Synthetic Musk Fragrances in Human Milk from the United States

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Synthetic musk compounds are used as additives in many consumer products, including perfumes, deodorants, and detergents. Earlier studies have reported the occurrence of synthetic musks in environmental and wildlife samples collected in the United States. In this study, human breast milk samples collected from Massachusetts, were analyzed for the determination of concentrations of synthetic musks such as musk xylene (1-*tert*-butyl-3,5-dimethyl-2,4,6-trinitrobenzene), musk ketone (4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone), 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), and HHCB-lactone, the oxidation product of HHCB. In addition, we estimated the daily intake of synthetic musks by infants based on the ingestion rate of breast milk. Synthetic musks were found in most of the samples analyzed, and the concentrations ranged from <2 to 150 ng musk xylene/g, <2 to 238 ng musk ketone/g, <5 to 917 ng HHCB/g, <5 to 144 ng AHTN/g, and <10 to 88.0 ng HHCB-lactone/g, on a lipid weight basis. The concentrations of HHCB were higher than the concentrations of other synthetic musks in breast milk samples. The mean concentration of HHCB (220 ng/g, lipid weight) was 5 times greater than the concentrations reported 10 years ago for breast milk samples collected in Germany and Denmark. Maternal age was not correlated with the concentrations of musk xylene, musk ketone, HHCB, or AHTN. There was a trend of decreasing concentrations of musk xylene, musk ketone, HHCB, and AHTN, with the number of children previously breast-fed, although the correlation was not significant. Based on average daily ingestion rate of breast milk, an infant is estimated to ingest 297 $\pm$ 229 ng musk xylene, 780 $\pm$ 805 ng musk ketone, 1830 $\pm$ 1170 ng HHCB, 565 $\pm$ 614 ng AHTN, and 649 $\pm$ 598 ng HHCB-lactone per day. The ingestion rate of synthetic musks by infants in the United States is lower than that estimated for persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs). Based on the residue patterns and accumulation features, it can be concluded that the exposure characteristics for synthetic musks are different from those of POPs, and that the major source of exposure to synthetic musks is probably via dermal absorption or inhalation.

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Introduction

Synthetic musks are fragrance additives used in a wide range of consumer products. Two major categories of synthetic musks, nitro musks and polycyclic musks, and the minor category of macrocyclic musks are used as substitutes for natural musks, because the natural musks are expensive and are derived from endangered wildlife species. Synthetic musks can be found in cleaning agents, detergents, and personal care products. Musk xylene (1-*tert*-butyl-3,5-dimethyl-2,4,6-trinitrobenzene) and musk ketone (4-*tert*-butyl-2,6-dimethyl-3,5-dinitroacetophenone) are in the nitro musk category. They are two of the most widely used nitro musks and are found in detergents and cosmetics (*1*). In the 1980s, musk xylene and musk ketone were reported to occur in fish from the Tama River, Tokyo, Japan (*2*). In more recent studies, musk xylene and musk ketone have been measured in human adipose tissue and milk from certain European countries (*1*, *3*−*7*). The production rate of nitro musks decreased from 1983 as a result of reports of photoallergenic reactions to musk ambrette (1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene) (*8*). In 1993, the German Cosmetic, Toiletry, Perfumery, and Detergent Association recommended that musk xylene not be used in the production of cosmetics, detergents, and other household commodities (*8*). Thus, there has been a decline in the production and use of nitro musks in Europe since the late 1980s. This decline was complemented with the increase of production and use of polycyclic musks (*8*).

Two of the most widely used synthetic 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), belong to the category of polycyclic musks. These two musks comprise about 95% of the European market and 90% of the United States market for all polycyclic musks (*9*). HHCB and AHTN were the most commonly detected polycyclic musks in wildlife, including marine mammals, in a recent study from the United States (*10*). Other studies have examined the concentrations of HHCB and AHTN in consumer products, wastewater treatment plant effluents, surface water, air, and soil from the United States (*11*−*16*). In studies from European countries and the United States, concentrations of HHCB-lactone, an oxidation product of HHCB, have been determined in wastewater treatment plant effluents and in consumer products (*15*−*19*).

