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Levels of synthetic musk fragrances in human milk from three cities in the Yangtze River Delta in Eastern China

Xiaolan Zhang[1,*], Gaofeng Liang[1], Xiangying Zeng[2], Jing Zhou[1], Guoying Sheng[1,2], Jiamo Fu[1,2]

1. Institute of Environmental Pollution and Health, School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, China. E-mail: zhangxiaolan@staff.shu.edu.cn
2. State Key Laboratory of Organic Geochemistry, Guangzhou Institute of Geochemistry, Chinese Academy of Sciences, Guangzhou 510640, China

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Abstract

Synthetic musks are used as additives in many household products. After absorption into the human body, they accumulate and their concentrations in human milk reflect both the mother and her infant's exposure level. Concentrations of four synthetic musks, musk xylene (1-*tert*-butyl-2,6-dimethyl-2,4,6-trinitrobenzene, MX), musk ketone (4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone, MK), 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB) and 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene (AHTN), were determined in human milk samples collected from Shanghai, Wuxi, and Shaoxing in Eastern China. The four synthetic musks were found in most samples analyzed, with HHCB the dominant component followed by MX. The median (mean) values for HHCB, AHTN, MX and MK concentrations were 63 (82), 5 (12), 17 (24) and 4 (9) ng/g lipid weight, respectively. These data suggested the total synthetic musk contamination was low, and the distribution percentage was HHCB > MX > AHTN ≈ MK. The relative high ratio of nitro to polycylic musk indicated that nitro musks were still widely used. The musk concentrations in these cities were not significantly different from each other ($p > 0.05$). Principal components score plots were obtained, which showed similar exposure sources. The amount of total synthetic musks in human milk were not associated with mother's age, although HHCB was significantly correlated with AHTN ($p < 0.05$). Daily ingestion of HHCB, AHTN, MX and MK for infants from human milk were estimated as (2526 ± 2926), (370 ± 524), (7391 ± 832), and (277 ± 462) ng/day, respectively. Those doses were 1–2 orders of magnitude below the provisional tolerable daily intakes.

Key words: synthetic musks; human milk; exposure of infant

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Introduction

Synthetic musks are widely used as additives in many household commodities as substitutes for natural musks. They consist of three main categories, i.e., nitro musks, polycyclic musks and macrocyclic musks. Musk xylene (1-*tert*-butyl-2,6-dimethyl-2,4,6-trinitrobenzene, MX) and musk ketone (4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone, MK) are two widely used nitro musks, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB) and 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene (AHTN) are two typical polycyclic musks. Because of the bioaccumulation potential and toxicity to organisms, the usage of MX was regulated (Maekawa et al., 1990) and gradually replaced by polycyclic musks over the past decades. Both HHCB and AHTN comprise about 95% of the European market and 90% of the USA market among all polycyclic musks (Reiner and Kannan, 2006).

Synthetic musks are lipophilic chemicals detected in most environmental areas in recent years, such as surface water (Moldovan, 2006), sediment (Peck and Hornbuckle, 2004), sewage (Artola-Garicano et al., 2003; Horii et al., 2007), sludge (Shek et al., 2008; McClellan and Halden, 2010), air and biota (Duedahl-Olesen et al., 2005), and also in human adipose tissue (Schiavone et al., 2010), human milk (Hutter et al., 2005; Raab et al., 2008), and blood (Hutter et al., 2009). Both HHCB and AHTN have been found to exist in human fat/breast milk in Europe, the United States, and South Korea (Kannan et al., 2005; Reiner et al., 2007; Raab et al., 2008; Kang et al., 2010). The concentration range varies in different regions, and also changes with sampling time. Lignell et al. (2008) suggested a significant decline in AHTN and MX concentrations in breast milk between 1996 and 2003,

* Corresponding author. E-mail: zhangxiaolan@staff.shu.edu.cn

but no temporal trend in HHCB concentration. Kang et al. (2010) observed lower concentrations in breast milk than in serum, and little correlation in concentrations among umbilical serum, maternal serum, and breast milk.

