Environ. Sci. Technol. **2008,** *42,* 6743–6748

Temporal Trends of Synthetic Musk Compounds in Mother's Milk and Associations with Personal Use of Perfumed Products

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Received March 4, 2008. Revised manuscript received May 26, 2008. Accepted June 13, 2008.

We analyzed two nitro musks (musk xylene and musk ketone) and five polycyclic musks (HHCB, AHTN, ADBI, ATII, and AHDI) in mother's milk from primiparae women ($N = 101$) living in Uppsala County, Sweden, 1996−2003. Possible temporal trends in musk concentrations and associations with lifestyle/medical factors, such as use of perfumed products during pregnancy were studied. HHCB showed the highest median concentration (63.9 ng/g lipid) followed by AHTN (10.4 ng/g) and musk xylene (MX) (9.5 ng/g). Concentrations of the other substances were, in most cases, below the quantification limit (2.0−3.0 ng/g). Women with a high use of perfume during pregnancy had elevated milk concentrations of HHCB, and elevated concentrations of AHTN were observed among women reporting use of perfumed laundry detergent. This strongly suggests that perfumed products are important sources of musk exposure both among the mothers and the nursed infants. Concentrations of AHTN and MX declined significantly between 1996 and 2003, suggesting a decline in the industrial use of the compounds in consumer products, or alterations in the consumer use pattern of perfumed products. No temporal trend in HHCB concentrations was seen. The lack of toxicity data makes it difficult to generalize about the safety of musk exposure of breast-fed infants.

Introduction

Synthetic musk compounds have widespread use as a substitute for natural musks in fragrances and can be found in a number of consumer products such as laundry detergents, fabric softeners, cleaning agents, and cosmetic and hygiene products (soaps, shampoos, body lotions, perfumes, etc.). The main classes of synthetic musks are nitro musks, such as musk xylene and musk ketone, and polycyclic musks, such as HHCB (galaxolide), AHTN (tonalide), ADBI (celestolide), ATII (traseolide) and AHDI (phantolide) (see Figure S1, Supporting Information). Musk ketone, musk xylene, HHCB, and AHTN currently represent approximately 95% of the market in Europe for all nitro and polycyclic musks (*1*).

Nitro- and polycylic musks have been found in many types of environmental matrices (*2*). To our knowledge, nitro musks in mother's milk were first reported in 1993 (*3*), and since then nitro musks and polycyclic musks have been detected in mother's milk as well as in adipose tissue and blood plasma (*4–10*). Nevertheless, information on the global occurrence of musks in human milk is still limited, and the various sources of human exposure have not completely been elucidated.

The major route of exposure is suggested to be percutaneous absorption after dermal application of cosmetics (*5, 11*). Further studies are needed, however, to confirm the relevance of dermal absorption in humans. To our knowledge no studies have reported associations between use of perfumed products and concentrations of musk compounds in mother's milk. Moreover, there is little information about temporal trends of musk compound concentrations in mother's milk, which may reflect changes in use of the compounds by the industry and alterations in the patterns of consumer use of perfumed products. Reiner et al. (*10*) draw the conclusion that HHCB levels in mother's milk have increased during the past decade, whereas MK, MX, and AHTN levels have not markedly changed. This conclusion was, however, based on results from different populations and the chemical analyses had not been performed by the same laboratory, making it difficult to interpret the results.

The aim of our study was to provide data on occurrence of nitro and polycyclic musks in mother's milk from Swedish women and to study possible time trends of infant exposure. All samples were analyzed by the same analytical laboratory, eliminating variation of results due to interlaboratory differences in analytical methods. We report relationships between musk concentrations and lifestyle/medical factors of the mothers, such as education level, smoking, age, body mass index, and weight change during pregnancy. All these potential determining factors have been shown to be significantly associated with levels of other persistent organic pollutants in humans, such as PCB (*12–14*). Associations between levels of pollutants and determining factors may be both due to direct or indirect influences of the factor on the pollutant levels. For instance, smoking may be associated with musk compound levels due to smoking-induced alterations in musk metabolism, and smoking habits may also be a marker of a life-style that influence musk exposure. In addition, we investigated if musk levels in mother's milk are related to the use of perfumed products (e.g., perfumes, deodorants, body lotions, laundry detergents). To assess possible health risks for infants, intakes of musk compounds from mother's milk were calculated and compared with proposed tolerable intakes.

