent with those for the concentrations of SCCPs and MCCPs in urban and rural areas. EDIs will vary during the lactation period because CP concentrations in human milk can vary along with intake, absorption, and metabolism, which shows that continuous monitoring will be important for CPs in breast milk.

The margin of exposure (MOE) was calculated to evaluate the health risks of exposure to CPs in breast milk for infants (Eq. (2)). NOAEL is the no observed adverse effect level, and $BMDL_{10}$ is the benchmark dose for a 10% change in the critical adverse effects for 95th percentile exposure. The NOAEL values are 100 and 23 mg kg^{-1} d^{-1} for SCCPs and MCCPs, respectively, based on tubular pigmentation effects in mammals set by European Chemicals Bureau (ECB) (ECB 2000; 2007). The $BMDL_{10}$ values used for SCCPs and MCCPs were 2.3 and 36 mg kg^{-1} d^{-1}, respectively, based on benchmark dose modeling of the effects observed in the kidneys developed by European Food Safety Authority (ESFA) (ESFA 2019). A total uncertainty factor of 1000 was used, and a MOE <1000 indicates that there might be significant risks to human health. The 95th percentile EDIs were applied to assess the human health risks posed by CPs. The MOE results are quite different as the use of different effect does (i.e., NOAEL or $BMDL_{10}$) (Table 2). In this study, the SCCP MOEs (ECB) in urban and rural China from 2007 to 2017 were all higher than the uncertainty factor of 1000, indicating there were no health concerns related to SCCPs for infants breastfeeding between 2007 and 2017. However, the MOEs (ESFA) of SCCPs in urban and rural China between 2007 and 2017 were all below 1000, which indicated that SCCPs pose continuous and significant health risks to infants. Although the results of assessment of the health risks posed by SCCPs to infants via breast milk varied because of different critical endpoints, it's necessary to continuously monitor SCCP concentrations and assess health risk.

The MCCP MOEs (ECB) and MOEs (ESFA) in 2017 were all close to 1000 (Table 2), and they will decrease every year as the EDIs of the MCCPs increase each year, which could increase the human health risks. MCCPs in breast milk could be toxic to infants through suppression of the coagulation system (Lassen C et al., 2014). The continuous growth in production of MCCPs is likely to cause steady release of MCCPs into the environment and exposure of humans to high doses, indicating the possibility of health risks to infants from MCCP exposure via breastfeeding. Our results indicate that routine, continuous, and long-term monitoring and risk assessment of SCCPs and MCCPs is required, and emission-reduction strategies for MCCPs need to be developed. Future research should focus on the occurrences and bioaccumulation of MCCPs in the human body.

3.4. Human exposure to SCCPs and MCCPs thorough dietary intakes

The human body burden of CPs could be caused by intake via various pathways, including inhalation, ingestion of dust, dermal contact, and the diet. Among these pathways, dietary intake is the main route for CPs to enter the human body. Dietary intake of SCCPs and MCCPs accounts for 88% and 93% of their total daily intakes, respectively, in adults (Gao et al., 2018). Total diet studies (TDI) have been carried out to monitor human dietary exposure in China (Cui et al., 2020). To investigate the relationship between dietary intake and the human body burden of CPs, bivariate correlation analyses were performed for SCCP and MCCP homologs in food and breast milk samples. Eight main foods, including vegetables, cereals, legumes, potatoes, aquatic foods, meats, eggs, and milk, from seven provinces (Guangxi, Guizhou, Hunan, Jiangsu, Jiangxi, Shanghai, and Zhejiang) were selected from our recent research under the sixth TDI started in 2017 (Cui et al., 2020). Breast milk samples were also collected in the seven provinces mentioned above. The dietary samples were all significantly correlated with the breast milk samples at the 0.01 level (Table S2), which proved the important role of dietary intake in human exposure.

Previous studies have demonstrated that the congener patterns of CPs change among different trophic levels in the food chain (Houde et al., 2008; Ma et al., 2014). To compare the different CP homolog compositions of foods from the 2017 TDI and breast milk samples, correspondence analysis was carried out in the correlation matrix of the relative abundances of SCCP and MCCP homologs. In the correspondence analysis plot, two main factors were extracted, which together explained 83.8% (60.0% + 23.8%) of the most original variables. Eggs, meat, and aquatic food samples were located near the breast milk samples (Fig. 3), suggesting that similar CP congener patterns were found for animal-origin foods (except for milk) and breast milk. These animal-origin foods and breast milk samples all had positive scores in the two dimensions, probably because of the relatively high contents of C_{12}-, C_{13}-, and Cl_{8-10}-