Although data on the toxicological properties of polycyclic musks are sparse, a dose of 100 mg/kg body weight of AHTN resulted in an increase in the relative liver weight of the rat (Steinberg et al., 1999). Both MK and MX were identified as strong inducers for phase I enzymes in rodents and cogenotoxicant *in vitro* in human derived cells (Schmeiser et al., 2001). Exposure to HHCB and AHTN can cause long term inhibition of multidrug efflux transporters responsible for multixenobiotic resistance on marine mussels (Luckenbach and Epel, 2005). Humans are exposed to synthetic musks through the use of personal care products and cleaning products, with dermal absorption thought to be the major route for adults (Raab et al., 2008). The contamination of human milk is concerning because of its implications for postnatal exposure, with some studies investigating the influence of synthetic musks in human milk for nursed infants (Reiner et al., 2007; Lignell et al., 2008).

However, there are few studies on musks in China (Wan et al., 2007). Shanghai (SH) is the largest commercial and financial center in China with 18.6 million inhabitants. It is located in the Yangtze River Delta alluvial plain, where it is surrounded by Jiangsu and Zhejiang Province. Shaoxing (SX) is a city with a population of 4.3 million in the north of Zhejiang Province. Wuxi (WX) is another city near the Yangtze River, located in the south of Jiangsu Province. It has a population of 4.6 million and is one of the fifteen economic centers in China. Economic development is fast in the Yangtze River Delta region, and the use of perfumed products is increasing in this region. But the influence of fragrance material on human bodies has rarely been discussed and there are currently no reports on human exposure to musk. The purpose of this article was to determine the levels and the distribution of synthetic musk fragrances, and to assess the exposure of dietary intake of infants through breast milk in these cities. Based on previous studies, HHCB, AHTN, MX and MK were measured in human milk samples.

1 Materials and methods

1.1 Samples collection

Milk samples were collected in 2006 and 2007 from 100 volunteer women living in three different cities of Shanghai, Wuxi and Shaoxing. They had all lived in these areas for at least two years. The milk samples were collected 1–2 weeks after delivery. The complete information about the mother's age and fat content of the milk are shown in Table 1. The milk samples were stored in brown glass flasks at –20°C until chemical analysis.

1.2 Chemicals and materials

Both HHCB and AHTN were purchased from Promochem, Germany, with purities of 75% and 99%, respectively. The MX, MK, phenanthene-d_{10} and hexamethylbenzene (HMB) were obtained from Dr. Ehrenstorfer GmBH, Germany, with purities of 99%, 98%, 99%, and 99%, respectively.

Table 1 Sample information data

Location	Age range (yr)	Mean age (yr)	Sample number	Mean lipid weight (%)
Shanghai	< 25		9	
	25–35	28.3	29	2.0
	> 35		2	
Shaoxing	< 25		14	
	25–35	26.7	24	2.4
	> 35		2	
Wuxi	< 25		11	
	25–35	26.3	6	2.4
	> 35		3	

Dichloromethane (DCM) and *n*-hexane (China National Medicines Corporation Ltd., China) were of analytical grade and re-purified prior to use, ethanol and diethyl ether were of analytical grade (Merck, Germany), anhydrous sodium sulfate (China National Medicines Corporation Ltd., China) was baked at 450°C for 4 hr prior to use. Silica gel (70–230 mesh, Merck, Germany) was activated at 180°C for 12 hr, deactivated with 3% redistilled water, and then kept in *n*-hexane before use.

1.3 Samples extraction and cleanup

Frozen milk samples were thawed and homogenized at room temperature. All samples were spiked with phenanthene-d_{10} (20 ng) as surrogate standard. An extraction and cleanup method was used with some modifications (Reiner et al., 2007). Briefly, 8% (*W*/*W*) potassium oxalate solution (6 mL), ethanol (10 mL), and diethyl ether (5 mL) were added before liquid-liquid extraction. Samples were extracted three times with *n*-hexane, the organic phases were combined together and concentrated to determine the lipid content gravimetrically. The lipid was re-dissolved in *n*-hexane, and the resulted solution was passed through gel permeation chromatography (GPC) using a Bio-beads S-X3 (Bio-Rad Laboratories, Hercules, CA) packed glass column (280 mm × 25 mm i.d.) to remove lipids. The mobile phase was DCM/*n*-hexane (*V*/*V* = 1:1). The first 65 mL of the fraction was discarded, and the following 100 mL containing musks was collected. The extract was concentrated and then passed through a silica gel column for further cleanup. *n*-Hexane and DCM were used consecutively, with the second fraction collected and concentrated to 0.1 mL. Internal standard (Hexamethylbenzene, HMB) was added prior to GC/MS analysis.