Humans are exposed to synthetic musks on a continuous basis through the use of personal care products and cleaning products. Because of the lipophilic nature of synthetic musks, these compounds are expected to accumulate in lipid-rich tissues (*10*). Human fat and human breast milk have been analyzed to elucidate the exposure levels of lipophilic pollutants such as organochlorine pesticides and polychlorinated biphenyls (PCBs) over the last few decades. The contamination of breast milk by xenobiotics is of concern because of its implications for childhood exposures. For adults, dermal sorption from personal care products can be a major route of exposure to synthetic musks (*10*). Musk xylene, musk ketone, HHCB, and AHTN have been found in human adipose tissue and human milk in European countries

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and the United States (1, 3−7, 10). The reports of human exposure to synthetic musks in the United States are few. In general, there is a trend of increasing HHCB and AHTN concentrations in adipose tissue and human milk (*3*−*7*, *10*). For instance, 2−3-fold increase in the concentrations of HHCB and AHTN in adipose tissue in the last 10 years has been reported in the United States (*10*). Three to 4-fold increases of HHCB concentrations were reported in human breast milk over the last 5 years in Europe (*1*, *5*). European countries such as Sweden and Germany have breast milk monitoring programs that measure persistent organic pollutants (POPs) and emerging pollutants (*20*). Emerging pollutants, such as synthetic musk fragrances, have not been studied in breast milk from the United States to date. This is the first study to report concentrations of the synthetic musks, musk xylene, musk ketone, HHCB, AHTN, and HHCB-lactone, from breast milk in the United States. This is also the first study to examine relationships between concentrations of synthetic musks and maternal age as well as the number of children previously breast-fed.

Materials and Methods

Breast Milk Samples. Milk samples (20−100 mL) were collected in 2004 from 39 women in Massachusetts. Information about residence, mother's age, infant's age, and the number of infants previously breast-fed was obtained from all participants. Women were asked to pump all the milk from one breast. Institutional Review Board approvals were obtained. Milk samples were immediately transferred to clean, sterile glass bottles and transported to the lab where they were diluted 1:1 with PBS (phosphate buffered saline). Samples were centrifuged at 100*g* for 15 min to pellet all of the cells in the milk. All of the fat and $^2/_3$ of the supernatant were transferred to clean amber glass jars and placed in a −20 °C freezer. After 1 week, the frozen milk samples were placed in a −80 °C freezer until analysis.

Chemicals. Musk xylene (99%) and musk ketone (99%) were purchased from Sigma-Aldrich (St. Louis, MO). HHCB, AHTN, and deuterated (d_3) AHTN were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany) with purities of 51, 98, and 99% respectively. HHCB-lactone was a gift from Dr. Daniel Berset (Water and Soil Protection Laboratory, Bern, Switzerland); its purity was 99%. Reported concentrations were not corrected for the purities of the standards. Deuterated (d_{10}) phenanthrene (Accustandard Inc., New Haven, CT) and deuterated (d_3) AHTN were used as surrogate standards.

Human Milk Extraction and Cleanup. Frozen milk samples were thawed at 20 °C and 10 mL of the milk sample were extracted. Samples were spiked with d_3-AHTN and d_{10}-phenanthrene as surrogate standards. Liquid−liquid extraction was performed using a method reported previously (*1*), with slight modifications. Briefly, 2.5 mL of 8% (w/w) potassium oxalate solution, 10 mL of ethanol, and 5 mL of diethyl ether were added to the samples. Samples were extracted twice with 5 mL of hexane. Of the 10 mL, 200 μL were set aside for HHCB-lactone analysis, and an aliquot of the sample was used to determine lipid content gravimetrically. The remaining sample was subjected to lipid removal using a procedure reported earlier (*10*). Briefly, lipids were removed from the sample by gel permeation chromatography (GPC) using a Bio-beads S-X3 (Bio-Rad Laboratories, Hercules, CA) packed glass column (380 mm × 22 mm i.d.). The mobile phase was a mixture of 50% dichloromethane in hexane. The first 100 mL fraction was discarded, and the following 120 mL fraction was collected. Musk xylene, musk ketone, HHCB, AHTN, d_3-ANTN, and d_{10}-phenanthrene, if present, occurred in this fraction. The extract was passed through a silica gel packed cartridge (100−200 mesh; Aldrich, Milwaukee, WI) for cleanup. The solvent was concentrated to 1 mL and was then injected into a gas chromatograph interfaced with a mass spectrometer (GC-MSD; Agilent Technologies 6890 GC and 5973 Series MSD). The GC column was a Restek (Bellefonte, PA) Rxi-5ms fused silica capillary column (30 m × 0.25 mm id). The ions monitored were at m/z 282 and 297 for musk xylene; 279 and 294 for musk ketone; 243, 258, and 213 for HHCB; 243, 258, and 159 for AHTN; 246 and 261 for d_3-AHTN; 257 and 272 for HHCB-lactone; and 188 for d10-phenanthrene.