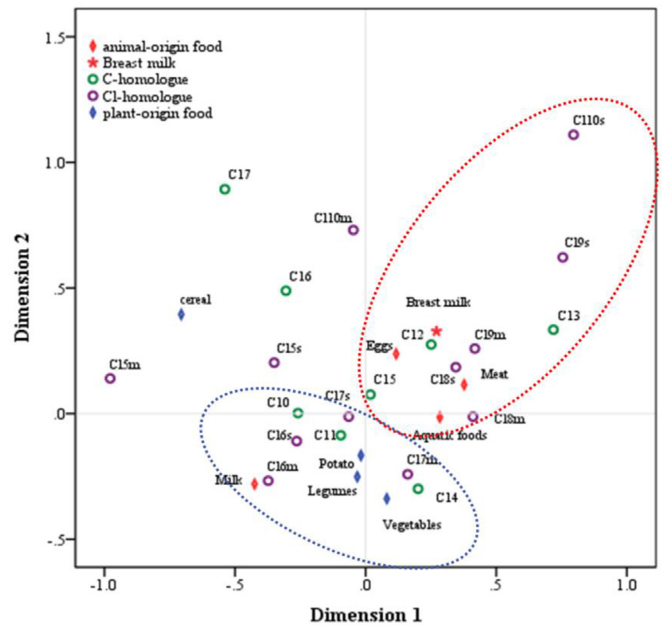

Fig. 3. Two-dimensional scatter plots from correspondence analysis of the SCCP and MCCP homologs. Cl5s–Cl10s represent the SCCP chlorine homologs, and Cl5m–Cl10m represent the MCCP chlorine homologs.

SCCPs, and Cl_8-and Cl_9-MCCPs. This indicated that CP congeners in breast milk with longer carbon chains and higher chlorine numbers might be directly derived from animal-origin food, including eggs, meat, and aquatic foods. In addition, the C_{10}-, C_{11}-, Cl_6-, and Cl_7-SCCPs, and C_{14}-, Cl_6-, and Cl_7-MCCPs were located near the potato, legume, and vegetable samples, and had negative scores in the second dimension. This result indicated that congeners with short carbon chains and low chlorine numbers were abundant in plant-origin foods and they were likely to be transformed into congeners with longer carbon chains and higher chlorine numbers after ingestion, and then assimilated and accumulated in the human milk. Previous studies have found that highly chlorinated biphenyls are more likely to accumulate in the human body because of increases in the lipophilicity of PCBs as the level of chlorine substitution increases (Xing et al., 2009; Zhang et al., 2016). The K_{ow} values of CPs increase with the number of carbon and chlorine atoms (Feo et al., 2009). Consequently, CP congeners with long carbon chains and high levels of chlorination tend to accumulate in the human body. In summary, dietary intake, especially of animal-origin foods, contributes to the human body burden of CPs. The relationship between the internal burden and external exposure (such as inhalation), and the metabolic pathways of CPs needs to be studied further.

4. Conclusions

The present study investigated temporal trends of SCCPs and MCCPs in breast milk samples in China between 2007 and 2017. SCCP levels declined in urban areas but rose in rural areas, while MCCP levels showed continuous growth. The significant increases in MCCP levels in breast milk could be related to the mass production and use of MCCPs. A temporal shift trend from shorter to longer carbon chain congeners was observed in the homolog patterns. SCCP ingestion presents a significant health risk to infants. Although MCCPs do not pose a significant risk currently, they need to be controlled in the future because of their increasing levels in breast milk and potential toxicity to infants. Animal-origin foods contribute to the human body burden of CPs and congeners with long carbon chains and high chlorine numbers tend to accumulate in the human body. Pollution prevention and control measures for MCCPs should be discussed and the potential toxic effects of SCCPs and MCCPs to mothers and infants should be studied.

Credit author statement

Chi Xu: Conceptualization, Formal analysis, Investigation, Writing—original draft, Visualization; **Kunran Wang:** Data curation, Investigation, Validation, Formal analysis; **Lirong Gao:** Conceptualization, Supervision, Methodology, Writing—review & editing, Funding acquisition, Project administration; **Minghui Zheng:** Conceptualization, Supervision; **Jingguang Li:** Resources, Funding acquisition; **Lei Zhang:** Resources, Formal analysis; **Yongning Wu:** Conceptualization, Resources, Supervision, Funding acquisition, Project administration; **Lin Qiao:** Methodology, Writing-review & editing; **Di Huang:** Formal analysis, Writing—review & editing; **Shuang Wang:** Formal analysis, Writing—review & editing; **Da Li**: Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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