1.4 GC/MS analysis

Musks were analyzed using a Hewlett-Packard 6890N GC equipped with a 5975 mass selective detector (Agilent Technologies, USA). The separation was carried out on an HP-5MS (30 m × 0.25 mm × 0.25 μm) fused-silica capillary column (Agilent J&W GC Columns, Agilent Technologies, USA). The temperature of the oven was programmed as follows: 100°C (hold for 1 min) to

160°C at 7°C /min, then at 3°C/min to 180°C, 1°C /min to 190°C and finally 10°C/min to 280°C. The flow rate of the carrier gas was 1.0 mL/min, and the injection was set to splitless mode at 280°C. The MS was operated in an electron impact with selected ion monitoring mode (EI-SIM). Target compounds were qualified by retention time and characteristic ions: m/z 243, 258 and 213 amu for HHCB; 243, 258 and 159 amu for AHTN; 282 and 297 amu for musk xylene; 279 and 294 amu for musk ketone; and 188 amu for phenanthrene-d_{10}.

1.5 Quality assurance/quality control

Standard mixture of HHCB, AHTN, MX and MK were spiked into six matrix samples at level of 1, 1, 0.2 and 0.2 μg, respectively, and the recoveries of these compounds were from 77% to 100%, from 76% to 98%, from 84% to 109%, from 79% to 110%, respectively. A blank, a spiked blank, a matrix spiking sample, and a matrix spiking duplicate sample were processed within each sample batch (about 12–15 samples). Low concentration of HHCB (10–22 ng/mL) was detected in the procedural blanks; hence blank values were subtracted from the sample measurements. A total of 20 ng of phenanthene-d_{10} was added to all samples, and the recoveries varied from 71% to 118%. Reported concentrations were not corrected with the recoveries. The limits of detection (LODs) and limits of quantification (LOQs) were calculated based on a signal-to-noise ratio of 5 and 10, respectively. The LODs were 5 ng/g lipid weight for HHCB, AHTN and MX; and 4 ng/g lipid weight for MK. Concentrations of musks were obtained by the internal standard calibration method based on a 7-point calibration curve.

1.6 Statistical analysis

Lipid adjusted concentrations were used. For statistical analysis, values below LOQ were assumed to be half of LOQ (1/2 LOQ) in the calculation. The Mann-Whitney U test was used to compare differences in musk concentrations among the three cities. Pearson's correlation analysis was used to examine the relationship between mother's age and musk concentrations, as well as musk concentrations themselves. Statistical significance was set at the threshold level of $p < 0.05$. Principal component analysis (PCA) (SPSS 18.0) was used to discuss the main influence factors on musk concentrations.

2 Results and discussion

2.1 Concentration levels and distribution profile of musks

All milk samples were found to contain at least one synthetic musk among HHCB, AHTN, MX and MK, with detection ratios of 99%, 75%, 83%, 60%, respectively, indicating the high occurrence of synthetic musk fragrances in human milk. The detection frequency of polycyclic musks (HHCB+AHTN) was different among the three cities, with SH < SX < WX, but for nitro musks (MX+MK), the trend was completely the reverse.