Materials and Methods

Recruitment. All late pregnancy primiparas (women having their first baby), participating as controls in a case-control study of risk factors for early miscarriages, were from early fall 1996 to late spring 1999 asked to participate in the study (*13, 15*). Of these 370 primiparae women, 188 agreed to donate mother's milk for chemical analysis. In addition, all early pregnancy primiparas registered at the prenatal clinic in Östhammar, Uppsala County ($N = 25$), who were not participating in the miscarriage study, were asked to participate in the study; 16 of these donated mother's milk (between fall 1997 and spring 1999). Primiparous mothers were also randomly recruited at Uppsala University Hospital

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10.1021/es800626n CCC: $40.75
Published on Web 08/02/2008

TABLE 1. Personal Characteristics of the Women Participating in the Study

parameter	N	median	range
age at the sampling occasion (years)	101	29.6	21.0−37.4
body mass index before pregnancy (kg m^{-2})	101	22.2	16.2−37.7
weight gain during pregnancy (%)[a]	101	0.58	0.03−1.23
weight reduction after delivery (%)[b]	98	9.7	−1.8−22
years of education(N)	≤13: 35		14−15:30 ≥16: 36
smoking during pregnancy (N)	no: 72		former: 18yes: 11
perfume during pregnancy (N)	≥once a week: 28		<once a week: 13
perfumed deodorant during pregnancy (N)	yes: 32		no: 11
perfumed laundry detergents (N)	yes: 26		no: 18

[a] % Change in body weight per week during pregnancy. [b] Weight reduction (minus birth weight of the child) in % of weight just before delivery (minus birth weight of the child).

from April 2000 to March 2001 and from March 2002 to February 2003. In 2000−2001, 31 of 67 women, and in 2002−2003, 31 of 49 women donated milk. The study was approved by the Ethics Committee of the Medical Faculty at Uppsala University, and the participating women gave their informed consent.

Questionnaires. The participating women answered extensive questionnaires about lifestyle and medical history (*13*) (Table 1). Personal interviews, using a standard-structure questionnaire, were conducted by certified midwives at 32−34 completed gestational weeks. Data on maternal characteristics included age, body length, body weight before pregnancy, years of education, home address, country of birth, and smoking and alcohol consumption during pregnancy. The height and body weight were recorded on the interview occasion. Blood samples for cotinine analysis, used as an indicator of smoking habits, were taken. After delivery, mothers also answered a questionnaire including delivery details (weight of the mother at delivery, birth weight of the child, etc) and questions about perfume use during the pregnancy (the 2000−2001 and 2002−2003 mother's milk sampling periods). The women ($N = 44$) were asked if they had used perfume, deodorant/antiperspirant, and body lotion. If the answer was yes, the woman was asked how often she used the product and if the product was perfumed or not (deodorant/antiperspirants and body lotion). In the question about washing detergent the women were asked if they used perfumed or nonperfumed detergents.

Sampling of Mother's Milk. The mothers sampled their milk during the third week after delivery (approximately day 14−21 postpartum). The milk was sampled during breast-feeding sessions, using a manual mother's-milk pump and/or a passive mother's-milk sampler. The women were instructed to sample milk at the beginning and at the end of the breast-feeding sessions. The goal was to sample a total of 500 mL from each mother during 7 days of sampling. The mother's milk was kept frozen in the home freezer in acetone-washed glass bottles and newly sampled milk was poured on top of the frozen milk.

To avoid contamination of the milk samples, the mothers were given instructions to refrain from touching the insides of the sampling equipment, and were asked not to use breast feeding creams during the sampling period. Moreover, the mothers were instructed to rinse hands and breasts thoroughly with water before sampling of mother's milk.