Quality Control. A standard mixture of musk xylene, musk ketone, HHCB, AHTN, HHCB-lactone, and d_3-AHTN was spiked into cow milk (2% fat) at levels of 5, 20, and 50 ng and then passed through the analytical procedure. The average recoveries for musk xylene, musk ketone, HHCB, AHTN, and HHCB-lactone were 95.1 ± 3.2%, 89.5 ± 4.4%, 108 ± 6.3%, 102 ± 9.9%, and 84.1 ± 28% ($n = 9$), respectively. There was good recovery for most compounds, except for HHCB-lactone which had high variability compared with the other standards (66−125%). The analyst took care not to use hand lotions, perfumes, or other possible sources of contamination during the analysis. Procedural blanks were analyzed with 2% cow's milk, to check for contamination through the analytical procedure. The limit of detection (LOD) was determined to be 2 ng/g, lipid weight, for musk xylene and musk ketone, 5 ng/g, lipid weight, for HHCB and AHTN, and 10 ng/g, lipid weight, for HHCB-lactone. Concentrations of musk xylene, musk ketone, HHCB, AHTN, and HHCB-lactone were determined using an external calibration curve, with concentrations ranging from 2 to 500 ng/mL. Sample concentrations were corrected for the recovery of d_3-AHTN, which was spiked to sample matrices prior to extraction. Recoveries of d_3-AHTN varied from 75 to 135%.

Statistical Analysis. All analyses were performed with the statistical software SPSS 13.0, using nonparametric tests.

Results and Discussion

Residue Concentrations. Concentrations of musk ketone, HHCB, and AHTN were log-normally distributed (Q−Q test; Figure 1). Musk xylene showed a log-normal distribution; however, the number of samples with concentrations above the detection limit was much smaller compared with those for musk ketone, HHCB, and AHTN (Q−Q test; Figure 1). All samples measured in this study contained at least one of the synthetic musk compounds analyzed (Table 1). A more comprehensive table itemizing maternal age, fat content of breast milk, and age of infant at the time of milk collection can be found in the Supporting Information (Table S1). It is important to note that women were not asked to wash their hands or breast before collecting the milk samples. It is possible that some of the synthetic musk concentrations measured is from the skin at the time of collection. Two or more synthetic musks were found in 82% of the samples. HHCB was the predominant compound found in breast milk, followed by musk ketone. Musk xylene was found, at concentrations ranging from <2 to 150 (mean: 30.0) ng/g, lipid weight, in 36% of the samples. Musk ketone was found in a considerably higher proportion of the samples (85%), at concentrations ranging from <2 to 238 (mean: 74.5) ng/g, lipid weight. HHCB was found in 97% of the samples analyzed, at concentrations ranging from <5 to 917 (mean: 220) ng/g, lipid weight. AHTN was found in 56% of the samples, at concentrations of <5−144 (mean: 46.8) ng/g. HHCB-lactone was found only in two samples (5%), with concentrations of 28.6 and 88.0 ng/g, lipid weight. The overall mean concentration of HHCB was higher than the mean concentration of musk xylene, musk ketone, AHTN, and HHCB-lactone combined. This predominance corresponds to the greater production and usage of HHCB compared with other synthetic musk fragrances. Production statistics for synthetic musks in the United States is not available; however,