The concentrations for the four musks showed log-normal distributions. The concentration of HHCB in SH, SX and WX ranged from < 5 to 278, from 5 to 782, from 24 to 281 ng/g lipid weight, respectively (Fig. 1). The highest concentration of HHCB (782 ng/g lipid weight) was found in a 25-year-old mother in SX, and the lowest concentration was found in a 23-year-old mother in SH. The median concentrations of MX and AHTN were 18 and 5 ng/g lipid weight in SH, 18 and 5 ng/g lipid weight in SX, and 15 and 8 ng/g lipid weight in WX, respectively. The MK concentration in the three cities ranged from < 4 to 105, from < 4 to 70, from < 4 to 24 ng/g lipid weight, respectively. The median concentration of HHCB (63 ng/g), the dominant compound in all samples, was higher than ANTH (5 ng/g), MX (17 ng/g), and MK (4 ng/g) combined. This corresponded to the greater production and usage of HHCB, compared with other synthetic musks (Heberer, 2002), although there is no domestic report on musk consumption in China. The concentration ranges in SH, SX and WX were slightly different, and the Mann-Whitney U test showed no significant concentration difference among the three cities ($p > 0.05$). High musk concentrations (101 ng/g) were found among primiparous women.

The HHCB, AHTN, MX and MK in human milk were monitored in different regions. Compared to the environmental level, total amount of synthetic musk in our study was relatively low (Table 2). The HHCB and total concentrations were similar to data from Sweden, but 1/10–1/2 lower than those in the USA, Denmark, and South Korea. This may be attributed to the low per capita consumption rates in Eastern China (Zhang et al., 2008). The concentration values of MX and MK in this study were close to the upper data from the USA and South Korea. Based on previous research, MX has been found to be carcinogenic after long-term exposure in mice and its amine metabolite is a mechanism-based inactivator of mouse CYP2B10 (Maekawa et al., 1990; Lehman-Mckeeman et al., 1997). Due to concern regarding its toxicity to organisms, MX was banned and regulated in Japan and Europe in 1980s (Maekawa et al., 1990; Liebl et al., 2000) as an ingredient in domestic products, and concentration in milk declined significantly in Europe (Rimkus and Wolf, 1996; Raab et al., 2008). It is still used as an additive in China (Zhang et al., 2008), however, and as a result high levels of MX have been observed in adipose tissue from Chinese Sturgeon (*Acipenser sinensis*), a large migrating fish living in the Yangtze River (Wan et al., 2007). The contamination of MX in the Yangtze River Delta is concerning.

The distribution patterns of musks based on median concentrations in human milk were calculated and compared (Table 2). HHCB was the main contaminant, with a contribution of 70% to total musk concentrations. The second dominant musk found in our study was MX 19%. The distributions of AHTN and MK were similar. Compared to data from other regions, HHCB was always the dominant compound, although the distribution pattern slightly changed. The nitro and polycyclic musk concen-