Of 266 samples collected a total of 101 mother's milk samples from all years between 1996 and 2003 were randomly selected for musk analysis.

Chemical Analysis. The samples were analyzed in 2002 and 2003 at the Institute of Chemical Technology, Department of Food Analysis, Prague, Czech Republic. This laboratory has a long time experience in musk compound analysis obtained mainly within the monitoring studies concerned with occurrence of these contaminants in biological environmental matrices and human milk collected in Czech Republic (*16, 17*). Method performance characteristics are reported in Hajková et al. (*17*).

Musk xylene, musk ketone, HHCB, AHTN, ADBI, and ATII were analyzed in all samples. AHDI was also included among the analyses performed in 2003 ($N = 80$). The samples were analyzed randomly, and the samples were coded. Thus the analytical laboratory did not have information about which year the mother's milk had been sampled and did not have information about the lifestyle and medical factors used in the statistical analyses of the results.

The analytical procedure was similar to that employed earlier for analysis of musk compounds in fish tissue (*17*). Briefly:10 mL of each mother's milk sample (weight determined) was mixed with 10 mL of ethanol and 1 mL of saturated solution of potassium oxalate in a separatory funnel. The sample was then extracted with 20 mL hexane:diethyl ether mixture (1:1, v/v) by shaking for 15 min. The bottom (aqueous) layer was reextracted with 10 mL of the same solvent mixture and 5 mL of ethanol in another funnel for 10 min. Combined organic extracts were rinsed with two 5 mL portions of deionized water, and the aqueous layers were removed to waste. Residual moisture was removed by passing the organic layer through anhydrous sodium sulfate. After evaporation of the solvent, the residue was dissolved in 4.5 mL of ethylacete:cyclohexane solvent mixture (1:1, v/v)—GPC mobile phase. Of this solution 2.5 mL was loaded on the Bio-Beads S-X3 column (50 cm × 0.8 cm i.d.) to separate lipidic coextracts from target analytes. The eluate in the range 14−30 mL was collected and after evaporation of an organic solvent it was transferred to 250 μL of isooctane containing isotopically labeled (deuterated) tonalide-D_3 and musk xylene-D_{15} (40 ng/mL each) as syringe internal standards to compensate matrix effects and improve overall precision of measurements. Identification and quantification of the analytes were performed by capillary gas chromatography coupled to a mass selective detector operated in a selected ion monitoring mode (HRGC/LRMS/EI-SIM). Agilent Technologies (U.S.) system consisting of HP 6890 gas chromatograph equipped with HP MSD 5973 was employed for this purpose.

Special precautions were taken to prevent secondary (intralaboratory) contamination that may occur from perfumes, deodorants, detergents etc. A single person, in an isolated air-conditioned room equipped with air filters, carried out all sample-handling operations. Within each batch of processed milk (eight samples) two blank samples were involved (10 mL of processed deionized water). Glassware cleaning procedures: following common washing machine cycle each piece was rinsed with hot distilled water and pure acetone and finally dried at 220 °C for 4 h. Attention was also paid to a possible cross-contamination during GC/MS analyses.

TABLE 2. Concentrations of HHCB, AHTN, ADBI, ATII, AHDI, Musk Xylene and Musk Ketone in Mother's Milk Sampled from 1996 to 2003

musk compound	N	median (ng/g lipid)	min (ng/g lipid)	max (ng/g lipid)	N < LOQ
HHCB	101	63.9	2.8	268	0
AHTN	101	10.4	<3.0	53.0	26
ADBI	101	<2.0	<2.0	11.0	75
ATII	101	<3.0	<3.0	12.6	77
AHDI	80	<3.0	<3.0	6.5	70
musk xylene	101	9.5	<6.0	83.9	31
musk ketone	101	<5.0	<5.0	24.4	83

