Synthetic Polycyclic Musks

Materials for November 14, 2013 Meeting of Scientific Guidance Panel (SGP)
Biomonitoring California[1]

Agenda Item: "Potential Designated Chemicals"

Introduction

At the November 8, 2012 meeting of the Scientific Guidance Panel (SGP), the Panel reviewed screening materials on various classes of synthetic musks and a structurally related aroma chemical (Iso E Super®). The Panel requested that Biomonitoring California prepare documents on these aroma chemicals to support their consideration as potential designated chemicals for Biomonitoring California. The current document focuses on the class "synthetic polycyclic musks."

The document reviews information relevant to the criteria for designating chemicals, as specified in Health and Safety Code section 105449:

- Exposure or potential exposure
- Known or suspected health effects
- Need to assess efficacy of public health actions to reduce exposure to a chemical
- Availability of a biomonitoring analytical method
- Availability of adequate biospecimen samples
- Incremental analytical cost.

Synthetic polycyclic musks are aroma chemicals that emulate the fragrance produced by natural musks. They are used in perfumes, personal care products such as body lotions and creams, deodorants, shower gels, and hair products and in household products like furniture polish, laundry detergent and fabric softener (Reiner and Kannan, 2006; Roosens et al., 2007). Data cited by Peck and Hornbuckle (2006) indicate that global use of polycyclic musks doubled from 1987 to 2000. This increase paralleled a decrease in the use of nitro musks, which by 2000 had dropped to less than one-third compared to use in 1987. Although use of polycyclic musks appears to have declined in Europe, the same decline has not occurred in the U.S. (IFRA, 2013).

[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

Two synthetic polycyclic musks are highlighted in the current document:

- 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran (HHCB; Galaxolide® is a trade name)
- 7-Acetyl-1,1,3,4,4,6-hexamethyltetrahydronaphthalene [1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)ethanone] (AHTN; Tonalide® is a trade name)

A table of other synthetic polycyclic musks is provided at the end of the document.

Chemical-specific data on exposure and factors related to the potential for biomonitoring are summarized in the sections on HHCB and AHTN later in the document. Known or suspected health effects, analytical considerations, and the need to assess public health actions are discussed for the class of synthetic polycyclic musks as a whole in the following sections.

Known or suspected health effects:

Christian et al. (1999) studied the developmental toxicity of HHCB, AHTN and other fragrance compounds in rats. Pregnant Sprague-Dawley rats (25/group) received gavage doses of 0 (corn oil), HHCB (50, 150 or 500 milligrams per kilogram body weight per day [mg/kg-d]) or AHTN (5, 15 or 50 mg/kg-d) on days 7 through 17 of gestation. The authors identified a maternal no observed adverse effect level (NOAEL) of 50 mg/kg-d and 5 mg/kg-d for HHCB and AHTN, respectively, based on reduced weight gain, feed consumption and/or clinical signs of toxicity. They identified a developmental NOAEL of 150 mg/kg-d and 50 mg/kg-day for HHCB and AHTN, respectively. For HHCB, the NOAEL was based on the observation of skeletal malformations in the 500 mg/kg-d dose group. Mean body weights of live fetuses were reported to be significantly decreased by HHCB (500 mg/kg-d) and AHTN (5 and 50 mg/kg-d), but the authors discounted these effects based on consideration of "severity, dosage-relationships, and historical ranges of the laboratory." Christian et al. (1999) concluded that "under conditions of normal use, the fragrances tested are not considered to pose a risk to human conceptuses." The European Commission (EC, 2008a, b) reviewed a submitted study report, which contained more complete data than the publication, and also concluded that this study did not provide evidence of developmental toxicity for either HHCB or AHTN.

There are indications of endocrine activity in a number of studies (see for example: Bitsch et al., 2002; Schreurs et al., 2002, 2005; Simmons et al., 2010; Mori et al., 2007) and other biological activity, summarized below.