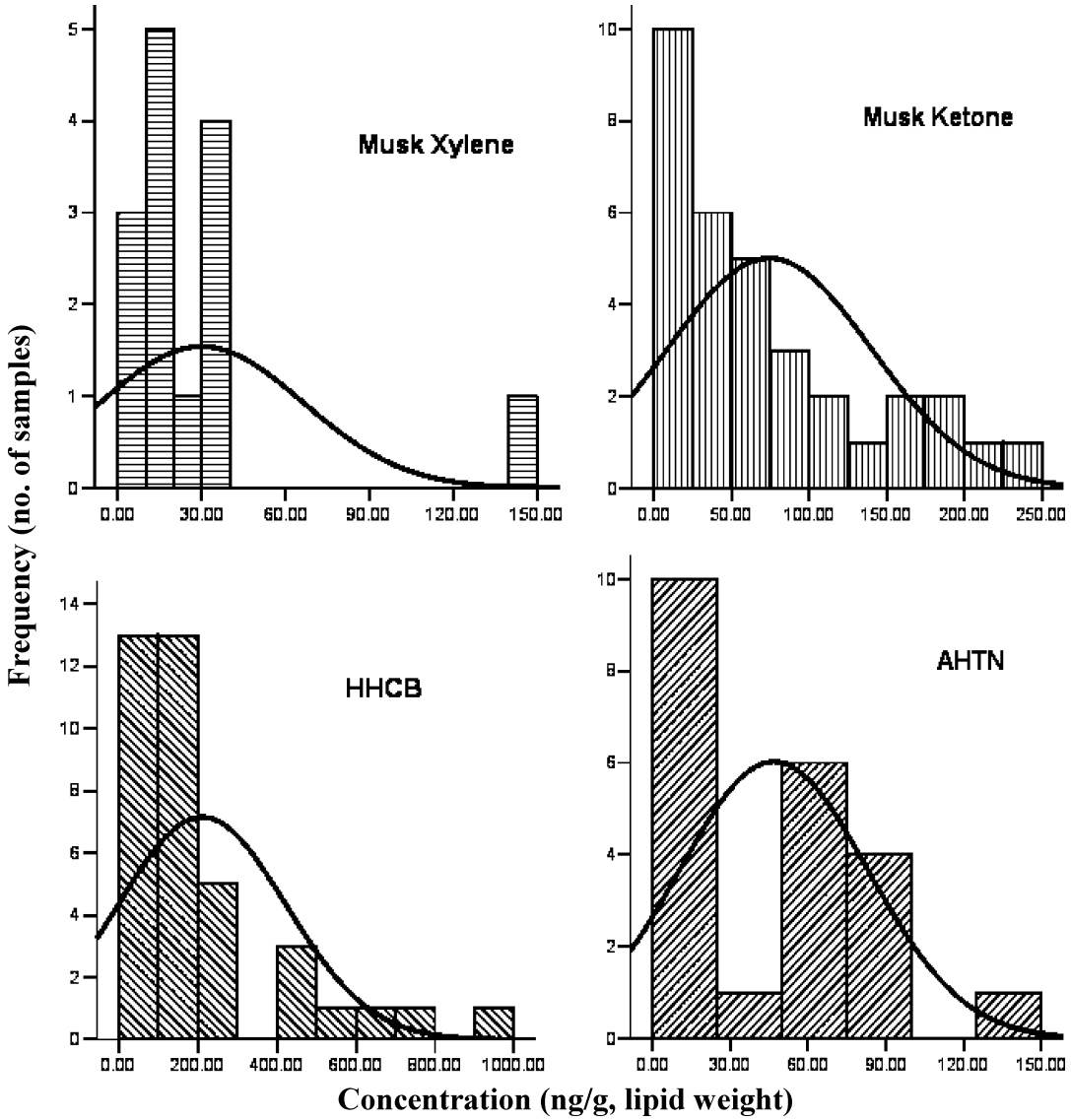

FIGURE 1. Frequency distribution of musk xylene, musk ketone, HHCB, and AHTN in human breast milk from Massachusetts.

TABLE 1. Mean, Median, and Range (ng/g, Lipid Weight) of Musk Xylene, Musk Ketone, HHCB, AHTN, and HHCB-lactone in Breast Milk Samples from Women in Massachusetts[a]

number of children previously nursed	statistic	musk xylene	musk ketone	HHCB	AHTN	HHCB-lactone
0 ($n = 31$)	mean ± SD	29.2 ± 37.6	83.3 ± 67.3	227 ± 228	50.5 ± 37.4	58.3 ± 42
	median	17.0	58.2	136	53.0	58.3
	range	<2−150	<2−212	<5−917	<5−144	<10−88.0
1 or more ($n = 7$)	mean ± SD	39.7[b]	25.0 ± 16.8	139 ± 138	29.9 ± 29.6	<10
	median	39.7	22.2	121	18.6	<10
	range	<2−39.7	<2−49.6	<5−415	<5−73.3	<10

[a] Values below the limit of quantitation were not included in the calculation of the mean. [b] Not available: There was only one sample above the detection limit.

manufacturers in the United Sates used 6500 tons of synthetic musks in 2000 (*14*). In contrast to the results of our previous study analyzing human adipose tissue (*10*), we did not find a correlation between HHCB and AHTN in human breast milk. This inconsistency suggests that the sources of synthetic musks are multiple.

The highest concentration of a single synthetic musk (HHCB at 917 ng/g, lipid weight) was found in a 31 year old woman, who had not previously nursed a child. However, there was no correlation between age and concentrations of musk xylene, musk ketone, HHCB, and AHTN (Figure 2) among women nursing for the first time ($p > 0.05$). In addition, women who had previously breast-fed one child or more showed no age-related increases in musk xylene, musk ketone, HHCB, and AHTN concentrations. These results are similar to our previous finding of a lack of age-related increase in concentrations of HHCB and AHTN, in human fat samples from New York (*10*). The lack of an age-dependent increase in synthetic musk concentrations is suggestive of metabolism and excretion of musks. The number of children

