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Occurrence and transport of synthetic musks in paired maternal blood, umbilical cord blood, and breast milk

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ABSTRACT

Although early exposure to environmental pollutants may have important toxicological consequences, the mechanisms of transplacental transfer of synthetic musks are still not well understood. The objective of the present study was to learn the musk contaminations in three matrices, including maternal blood, umbilical cord blood, and breast milk; and investigate their placental transfer mechanisms.

The concentrations of eight commonly used synthetic musks were measured in 42 paired samples (126 individual samples in total) of maternal serum, umbilical cord serum, and breast milk from Chinese women living in Shanghai.

Musks were ubiquitously detected, especially galaxolide (HHCB) and musk xylene (MX). The total lipid-based concentrations were higher in umbilical cord sera (87.3 ng/g), but lower in breast milk (35.2 ng/g), compared with maternal serum concentrations (71.2 ng/g). There were significant correlations between maternal serum concentrations of HHCBs (HHCB and HHCB-lactone) and umbilical cord serum concentrations, and between maternal serum concentrations and breast milk concentrations (Spearman's rho = 0.338–0.597, $p < 0.05$), when outliers are excluded. The average transfer ratios of HHCB and HHCB-lactone between maternal sera and umbilical cord sera were >1. And the HHCB-lactone/HHCB ratio in maternal sera was higher compared with umbilical cord sera.

Contamination levels were low compared with other regions and HHCBs were found to be the predominant constituents. No regional differences or age-related accumulations were observed. Our study suggests that prenatal exposure to HHCBs occurs and that transplacental transfer is the main route of exposure. Preferential accumulation in umbilical cord blood was observed. The results showed that transplacental transfer of HHCB did not correspond to passive diffusion since the transfer ratios were significantly different from 1. The transfer ratio for HHCB was also larger than that of HHCB-lactone, although HHCB has higher lipid solubility. Low fetal metabolism of HHCB was suggested by the HHCB-lactone/HHCB ratio in maternal and umbilical cord blood.

Introduction

Musks are emerging pollutants that are widely used as fragrance additives in personal care products (Liu and Wong, 2013). There are three main groups, i.e. polycyclic musks, nitro musks, and macrocyclic musks. Galaxolide (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran, HHCB) and tonalide (7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene, AHTN) are the most common polycyclic musks, and musk xylene (1-*tert*-butyl-3,5-dimethyl-2,4,6-trinitrobenzene, MX) and musk ketone (4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone, MK) are the main nitro musks. These chemicals are lipophilic and can accumulate in the human body following inhalation and/or percutaneous absorption of musk-containing skin care products (Reiner et al., 2007; Lu et al., 2011a).

The potential for musk toxicity in humans has raised considerable concern because products containing musks may be applied

Abbreviations: ADBI, 4-acetyl-1,1-dimethyl-6-*tert*-butylindan; AHMI, 6-acetyl-1,1,2,3,3,5-hexamethylindan; AHTN, 7-acetyl-1, 1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene; ATII, 5-acetyl-1,1,2,6-tetramethyl-3-isopropylindan; HHCB, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran; lw, lipid weight; MK, 4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone; MX, 1-*tert*-butyl-3,5-dimethyl-2,4,6-trinitrobenzene.

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daily, usually directly onto the skin, and musks have the potential to bioaccumulate (Moon et al., 2012; Schiavone et al., 2010). Musks do not persist in the environment but, because they are continuously introduced, they behave as though they were persistent (Chase et al., 2012) and have been termed "pseudo-persistent" contaminants. Although polycyclic musks have not shown obvious mutagenic potential in recognized toxicology tests, obvious effects on endocrine activity have been associated with nitro musks and polycyclic musks (Schnell et al., 2009; Witorsch and Thomas, 2010). HHCB and AHTN were found to inhibit progesterone and cortisol production by the suppression of two genes involved in steroidogenic pathways (Li et al., 2013). Exposure to these chemicals during sensitive periods of development may pose a risk to human health, especially for the fetus (Kang et al., 2010).

Musks have been detected in human breast milk, lipids and blood, suggesting ubiquitous contamination of the body (Duedahl-Olesen et al., 2005; Lignell et al., 2008; Hutter et al., 2010; Kang et al., 2010; Schiavone et al., 2010; Moon et al., 2012). HHCB and AHTN were generally found to be the predominant congeners, while MX and MK showed lower concentrations in these matrices (Lignell et al., 2008; Hutter et al., 2010; Moon et al., 2012; Yin et al., 2012). Varying concentrations and distribution patterns have been found in different geographical regions. For example, in breast milk, the concentrations of HHCB and AHTN ranged from <1 to 17 ng/g lipid weight (lw) and from <0.6 to 794 ng/g lw, respectively (Duedahl-Olesen et al., 2005; Reiner et al., 2007; Lignell et al., 2008; Kang et al., 2010; Yin et al., 2012). Frequent use of perfumed skin care products has been associated with increased musk levels in human breast milk and blood (Hutter et al., 2010; Yin et al., 2012). Several studies have reported musk concentrations in breast milk and blood samples from women living in China (Hu et al., 2010; Yin et al., 2012; Zhou et al., 2012).