The internal standard calibration technique was used for quantification of musk compounds. Limit of quantifications (LOQs) were determined at concentrations 10 times higher than the background. LOQ was 2.0−6.0 ng/g milk lipid for HHCB, AHTN, ADBI, ATII, and AHDI, and 5.0−9.0 ng/g milk lipid for musk xylene and musk ketone. The relative standard deviation (RSD) of the whole analytical procedure was 3.6−22.4%. RSD was calculated from six repeated injection of extract prepared from breast milk containing common musks level, comparable with those shown in Table 2. Since RSD is concentration dependent, higher values were obtained for those analytes occurring at lower levels; the highest RSD was a repeatability determined for ATII. The recoveries were 95.1−106.1%.

Statistics. Lipid adjusted mother's milk musk concentrations were used in the statistical analysis. The levels of ADBI, ATII, AHDI and musk ketone were low (>74% below LOQ), and these musks were therefore omitted from the statistical analysis of associations between the musk concentrations and personal characteristics of the mothers. Statistical analysis was performed using MINITAB For Windows, 14. Simple linear regression was used to analyze possible associations between log-normal-transformed musk concentrations and sampling year, age of the mother, prepregnancy body mass index, weight gain during pregnancy, and weight reduction after delivery. Regression analysis was only performed for compounds with >32% of the results above LOQ. In cases of results below LOQ, the levels were set at 1/2 LOQ. Lognormal transformation of the concentration data improved the fit of the regression models, as shown by regression quality plots such as histograms of residuals, normal plots of residuals and plots of residuals versus fits.

Mann−Whitney U-test was used when musk concentrations were compared among study participants in different categories of perfumed products use, years of education, and smoking habits during pregnancy. The reported use of body lotion during pregnancy was low and statistical analysis of the results was therefore not meaningful. When a temporal trend of musk compound concentrations was evident, adjusted geometrical means of musk compound concentrations were calculated using the general linear model (GLM) procedure.

In the analyses of the women's use of perfumed products an attempt was made to quantify the total use of perfumed products. The women with a perfume use of once a week or less was assigned the number 0, whereas women with a use of more than once a week was assigned the number 1. For deodorant/antiperspirant use, those with no use of the products at all and those using the nonperfumed products were assigned a 0, whereas those using perfumed products were assigned the number 1. For laundry detergent use those using the nonperfumed products were assigned a 0 whereas those using perfumed products were assigned the number 1. Finally the numbers assigned to each woman were summarized into three categories where women with a sum of 0−1 was placed in the low category, women with the sum of 2 were placed in the medium category, and women with a sum of 3 was placed in the high category.

Results and Discussion

Musk Concentrations. HHCB showed the highest median concentration (Table 2), followed by AHTN and musk xylene (MX). The concentrations of ADBI, ATII, AHDI, and musk ketone (MK) were below LOQ in 74−88% of the analyzed samples. The musk concentrations in Swedish mother's milk are of the same order of magnitude as those reported from Germany and Denmark (*5, 18*), with HHCB found in the highest concentrations, followed by AHTN and MX/MK. In both Sweden and Germany, the levels of ADBI, ATII, and AHDI were low. Higher levels of polycyclic musks (HHCB and AHTN) compared to nitro musks are in accordance with the replacement of nitro musks by polycyclic musks in recent years (*2*). Interestingly, in a study from the U.S. (*10*), median MK concentration in mother's milk was higher than for MX, whereas the reverse was evident in the Swedish samples. This suggests that there may be differences in the contamination pattern of the compounds between Europe and North America.

Use of Perfumed Products. A positive correlation between AHTN and HHCB concentrations was found (Pearson $r = 0.49$, $p \leq 0.001$), whereas no correlation between these two compounds and MX were evident ($r = -0.22$ (HHCB) and $r = 0.06$ (AHTN), $p > 0.05$). This indicates that sources of exposure to HHCB and AHTN may differ from those of MX. This is also illustrated by our finding of a significant positive association between use of perfumed products and mother's milk concentrations of HHCB (perfumes) and AHTN (perfumed laundry detergents), whereas no significant associations were found for MX (Figure 1).