Studies related to endocrine effects

Most of the studies of endocrine activity have focused on HHCB and/or AHTN but some studies have looked at other polycyclic musks as well. Some studies have reported weak estrogenic activity. In an estrogen receptor (ER) competitive binding assay, both HHCB and AHTN bound to both ERα and ERβ, although with low affinity (Schreurs et al., 2002). Several studies reported that in cell-based reporter gene assays HHCB, AHTN and other polycyclic musks slightly stimulated ER-mediated transcriptional activity (Mori et al., 2007; Schreurs et al., 2002; Seinen et al., 1999). In one study, Seinen et al. (1999) reported that both HHCB and AHTN induced a slight but dose-dependent increase in transcriptional activity; however, neither musk was positive in the mouse uterotropic assay. In the E-screen cell proliferation assay, Bitsch et al. (2002) reported that AHTN, but not HHCB, significantly increased cell proliferation, an indicator for estrogenicity.

Several polycyclic musks have been found to possess anti-estrogenic activity (Schreurs et al., 2002; 2004; 2005; Simmons et al., 2010). HHCB and AHTN inhibited estrogen-induced transcriptional activation of both human and zebrafish ERs *in vitro* in a reporter gene assay and *in vivo* in transgenic zebrafish (Schreurs et al., 2004). In a study in rainbow trout, Galaxolide® decreased estrogen-induced plasma vitellogenin (Simmons et al., 2010).

Several polycyclic musks (HHCB, AHTN, AETT[2] and AHMI) suppressed androgen- and progesterone-induced transcriptional activity as well as estrogen-induced activity (Schreurs et al., 2005). Although antagonistic effects on transcriptional activation of estrogen and androgen receptors were considered weak compared to known antagonists, two polycyclic musks, AHTN and AHMI, were progesterone receptor (PR) antagonists at nanomolar concentrations (20 nM), although antagonistic effects on transcriptional activation of estrogen and androgen receptors were considered weak compared to known antagonists. Other environmental contaminants that have been shown to act like PR antagonists include DDT and its metabolites, 4-tert-octylphenol, and 4-nonylphenol (as reported in Schreurs et al., 2005).

Li et al. (2013) reported that HHCB and AHTN significantly decreased progesterone and cortisol synthesis in a human adrenocortical carcinoma cell line. These authors report that HHCB and AHTN down-regulate expression of enzymes in the synthetic pathways for these hormones – for progesterone, 3β-hydroxysteroid dehydrogenase and for cortisol, a cytochrome P450 isozyme, steroid 21-hydroxylase (CYP21).

[2] The table at the end of this document provides full names and other details on polycyclic musks other than HHCB and AHTN.

Other biological activity

Shi et al. (2013) studied gene expression in mouse embryonic stem (ES) cells after exposure to AHTN. The study, conducted using microarray analysis and validated by polymerase chain reaction analysis, found that AHTN caused changes in the activation of certain signaling pathways, such as mitogen-activated protein kinases (MAPK) signaling pathway.

Four polycyclic musks (HHCB, AHTN, ADBI, ATII) were tested for their ability to inhibit multidrug efflux transporters in the gill tissue from marine mussels (Luckenbach and Epel, 2005). Each of the tested musks inhibited transporter activity. Inhibition of transporter activity for some of the musks continued after the two hour exposure period ended, with inhibition still statistically significant 24 hours after exposure was terminated. The study also reported that inhibitory effects were additive, with lower concentrations of several different musks causing the same degree of inhibition as did a higher concentration of a single musk. The authors noted that multi-drug efflux transporters are widely distributed in mammalian tissue.

Schnell et al. (2009) reported that Galaxolide® and Tonalide® (referred to by the authors as "galaxolide and tonalide") inhibited Phase 1 and Phase 2 metabolism in *in vitro* studies using enzymatic systems from carp. Cytochrome P-450 activity was inhibited in hepatic (CYP3A) and ovarian (CYP19) microsomes and testicular (CYP17 and CYP11β) mitochondria. Galaxolide® and Tonalide® also significantly inhibited sulfation of estrogen in carp hepatic cytosol.