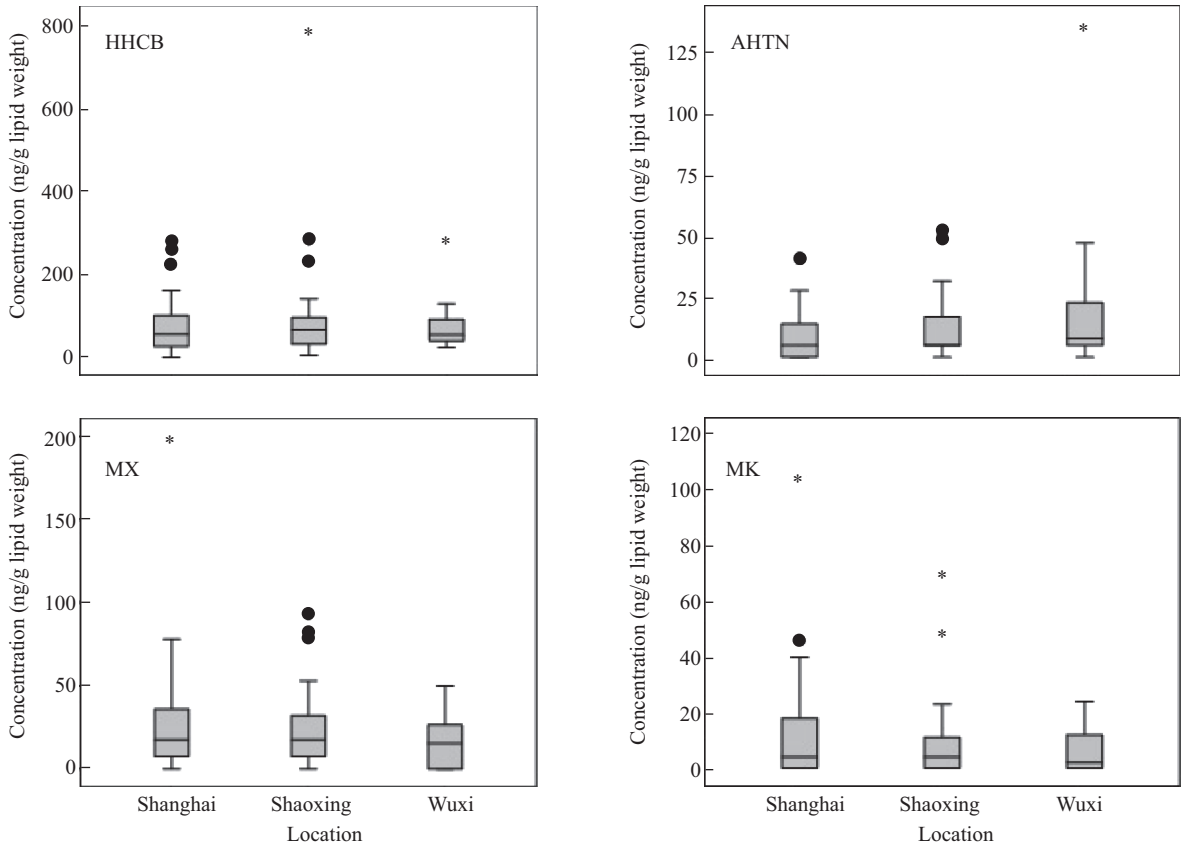

Fig. 1 Box-and-whisker plots of musk concentrations in human milk samples. The boxes indicate the interquartile range of the concentrations; the line within each box represents the median; the whisker extends to the last observation within 1.5 times the interquartile range; and the circles and asterisks outside the whiskers represent observations outside the interquartile range.

Table 2 Concentration of musks in human milk samples (unit: ng/g lipid weight)

Location		HHCB	AHTN	MX	MK	Reference
Germany	Range	16–108	11–58	10–30	5–15	Rimkus and Wolf, 1996
(n = 5)	Median	37	22	30	10	
	Percentage	38%	22%	30%	10%	
Denmark	Range	38.0–422	5.58–37.9	< LOQ–46.4	< LOQ–26.9	Duedahl-Olesen et al., 2005
(n = 10)	Median	147	17.5	9.44	14.9	
	Percentage	78%	9%	5%	8%	
USA	Range	< 5–917	< 5–144	< 2–150	< 2–212	Reiner et al., 2007
(n = 31)	Median	136	53.0	17.0	58.2	
	Percentage	52%	20%	6%	22%	
Sweden	Range	2.8–268	< 3.0–53.0	< 6.0–83.9	< 5.0–24.4	Lignell et al., 2008
(n = 101)	Median	63.9	10.4	9.5	< 5.0	
	Percentage	72%	12%	11%	5%	
Germany	Range			< LOQ–240	< LOQ–6	Raab et al., 2008
(n = 85)	Median			8	n.d.	
South Korea	Range	55–515	15–91	15–220	15–150	Kang et al., 2010
(n = 20)	Geometric Mean	180	24	18	32	
	Percentage	71%	9%	7%	13%	
China	Range	< 5–782	< 5–139	< 5–198	< 4–105	This study
(n = 100)	Median	63	5	17	4	
	n.d.	1	25	17	40	
	Percentage	70%	6%	19%	4.5%	

n: the sample number; n.d.: not detected sample number; LOQ: limit of quantification.
HHCB: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran; AHTN: 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene; MX: 1-*tert*-butyl-2,6-dimethyl-2,4,6-trinitrobenzene; MK: 4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone.

tration ratio in our study (21:68) was higher than the data from South Korea, Sweden, and Denmark, but lower than that from USA. Musks were mainly absorbed through human skin (Reiner and Kannan, 2006), and the difference in human milk may be caused by the different usage and use pattern in household products.