No data on musk content of consumer products on the Swedish market have been published. A survey of synthetic musk compounds in personal care products, performed in Belgium, showed that the 19 different products classified as perfumes, including Eau de toilette and perfume, did not contain detectable levels of MX (*19*). Many of these types of products contained high levels HHCB (*19*), supporting our finding of a positive association between use of perfume and HHCB concentrations in mother's milk. AHTN was present in the majority of perfumes but the concentrations were in many cases considerably lower than those of HHCB (*19*). Similar results were found in a survey of household commodities from the United States (*20*). The Belgian study did not report musk content of laundry detergents, and in the U.S. study only two different laundry detergent products were analyzed (*19, 20*). One product had high concentrations of both HHCB and AHTN, whereas the other product had low or nondetectable concentrations of the compounds (*20*).

It has been suggested that percutaneous absorption may be the most relevant route of exposure to musk compounds (*5, 11*). Significant amounts of musk compounds are absorbed through the skin of humans (*21*) and rats (*22*) in vivo, and through guinea-pig skin and human skin in vitro (*23*). A study by Käfferlein and Angerer (*4*) suggests that higher musk xylene concentrations in body-care products result in higher musk xylene concentrations in plasma samples from exposed persons, and Hutter et al. (*9*) showed statistically significant associations between blood plasma HHCB levels and use of perfume and body lotion among young adults in Austria.

Our study was small ($N = 44$), which makes our results regarding increased concentrations of HHCB and AHTN in mother's milk from users of perfumed products uncertain. Furthermore, it must have been difficult for the study participants to estimate their use of perfumed products. The musk content in the products that the women used was not determined by us. The studies of consumer products from