Need to assess efficacy of public health action

Measuring polycyclic musks would help the Program determine whether these chemicals are found in California residents and at what levels. Biomonitoring will also allow the Program to track whether levels of polycyclic musks decrease with the increase in use of newer synthetic musks.

Availability of a biomonitoring analytical method

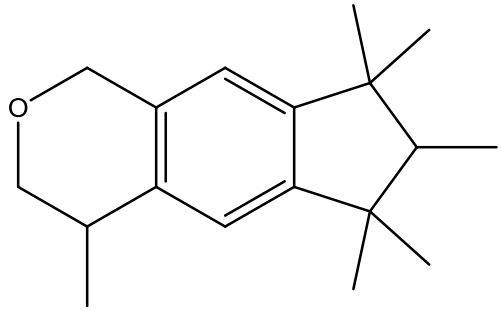
Analytical methods for measuring polycyclic musks in plasma, serum, breast milk and adipose tissue are available in the published scientific literature. Commercial standards are available for HHCB, AHTN, and several other synthetic polycyclic musks. The Program laboratory[3] would likely analyze serum samples with gas chromatography tandem mass spectrometry (GC-MS/MS) instrumentation, using electron ionization (EI) and multiple reaction monitoring (MRM).

[3]Environmental Chemistry Laboratory (ECL) of the Department of Toxic Substances Control (DTSC)

1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran

HHCB

CASRN 1222-05-5



Exposure or potential exposure to the public or specific subgroups:

HHCB has been detected in a number of personal care products such as perfumes, body lotions and creams, deodorants, and shower products (e.g., soaps, shampoos and conditioners). HHCB has also been detected in household items like furniture polish, laundry detergent, and fabric softener. Reiner and Kannan (2006) analyzed 60 consumer products from the U.S. (New York) and found HHCB at high levels in personal care products: In one perfume sample (body splash) the level of HHCB was 4990 microgram per gram (µg/g). In body lotions and creams, levels were as high as 3740 µg/g, with an average of 1220 µg/g (n=7) and in deodorants, one sample contained 2250 µg/g product, with an average concentration of 737 µg/g (n=4). One shaving cream sample contained 1230 µg /g product. Reiner and Kannan (2006) also analyzed for HHCB in some cleaning products. Examples, with highest concentrations noted in parentheses, are: furniture polish (646 µg/g), laundry detergent (84.9 µg/g), fabric softener (0.966 µg/g), disinfecting wipes (0.786 µg/g) and liquid bleach (326 µg/g). HHCB-lactone, a HHCB oxidation product, was found in many products that contained HHCB. For example, one sample of body cream contained 217 µg HHCB-lactone /g product.

Import/production volume of 1 to 10 million pounds (lbs) per year has been reported to U.S. EPA every reporting year since 1990 (U.S. EPA, 2002; 2006). The International Fragrance Association of North America (IFRA-NA, 2013) reported volume of use data for North America as 1500-2000 metric tons (3.3 – 4.4 million lbs) in 2011. This is consistent with the most recent use volume reported to U.S. EPA of 3.1 million pounds for the 2011 calendar year (U.S. EPA, 2012a).

There are four HHCB stereoisomers. The commercial HHCB mixture is reported to be made up of approximately 75% CASRN 1222-05-5, with each of the other stereoisomers contributing about 5-10% (EC, 2002). As reported by Kallenborn et al. (1999), only two of the enantiomers emit a musky odor.

HHCB and its degradation product HHCB-lactone were found in 100% of house dust samples from a Canadian study (n=49). Dust samples were collected by researchers ("fresh dust" or FD) and from personal home vacuum cleaners ("house dust" or HD). Maximum HHCB levels were 9 µg/g (FD) and 31.1 µg/g (HD). Median levels were 0.676 µg/g (FD) and 0.992 µg/g (HD) (Kubwabo et al., 2012). HHCB dust levels of 1.2 ± 0.14 µg/g were found in Standard Reference Material (SRM) 2585 (house and motel dust from 1993-1994) (Kubwabo et al., 2012). Fromme et al. (2004) found a median HHCB level of 0.7 µg/g in household dust samples from Berlin, Germany. HHCB was detected in 100 % of house dust samples in China (n=56), at a median level of 0.0379 µg/g (Lu et al., 2011). HHCB has also been detected in indoor air (Sofuoglu et al., 2010; Fromme et al., 2004).