Prenatal life is the most sensitive period of human development since the immune system and detoxification mechanisms are not fully developed in the fetus. Early exposure to environmental pollutants may increase the risk of serious adverse health effects during childhood, including teratogenicity, low birth weight, neurological development delays (Herbstman et al., 2010; Lee et al., 2013). A relationship between elevated placental concentrations of polycyclic aromatic hydrocarbons and increased risks of neural tube defects was suggested (Ren et al., 2011). Prenatal exposure to some organochlorine pesticides with endocrine-disruption activity may interfere with neonatal hormone status (Freire et al., 2011). Passage of environmental pollutants across the placenta has important toxicological consequences (Liu et al., 2011; Jakobsson et al., 2012). Although the placenta may prevent transfer of some contaminants, there is evidence that other pollutants can reach the fetus (Needham et al., 2011; Tsang et al., 2011; Vizcaino et al., 2014). Exposure to environmental contaminants in utero has thus become an important public health concern. Some studies have reported prenatal concentrations of polychlorobiphenyls (PCBs), polybromodiphenyl ethers (PBDEs), perfluoroalkyl acids (PFOAs), and bisphenol A (Fromme et al., 2010; Wan et al., 2010; Needham et al., 2011; Nahar et al., 2013; Vizcaino et al., 2014). The mechanisms of transfer of xenobiotics during pregnancy are still not well understood, especially for musks. Although the transfer of musks from mother to offspring has been studied in wildlife (Nakata et al., 2007), data on musk distribution and transfer from mother to offspring in humans is lacking (Kang et al., 2010). It is therefore very important to investigate the transfer of musks from mothers to fetuses.

The matrices that have been most widely used to assess prenatal exposure are maternal and umbilical cord blood. Umbilical cord blood has the advantage that it can be sampled non-invasively and has therefore been used for assessing exposure to a variety of organohalogen compounds (Fromme et al., 2010; Needham et al., 2011). Contaminants are also excreted via human breast milk. The amount of contaminant transferred to the infant via breast milk can reflect the maternal body burden as well as the frequency of nursing (Tsang et al., 2011; Zhou et al., 2012). Maternal blood, umbilical cord blood, and breast milk are all suitable bio-indicators to assess prenatal exposure and the mechanism of transfer of environmental contaminants, especially in individual paired mother–infant samples (Kim et al., 2011; Jakobsson et al., 2012; Zhao et al., 2013).

To comprehensively study the partition of synthetic musks from mother to fetus in healthy pregnant women, a total of 42 paired samples of maternal serum, umbilical cord serum, and breast milk from a mother–infant cohort were collected and analyzed. The concentrations of seven synthetic musks and a metabolite were measured. The main objectives of the present study were: (1) to assess the body burdens and prenatal exposure to synthetic musks; (2) to investigate the transfer of predominant musk contaminants between mother and fetus.

Materials and methods

Sample collection

The volunteers, lived for at least 5 years in sampling areas, were randomly recruited by their midwives and gynecologists, during the period of their deliveries at two hospitals located in urban and rural areas of Shanghai in 2007. Information including age, parity, occupation, and smoking habit was recorded in the form of questionnaires. The multipara volunteers or volunteers who may have occupational exposure were not selected. All samples and data were processed blind, although the selection bias could not be excluded. A total of 42 paired samples of maternal blood, umbilical cord blood, and breast milk (126 individual samples in total) were collected. Samples of maternal blood and umbilical cord blood were obtained at the time of delivery, and samples of breast milk were obtained within 5 days of delivery. Blood samples were centrifuged to separate the sera, which were transferred to brown glass test-tubes and stored at −20 °C until analysis. The study protocol was approved by the ethics committees of the two hospitals, and informed consent was obtained from the pregnant women.

Chemicals

Musk standards, including five polycyclic musks [celestolide, (4-acetyl-1,1-dimethyl-6-*tert*-butylindan, ADBI), phantolide (6-acetyl-1,1,2,3,3,5-hexamethylindan, AHMI), traseolide (5-acetyl-1,1,2,6-tetramethyl-3-isopropylindan, ATII), HHCB and AHTN] and two nitro musks (MX, and MK), were purchased from Promochem, Germany. The HHCB was 75% pure (gas chromatography grade), and the other musks were 99% pure (gas chromatography grade). AHTN-d_3 and MX-d_{15} (obtained from Dr. Ehrenstorfer GmBH, Germany) were used as surrogate standards. Hexamethylbenzene (obtained from Dr. Ehrenstorfer GmBH, Germany) was used as an internal standard. HHCB-lactone, an oxidative metabolite of HHCB is those used in our previous study (Zhou et al., 2012). It was synthesized in our lab according to methods described in the literature (Berset et al., 2004). After silica gel chromatography refinement, crystallization, and high performance liquid chromatography purification, the HHCB-lactone obtained was 97% pure based on gas chromatography analysis (Zhou et al., 2012). All solvents were of analytical grade and hexane and dichloromethane were re-distilled before using glass apparatus.

Sample extraction and cleanup

Frozen breast milk (8–10 mL) and serum samples (2–4 mL for maternal serum, 8–10 mL for umbilical cord serum, respectively)