2.2 Relationship of musk concentrations and principal component analysis

The influence of mother's age on musk concentrations was considered, with no correlation between age and concentrations detected in human milk samples ($p > 0.05$). This result was similar to previous reports in human milk and adipose tissue samples, where no age-related increasing trend in the concentrations of HHCB and AHTN were discerned (Kannan et al., 2005; Reiner et al., 2007). Kannan et al. (2005) suggested that the lack of age-related increase might be explained by metabolism and excretion of musks in human bodies. There would be an age dependency if metabolism was slow in humans as continued use of musk products would lead to musk buildup in the body. The half-life of MX in humans is about 63–107 days, and excretion is relatively fast (Minegishi et al., 1991). HHCB is transformed to HHCB-lactone in human milk (Biselli et al., 2004). The lack in age-related increase may also be explained by high individual preference in household commodities, with exposure to HHCB and AHTN increasing up to 10,000 fold between low- and high-exposure (Roosens et al., 2007).

Concentrations of HHCB in human milk samples were significantly correlated with AHTN and MK concentrations (Pearson r = 0.467, 0.238, $p < 0.05$) (Fig. 2). These results were similar to those reported by Lignell et al. (2008), in which they proposed a significant positive association between use of perfumed products and milk concentration of HHCB (perfumes) and AHTN (perfumed laundry detergents). Kannan et al. (2005) also proposed a correlation between HHCB and AHTN in human adipose tissue, while Reiner et al. (2007) did not find a similar correlation in human milk in the USA. No correlations between HHCB and MX, MK and MX (r = 0.120, 0.143, $p > 0.05$) were found in our study, and the levels of AHTN did not correlate with MX and MK (r = 0.127, 0.041, $p > 0.05$). These results suggested that there were multiple sources of musk fragrances.

Principal component analysis (PCA) was used on musk concentrations to extract principal components. The use of the two factors (eigenvalue >1) that contributed the largest variance in the model allowed for an interpretation of the data. The first component (Factor 1) explained 41.3% of the variance and was correlated with polycyclic musks (HHCB and AHTN). The second component (Factor 2) explained 25.8% of the variance and was correlated with nitro musks (MX and MK). It was hard to identify the exact sources of Factor 1 and 2. Dermal exposure was considered to be a major pathway of human exposure. Body lotions, perfume, and body washes are all important sources (Reiner and Kannan, 2006). But use pattern and concentrations in these perfumed products differ by manufacturer depending on the formula and sometimes polycyclic and nitro musks were used together (Roosens et al., 2007).

The score plot (Fig. 3) showed all milk samples from the three cities were distributed along two principal components. The data were located in all quadrants, with some of