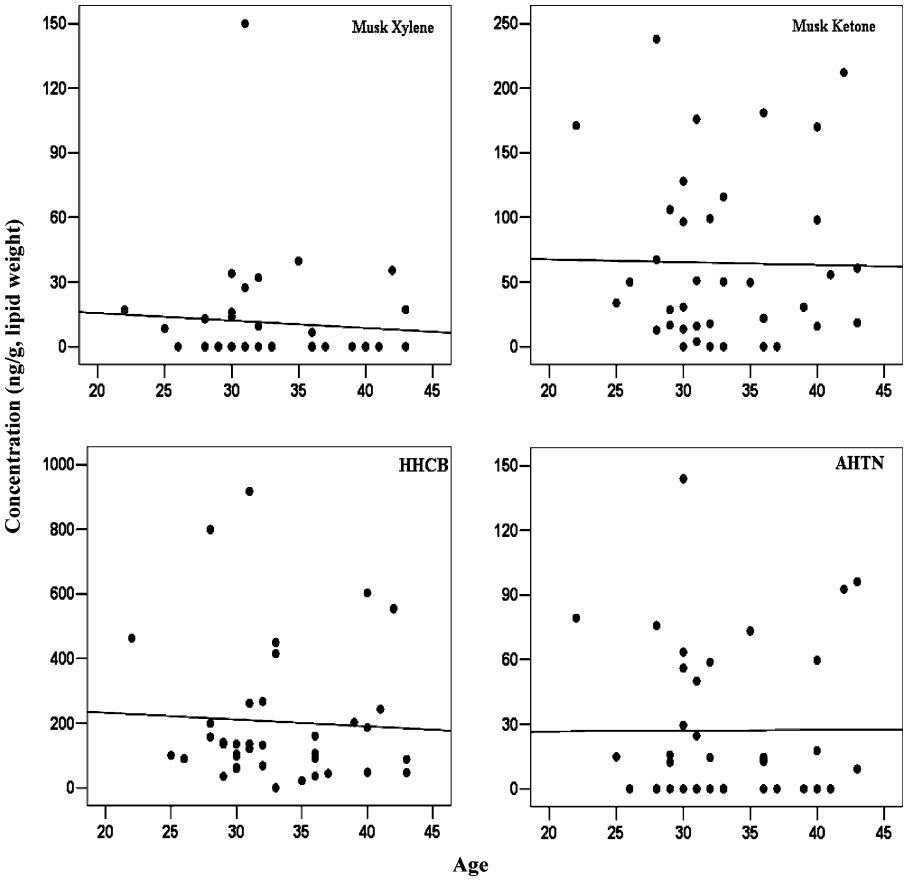

FIGURE 2. Relationship between maternal age and concentrations of musk xylene, musk ketone, HHCB, and AHTN in human breast milk of women nursing children for the first time.

that a woman had nursed previously can have an effect on the concentrations of musks in the breast milk. Relatively high concentrations of synthetic musks were found among women nursing for the first time (Figure 3). This is especially true for musk ketone, HHCB, and AHTN. Median concentrations decreased depending on the number of children previously breast-fed. Nevertheless, there was not a significant difference in the concentrations of musk xylene, musk ketone, HHCB, or AHTN between women nursing for the first time and those nursing for at least the second time ($p > 0.05$).

Other factors, including the infant's age at the time of collection were examined. There was no correlation between the infant's age and the concentration of musk xylene, musk ketone, HHCB, or AHTN in breast milk. We did not obtain information such as fragrance usage or dietary habits of the nursing mothers to examine the relationship between these parameters and musk concentrations. This information would be important in future studies. Maternal smoking habits showed no correlation with the concentrations of musks in breast milk.

Spatial and Temporal Patterns. The occurrence of musk xylene, musk ketone, HHCB, and AHTN has been documented in three European countries during the 1990s (Table 2). The mean concentrations of HHCB in breast milk have increased 5-fold over the last 10 years, while the increase in the mean concentrations of musk xylene, musk ketone, and AHTN over this time period was minimal (*1*, *5*, *7*). Very few studies have reported synthetic musk concentrations in human breast milk (*1*, *5*, *7*). On a lipid weight basis, concentrations of musk xylene and HHCB measured in the present study were similar to the concentrations measured in breast milk from Denmark in 1999 (*1*), whereas the concentrations of musk ketone and AHTN were 2−3 fold higher than those reported in milk samples from Denmark (Table 2). Similarly, concentrations of synthetic musks were greater in samples analyzed in this study than in breast milk samples from Germany, except for musk xylene which was found at higher levels in Germany (Table 2). The samples from Germany were collected during 1993−1995, while the samples from Denmark and the United States were collected in 1999 and 2004, respectively. Variations in synthetic musk concentrations may arise from differences in both locations and time of collection. Increase in HHCB concentrations in human adipose tissue (*10*) and in breast milk samples, over the past 10 years, is similar to the increase in HHCB concentrations found in sediment cores collected from Lake Erie from 1990 to 2004 (*14*). Marine mammals collected from the coastal waters of Japan exhibited an increase in HHCB concentrations from the early 1990s (*21*). The increase in HHCB concentration is likely due to the use of synthetic musks in the United States, which has increased during the same time period.