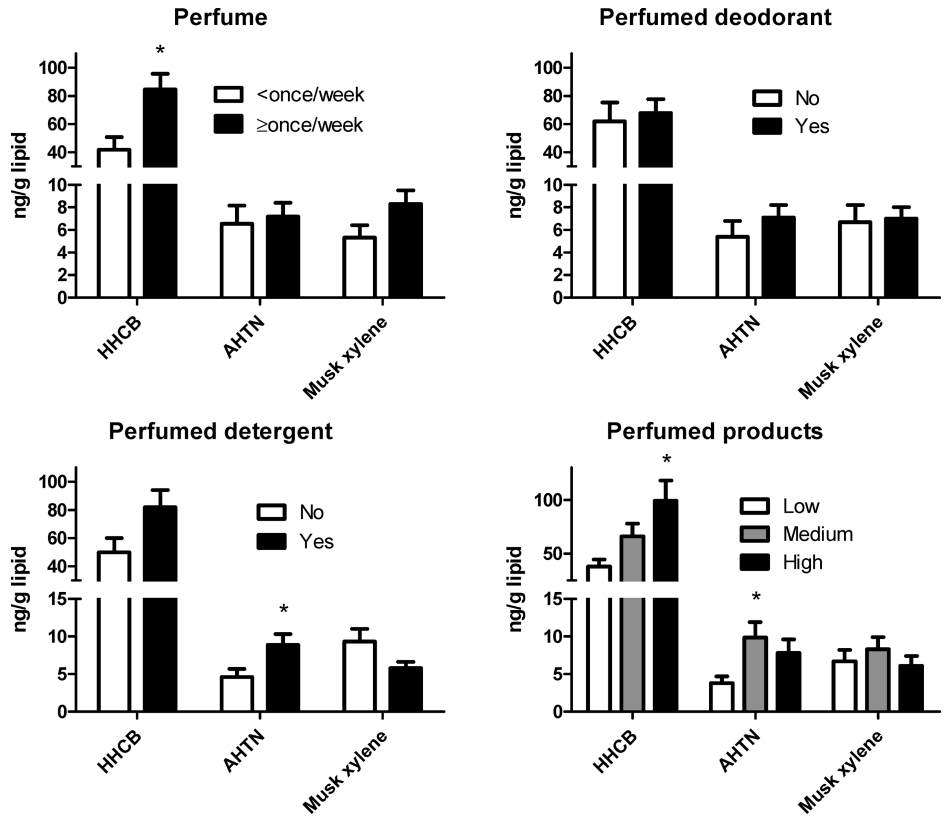

FIGURE 1. Concentrations of musk compounds in mother's milk from mothers with different patterns of use of perfumed hygiene products during pregnancy (mean (SE)). Concentrations of AHTN and musk xylene were adjusted for sampling year. *Significantly different from the reference category with the lowest use of perfumed products ($p \leq 0.05$, $N = 41-43$).

Europe and North America show that the musk composition and concentrations in products of the same type may differ considerably (*19, 20*). Furthermore we did not quantify the applied amounts. Albeit all these uncertainties, our results suggest that use of perfumed products among mothers may cause contamination of mother's milk during the following nursing period.

Temporal Trends. Reiner et al. (*10*) summarized the results of previous studies of musk compounds in mother's milk. They draw the conclusion that the concentrations of HHCB appeared to have increased 5-fold during the past decade, whereas the concentrations of MK, MX, and AHTN have not changed markedly (*10*). This conclusion is, however, hampered by the fact that the studies were performed in different areas of the world, and that different analytical laboratories performed the analysis of mother's milk in some cases. Our results show that concentrations of AHTN and MX declined significantly between 1996 and 2003, whereas no change in HHCB concentrations was seen (see Figure S2 and Table S1, Supporting Information). The regression coefficients (mean ± SD) obtained in the linear regression between musk compound concentrations (ln-transformed) and year of sampling were -0.055 ± 0.036 ($p = 0.127$) for HHCB, -0.12 ± 0.052 ($p = 0.023$) for AHTN, and -0.19 ± 0.041 ($p < 0.01$) for MX. The estimated yearly mean decline in AHTN and MX concentrations was 11 ± 4.5% (mean ± SE) and 17 ± 3.5%, respectively.

Temporal trends of musk compounds in mother's milk may be influenced by changes in general contamination of the environment, in the musk content of products, and in the pattern of use of perfumed products within the studied population. A downward trend regarding MX is likely, since the industry has voluntarily replaced the nitro musks with polycyclic musks (*2*). A study by Waizenegger et al. (*24*) also indicated a decrease in levels of nitro musks in human milk from 1993 to 1996, and Käfferlein and Angerer (*4*) reported lower levels of musk xylene in human plasma from 1992−1993 compared to 1998.

The strength of our study is that the study participants came from a homogeneous population of young Swedish women, and that mother's milk was sampled during consecutive years for a 7 year period. Moreover, the samples were randomly analyzed by the same laboratory during a short time period and the samples were coded.

Other Personal Characteristics. Age showed no significant association with musk concentrations in milk (see Table S1, Supporting Information), as also found for nursing women in the U.S. (*10*). Because of their high lipophilicity, musk compounds can be expected to bioaccumulate in the human body. However, Kokot-Helbling et al. (*25*) reported that the half-life of MK in human subjects is relatively rapid (about 100 days). This may explain the absence of associations between MK and age. Moreover, a high individual difference in exposure to musk compounds, e.g. use of perfumed products, may mask any variation in musk levels in mother's milk due to age. Hutter et al. (*9*) showed that plasma concentrations of HHCB were significantly higher in younger persons (19−25 years) compared to older (26−43 years). This age difference may have been explained by the fact that younger participants appeared to use more perfumed products than older participants (*9*). We did not find such an age-related concentration pattern.

Indicators of the bodily constitution of the participating mothers, i.e., prepregnancy BMI, weight gain during pregnancy, and weight reduction after delivery, were not significantly associated with concentrations of musk compounds in mother's milk, with one exception (see Table S1, Supporting Information). BMI showed a significant negative association with the level of AHTN. The relationship between body mass index and AHTN was, however, solely dependent on low AHTN concentrations among five women with a prepregnancy BMI higher than 30. The lack of associations

with the indicators of bodily constitution is in contrast with the significant associations between the indicators and body burdens of polychlorinated biphenyls among our study participants (*13*). The reason for this difference between the two lipophilic compound groups may be a lower persistence of the musk compounds in the body (*7, 10, 25, 26*).