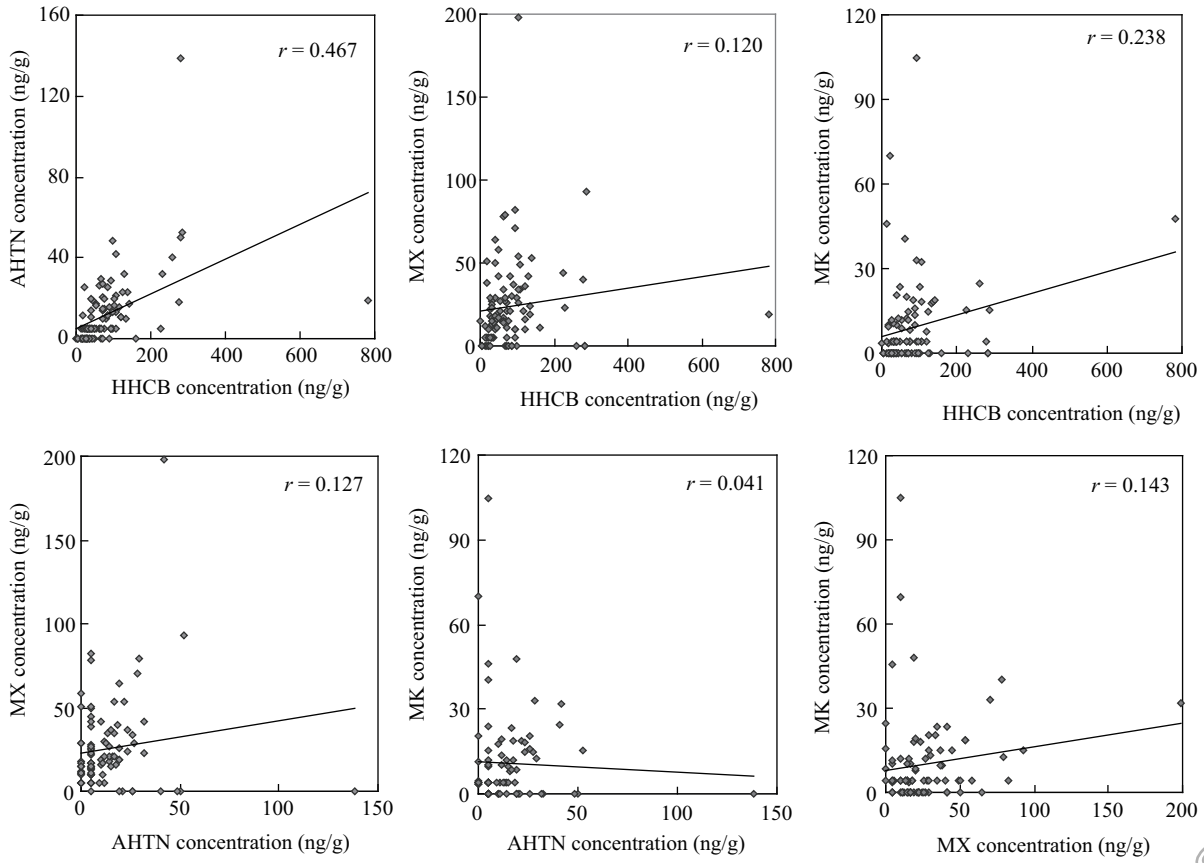

Fig. 2 Correlations of synthetic musk concentrations in human milk samples. r: Pearson's correlation coefficient; data for the three locations were pooled together.

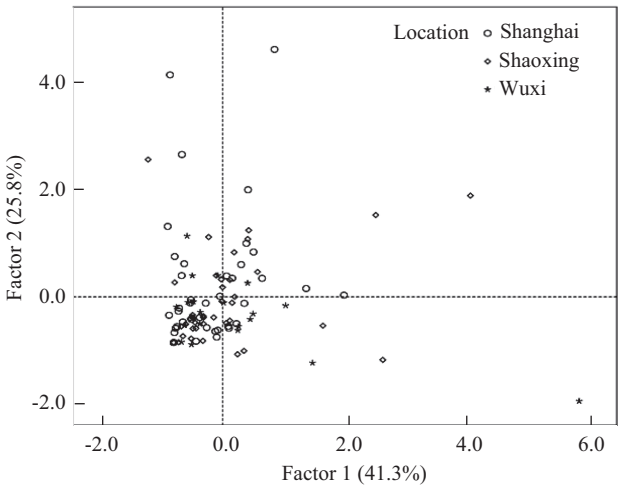

Fig. 3 Score plot of principal component analysis on musk.

them were near the origin, which indicated low pollution levels. From the score plot, the spatial distribution of the samples can be observed. Some of the SH and SX samples were located in the first and third quadrant, while 80% of WX samples were located in the third and fourth quadrant. These data could not be separated clearly, which indicated likely similar exposure sources among those cities.