Accumulation Features. The exposure and accumulation characteristics of synthetic musks are different from those of other POPs such as PCBs. Concentrations of most POPs in breast milk are influenced by mother's age, number of children previously breast-fed, the time of lactation, local use of the compounds, and the diet (*20*). The major source of PCB exposure, for instance, is from contaminated diet (*22*). The major source of synthetic musk exposure is thought to be from dermal absorption of personal care products (*15*). The lack of an age-related increase and parity-related decrease supports the hypothesis that dermal application and consumer habits are the major influences on the exposure levels to musks. Additional exposure routes, such as inhalation, cannot be ruled out. Concentrations of synthetic musks in indoor air were higher than the concentrations of PCBs

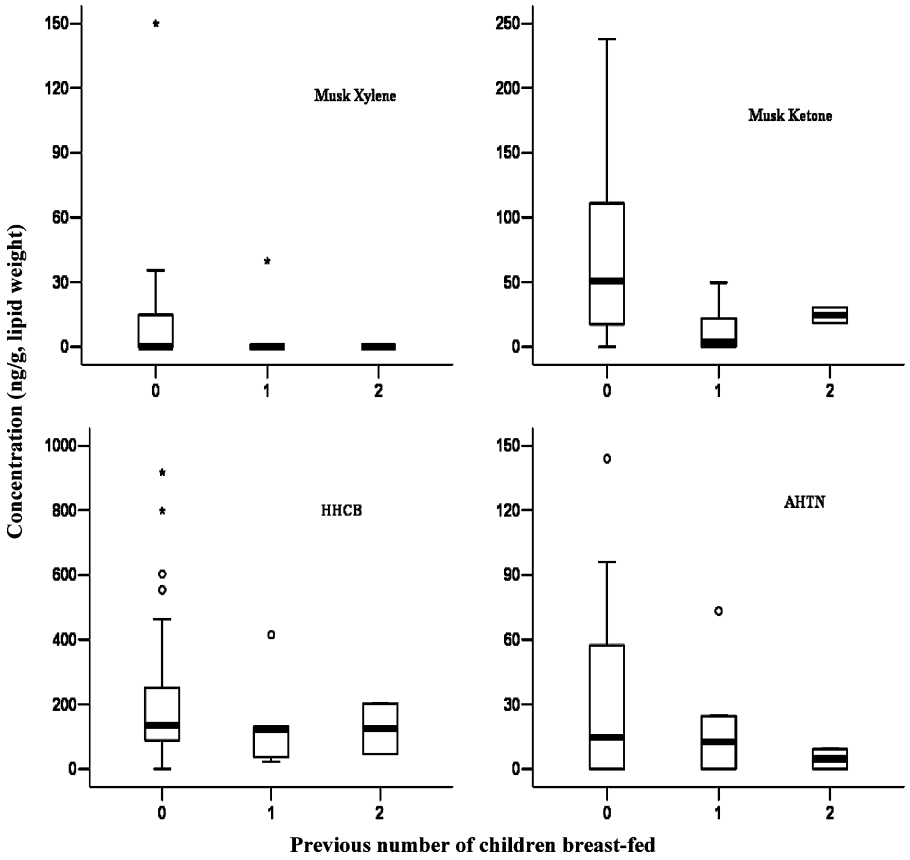

FIGURE 3. Box and whisker plots of human breast milk concentrations of musk xylene, musk ketone, HHCB, and AHTN, stratified by previous number of children breast-fed (for zero children, $n = 31$; one child, $n = 5$; two children, $n = 2$). The boxes indicate the interquartile ranges of the concentrations; the line within each box is the median; the whiskers extend to the last observation within 1.5 times the interquartile range; and the open circles and asterisks outside the whiskers represent observations outside the interquartile range.

TABLE 2. Mean and Standard Deviation of Musk Xylene, Musk Ketone, HHCB, and AHTN Concentrations (ng/g, Lipid Weight) in Human Adipose Tissue and Breast Milk in Studies from 1983 through 2004, Europe and USA

sample date	location	musk xylene	musk ketone	HHCB	AHTN	reference
human adipose tissue						
1983−1994 ($n = 15$)	Switzerland	53 ± 70	20 ± 45	66 ± 54	9.0 ± 7.6	6
1993−1995 ($n = 14$)	Germany	19 ± 12	10.4 ± 8.7	82 ± 44	19 ± 8.2	5
2003−2004 ($n = 49$)	United States	n.m.[a]	n.m.[a]	180 ± 170	42 ± 24	10
human milk						
1993−1995 ($n = 5$)	Germany	25 ± 8.7	11 ± 4.2	49 ± 36	26 ± 18	5
1995 ($n = 55$)	Germany	41	10	n.m.[a]	n.m.[a]	7
1999 ($n = 10$)	Denmark	23.6 ± 15.6	17 ± 6.12	180 ± 110	20 ± 9.8	1
2004	United States	30 ± 36	74 ± 66	220 ± 212	47 ± 36	this study

[a] Not measured.

in households (*23*). Further studies are needed to examine the other routes of human exposure to musks.