MX was the only compound that was associated with the number of years of education (see Figure S3, Supporting Information). The MX level increased with increasing number of years of education, with an adjusted mean of 2.0 ± 0.14 ng MX/g lipid (mean ± SE) among women with 13 years of education or less, 2.3 ± 0.15 ng MX/g lipid for women with 14−15 years of education, and 2.6 ± 0.14 ng MX/g lipid among women with 16 years or more of education. This may indicate that women with a high education level have a life style that causes increased exposures to MX. Smoking was not associated with musk concentrations, except for a significantly lower AHTN concentration among women that were former smokers compared to women who never had smoked (see Figure S3, Supporting Information). Similar to us, no associations were found between smoking habits and musk concentrations in mother's milk among mothers from the U.S. (*10*). In that study median HHCB and AHTN concentrations decreased with the number children the mothers had nursed (*10*). We only sampled women that had given birth to their first child so the associations with number of children nursed could not be determined.

Exposure of Infants via Mother's Milk. Our results on HHCB, AHTN, and musk xylene were used to calculate the musk exposure of infants via mother's milk. A daily milk consumption of 0.7 L milk (lipid content of 3.7%) was assumed. The calculated total daily intakes (median (range)) were 1650 (50−6950) ng HHCB, 250 (50−1350) ng AHTN, and 250 (100−2150) ng MX. These estimates are in the same order of magnitude as those obtained for infants in the U.S. (*10*). For an infant with a body weight of 5 kg the maximum intakes correspond to 1.4 μg HHCB/kg body weight, 0.27 μg AHTN/kg, and 0.43 μg MX/kg. In risk assessments of the use of HHCB, AHTN, and MX in cosmetic products, the European Union Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) concluded that the substances can be safely used as fragrance ingredients in cosmetic products (*27–29*). For AHTN and MX defined maximum concentrations in the final products were proposed. Risk assessment of MX was based on the findings of liver cytochrome P-450 induction and tumors in rodents (*28*). Critical end points for HHCB and AHTN were maternal toxicity after gestational exposure (*27, 29*). The SCCNFP did not, however, estimate a tolerable intake of the musk compounds from food (and mother's milk). Slanina (*30*) reviewed the toxicological literature regarding musk compounds and estimated provisional tolerable daily intakes (PTDI) of HHCB, AHTN, and MX, to 500 μg/kg body weight, 50 μg/kg, and 7 μg/kg, respectively. These PTDIs were based on the same toxicological end points as those used by SCCNFP (*27–30*). The estimated maximum daily intakes of the musk compounds by Swedish infants were considerably lower than these PTDI. The comparison between infant intake and PTDI is however questionable since the proposed PTDIs are based on adult exposure to the musk compounds. It is also obvious that the total exposure of infants to musk compounds is unknown, since the contribution of exposure from other sources than mother's milk, e.g., perfumed napkins, soaps, and lotions has not been quantified.

The knowledge about the positive effects of breast-feeding on health development later in life is rapidly accumulating (*31, 32*). WHO encourage exclusive breast-feeding of infants for 6 months (*33*). It is currently not possible to draw firm conclusions about the influence of chemical contamination on the quality of mother's milk. It may well be possible that the chemical contamination of mother's milk results in a less than optimal health-based quality of mother's milk.

Acknowledgments

Appreciation is expressed to the participating women, to the midwives Irma Häggbom, Ragnhild Cnattingius, Margareta Aveskog, Ingela Wessén, Astrid Bengtson, Toni Eriksson, and Ann Rydberg who assisted in recruitment, interviewing, and sample collection. Laboratory technicians Ingalill Gadhasson, Lotta Larsson, and Elvy Netzel are appreciated for technical assistance.

Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

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ES800626N