A survey of synthetic musk fragrances in household commodities in China provided the mean concentration for lotions, perfumes, and body washes (Zhang et al., 2008). By combining these results with average usage, exposure profiles through dermal application were estimated (Table 3). The estimated exposure data indicated a more extensive use of polycyclic musks than nitro-musks. The amounts in China were low and the ratio of HHCB and AHTN was high, compared to those in Belgium (Roosens et al., 2007). The absorption rates of individual musks ranged from 0.3% to 5% (Slanina, 2004), using the average absorption rate (3%), dermal uptake was estimated at 55 μg for HHCB, 6 μg for AHTN, 1 μg for MX and 3 μg for MK per person per day. The absorption amount ratio of HHCB, AHTN and MK (55:6:3) was close to the concentration ratio in milk samples (63:5:4). This indicated that milk concentrations were mainly influenced by exposure amount. Lower musk concentrations in perfumed products may result in lower concentrations in human milk. This was also suggested by Hutter et al. (2005) and Lignell et al. (2008). The absorption amount of MX might be underestimated in this study, with low occurrence rate of MX in lotions, perfume and body washes (Zhang et al., 2008), and their abundance in other perfumed products such as soaps (Käfferlein et al., 1998).

2.3 Estimated exposure amount for infants

Synthetic musk fragrances as well as other contaminants accumulated in human milk are of concern due to their potential negative effects, particularly during critical periods of development, such as in infants who are more susceptible to environmental contaminants. To understand the magnitude of infant exposure to synthetic musk fragrances, concentrations of HHCB, AHTN, MX and MK were used to calculate the musk exposure via breast milk. A daily milk consumption of 0.77 L milk (lipid content of 4.0%) was assumed (US EPA, 2008). The calculated total daily intakes were (2526 ± 2926) ng for HHCB, (370 ± 524) ng for AHTN, (739 ± 832) ng for MX and (277 ± 462) ng for MK per day, assuming that human milk was the only food source for nursing infants (3–6 months old). When assuming a 7.0 kg body weight for a 3–6 months old boy, the maximum intakes are 0.8 μg/kg body weight for HHCB, 0.1 μg/kg body weight for AHTN, 0.2 μg/kg body weight for MX, and 0.1 μg/kg body weight for MK. Slanina (2004) reviewed the toxicological literature regarding musk compounds and estimated provisional tolerable daily intakes (PTDI) of HHCB, AHTN, MX and MK to 500, 50, 7, and 7 μg/kg body weight, respectively. The estimated maximum daily intake of musks by infants was considerably lower than the PTDI, although the proposed PTDIs were based on adult exposure to musk compounds. It could be concluded that the musk exposure of infants via breast milk was low.

There are still other exposure routes for infants. In a previous study, two personal care products for infant were examined, one of which contained 0.4 μg/g HHCB and 17 μg/g AHTN (Zhang et al., 2008). The contribution of dermal absorption to total exposure for an infant must be taken into account, and the use of fragrance materials for or on infants should be minimized.

3 Conclusions

Synthetic musk was detected in most human milk samples collected from SH, SX and WX in the Yangtze River Delta in Eastern China, with HHCB being the dominant compound followed by MX. The concentrations calibrated by lipid weights were similar to those found in Sweden, but lower than those in the USA and South Korea. The distribution percentage was HHCB > MX > AHTN ≈ MK, slightly different from other regions. The musk exposure of

Table 3 Estimated exposure amount through dermal application

	Usage[a] (g/day)	Belgium[b] (μg/day)				China[c] (μg/day)			
		HHCB	AHTN	MX	MK	HHCB	AHTN	MX	MK
Perfume	0.53	3470	615	0	0	278	3	42	1
Body lotion	8.7	619	592	113	0	14	0	0	23
Body wash	14.5	1290	160	0.4	0	870	35	0	46
Shampoo	12.8	448	166	0.6	21	666	154	0	17
Sum		5827	1533	114	21	1828	192	42	87

[a] Loretz et al., 2005, 2006; [b] estimated median exposure in Belgium, provided by Roosens et al. (2007); [c] estimated exposure amount in China, musk concentrations in household products were provided by Zhang et al. (2008).

infants via breast milk was low.

The musk concentrations showed no significant difference ($p > 0.05$) among SH, WX and SX. PCA also showed similar exposure source. There was no relationship between the mother's age and the concentrations of synthetic musks in this study, but HHCB were highly correlated with AHTN.

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