The lack of age-related increase found here for the concentrations of musk xylene, musk ketone, HHCB, and AHTN confirms that there is metabolism and excretion of these compounds (1, 5−7, 10). If we had seen an age-related increase in concentrations that would have suggested that metabolism of synthetic musks is slow. The biotransformation of nitro musks and polycyclic musks into their metabolites has been shown in rats and fish (*24*−*25*). Excretion of nitro musk metabolites (as amino compounds) in the feces and bile suggested the elimination of nitro musks in rats (*26*). HHCB-lactone has been detected in fish and mussels (*24*−*25*). The detection of HHCB-lactone in only two milk samples here suggests that HHCB-lactone is eliminated quickly from the human body. An earlier study reported the half-life of musk xylene in humans to be 63−107 days (*27*).

Daily Intake of Musks by Infants. The detection of synthetic musks in breast milk suggests that these compounds can be transferred to breast-fed infants. Intake rates of breast milk by an infant in the United States range from 450 to 1200 g/day, with an average of 750 g/day (*28*). Based on the daily consumption rate of breast milk and the mean concentrations of synthetic musks, it was estimated that an infant would ingest 297 ± 229 ng musk xylene, 780 ± 805 ng musk ketone, 1830 ± 1170 ng HHCB, 565 ± 614 ng AHTN, and 649 ± 598 ng HHCB-lactone per day. For this calculation, concentrations were converted to a wet weight (whole milk: mean lipid content 1.74%) basis. These individual values are lower than the average daily intake of 85 ± 623 μg/day for polybrominated diphenyl ethers (PBDEs) in the United States (*29*). Toxic effects of synthetic musks are not clearly understood, and further studies are needed on this issue.

In summary, ours is the first study to report concentrations of musk xylene, musk ketone, HHCB, AHTN, and HHCB-lactone in human milk from the United States. The wide range of concentrations of musk xylene, musk ketone, HHCB, and AHTN suggests that personal consumption habits have a large effect on the concentrations of synthetic musks. The variables of maternal age, number of children previously breast-fed, and duration of lactation appear to have little effect on the concentrations of synthetic musks in milk. This study shows a lack of relationship between maternal age and concentrations of synthetic musks, as well as a lack of relationship between number of children breast-fed and synthetic musk concentrations. Personal consumption habits and specific products used by the nursing mothers were not examined in this study. Such information would be important to determine the contributions of consumer products and application behavior on the concentration of synthetic musks in human breast milk.

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Supporting Information Available

Concentrations (ng/g, lipid weight) of musk xylene, musk ketone, HHCB, AHTN, and HHCB-lactone in breast milk of individual samples are given. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Duedahl-Olesen, L.; Cederberg, T.; Pedersen, K. H.; Hojgard, A. Synthetic musk fragrances in trout from Danish fish farms and human milk. *Chemosphere* **2005**, *61*, 422−431.
(2) Yamagishi, T.; Miyazaki, T.; Horii, S.; Akiyama, K. Identification of musk ketone in freshwater fish collected from the Tama River, Tokyo. *Bull. Environ. Contam. Toxicol.* **1981**, *26*, 656−662.
(3) Rimkus, G.; Rimkus, B.; Wolf, M. Nitromusk in human adipose tissue and breast milk. *Chemosphere* **1994**, *28*, 421−432.
(4) Liebl, B.; Ehrenstorfer, S. Nitro musks in human milk. *Chemosphere* **1993**, *27*, 2253−2260.
(5) Rimkus, G. G.; Wolf, M. Polycyclic musk fragrances in human adipose tissue and human milk. *Chemosphere* **1996**, *33*, 2033−2043.
(6) Müller, S.; Schmid, P.; Schlatter, C. Occurrence of nitro and non-nitro benzenoid musk compounds in human adipose tissue. *Chemosphere* **1996**, *33*, 17−28.
(7) Ott, M.; Failing, K.; Lang, U.; Schubring, C.; Gent, H. J.; Georgii, S.; Brunn, H. Contamination of human milk in Middle Hesse, Germany−A cross-sectional study on the changing levels of chlorinated pesticides, PBC congeners and recent levels of nitro musks. *Chemosphere* **1999**, *38*, 13−32.
(8) Sommer, C. The role of musk and musk compounds in the fragrance industry. In *The Handbook of Environmental Chemistry*, Part X; Springer-Verlag: Berlin, Heidelberg, 2004; Vol. 3 pp 1−16.
(9) HERA. Polycyclic musks AHTN (CAS 1506-02-1) and HHCB (CAS 1222-05-05). Human and environmental risk assessment on ingredients of household cleaning products. In *Environmental Section. Version 2*; Human and Environmental Risk Assessment: Brussels, Belgium, 2004; pp 1−81.
(10) Kannan, K.; Reiner, J. L.; Yun, S. H.; Perrotta, E. E.; Tao, L.; Johnson-Restrepo, B.; Rodan, B. D. Polycyclic musk compounds in higher trophic level aquatic organisms and humans from the United States. *Chemosphere* **2005**, *61*, 693−700.
(11) Peck, A. M.; Hornbuckle, K. C. Synthetic musk fragrances in Lake Michigan. *Environ. Sci. Technol.* **2004**, *38*, 367−372.
(12) Simonich, S. L.; Begley, W. M.; Debarere, G.; Eckhoff, W. S. Trace analysis of fragrance materials in wastewater and treated wastewater. *Environ. Sci. Technol.* **2000**, *34*, 959−965.
(13) Simonich, S. L.; Federle, T. W.; Eckhoff, W. S.; Rottiers, A.; Webb, S.; Sabaliunas, D.; de Wolf, W. Removal of fragrance materials during U.S. and European wastewater treatment. *Environ. Sci. Technol.* **2002**, *36*, 2839−2847.
(14) Peck, A. M.; Linebaugh, E. K.; Hornbuckle, K. C. Synthetic musk fragrances in Lake Erie and Lake Ontario sediment cores. *Environ. Sci. Technol.* **2006**, *40*, 5629−5635.
(15) Reiner, J. L.; Kannan, K. A survey of polycyclic musks in selected household commodities from the United States. *Chemosphere* **2006**, *62*, 867−873.
(16) Reiner, J. L.; Berset, J. D.; Kannan, K. Mass flow of polycyclic musks in two wastewater treatment plants. *Arch. Environ. Contam. Toxicol.* **2007**. in press.
(17) Bester, K. Retention characteristics and balance assessment for two polycyclic musk fragrances (HHCB and AHTN) in a typical German sewage treatment plant. *Chemosphere* **2004**, *57*, 863−870.
(18) Berset, J. D.; Kupper, T.; Etter, R.; Tarradellas, J. Considerations about the enantioselective transformation of polycyclic musks in wastewater, treated wastewater and sewage sludge and analysis of their fate in a sequence batch reactor plant. *Chemosphere* **2004**, *57*, 987−996.
(19) Kupper, T.; Berset, J. D.; Etter-Holzer, R.; Furrer, R.; Tarradellas, J. Concentration and specific loads of polycyclic musks in sewage sludge originating from a monitoring network in Switzerland. *Chemosphere* **2004**, *54*, 1111−1120.
(20) Solomon, G. M.; Weiss, P. M. Chemical contaminants in breast milk: time trends and regional variability. *Environ. Health Perspect.* **2002**, *110*, A339−A347.
(21) Nakata, H.; Sasaki, H.; Takemura, A.; Yoshioka, M.; Tanabe, S.; Kannan, K. Bioaccumulation, temporal trend, and geographical distribution of synthetic musks in the marine environment. *Environ. Sci. Technol.* **2007**, in press, doi: 10.1021/es0623818.
(22) Kannan, K.; Tanabe, S.; Giesy, J. P.; Tasukawa, R. Organochlorine pesticides and polychlorinated biphenyls in foodstuffs from Asian and Oceanic countries. *Rev. Environ. Contam. Toxicol.* **1997**, *152*, 1−55.
(23) Kallenborn, R.; Gatermann, R. Synthetic musks in ambient indoor air. *In The Handbook of Environmental Chemistry*, Part X; Springer-Verlag: Berlin, 2004; Vol. 3, pp 85−104.
(24) Biselli, S.; Gatermann, R.; Kallenborn, R.; Sydnes, L. K.; Hühnerfuss, H. Synthetic musk fragrances in the environment. *In The Handbook of Environmental Chemistry*, Part X; Springer-Verlag: Berlin, 2004; Vol. 3, pp 189−212.
(25) Gatermann, R.; Biselli, S.; Hühnerfuss, H.; Rimkus, G. G.; Hecker, M.; Karbe, L. Synthetic musks in the environment. Part 1: Species-dependent bioaccumulation of polycyclic and nitro musk fragrances in freshwater fish and mussels. *Arch. Environ. Contam. Toxicol.* **2002**, *42*, 437−446.
(26) Minegishi, K.; Nambaru, S.; Fukuoka, M.; Tanaka, A.; Nishimaki-Mogami, T. Distribution, metabolism, and excretion of musk xylene in rats. *Arch. Toxicol.* **1991**, *65*, 273−282.
(27) Kokot-Helbling, K.; Schmid, P.; Schlatter, C. 1995. Die Be-lastung des Menschen mit Moschus Xylol - Aufnahmewege, Pharmakokinetk und toxikologi-sche Bedeutung. *Mitt. Geb. Lebensmittelunters. Hyg.* **1995**, *86*, 1−13 (in German).
(28) National Academy of Sciences (NAS). *Nutrition During Lactation*; National Academy Press: Washington, DC, 1991.
(29) Schecter, A.; Pavuk, M.; Päpke, O.; Ryan, J. J.; Birnbaum, L.; Rosen, R. Polybrominated diphenyl ethers (PBDEs) in U.S. mothers' milk. *Environ. Health Perspect.* **2003**, *111*, 1723−1729.

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