The major environmental source of HHCB is from the discharge of wastewater treatment plant (WWTP) effluent (Peck and Hornbuckle, 2006). In a study of effluent-dominated rivers receiving discharge from WWTPs in five U.S. municipalities, HHCB was detected in fish caught at all sampled locations. Mean tissue concentrations ranged from 100 to 1800 nanogram per gram (ng/g). Levels were lower in municipalities with more advanced wastewater treatment (Ramirez et al., 2009). Wombacher and Hornbuckle (2009) reported 67-70% average removal of HHCB in a wastewater treatment plant in Iowa.

HHCB was among the chemicals tentatively identified in run-off from agricultural crops treated with WWTP effluent in Ventura County, Southern California (Pedersen et al., 2005). Low levels of HHCB have also been detected in drinking water (Wombacher and Hornbuckle, 2009; Benotti et al., 2009).

According to Peck and Hornbuckle (2006), the primary removal process for HHCB during wastewater treatment is via adsorption to sludge (biosolids). Levels in biosolids measured by DiFrancesco et al. (2004) from two different WWTPs in Delaware in 2002 were reported as 21.8 ± 4.3 µg/dry g and 37.6 ± 4.5 µg/dry g.

HHCB has been found in mussels, clams and oysters. In sampling in 2002 and 2003 in the San Francisco Bay, median HHCB levels were 246 ng/g dry weight in clams (n=2), 221 ng/g in mussels (n=7), and 386 ng/g in oysters (n=5). HHCB levels of up to 855 ng/g dry weight were found in oysters (Hoenicke et al., 2007). In samples collected in 2009-2010 from the San Francisco Bay, HHCB was found in19/39 mussels, with a

maximum of 855 ng/g wet weight (reported in Klosterhaus et al., 2013). In another study, Nakata et al. (2012) reported detection of HHCB in 93% of mussels (n=15) obtained from the Pacific Coast in 2004-2005, with a geometric mean concentration of 210 ng/g lipid.

Kannan et al. (2005) detected HHCB at levels generally around 1-5 ng/g wet weight in marine mammals and other aquatic wildlife from U.S. waters; levels of up to 25 ng/g wet weight were measured in dolphins off the Florida coast. In Japan, Nakata (2005) detected HHCB in the blubber of finless porpoises (n=8) at levels ranging from 13 to 149 ng/g wet weight. In this study, HHCB levels in three fetal porpoises were also measured. In two very immature fetuses, skin was used for chemical analysis as blubber was not developed. No HHCB was detected in these samples. In the third fetus, the level of HHCB measured in blubber, 26 ng/g wet weight, was comparable to the level in its mother, 39 ng/g wet weight.

HHCB was recommended for monitoring in freshwater systems and coastal embayments by the California State Water Resources Control Board Science Advisory Panel for contaminants of emerging concern in California's aquatic ecosystems (Anderson et al., 2012).

***Potential to biomonitor*:**
Physical and chemical properties (SRC, 2013):
Molecular weight: 258.41
Vapor pressure: 5.45×10^{-4} mm Hg
Water solubility: 1.75 mg/liter (L) at 25°C
Octanol/water partition coefficient (log K_{ow}): 5.9

Persistence:
Peck et al. (2006) studied sediment in Lake Erie during the period 1979-2003. An increase of HHCB in sediment occurred from 1990-2003, but the increase was attributed to the increased input of HHCB into the lake. DiFrancesco et al. (2004) monitored the decrease in HHCB levels over time in four different soils amended with sludge containing HHCB. At three months, HHCB was one of seven fragrance chemicals (out of a total of 22 fragrances) present above the quantification limit. HHCB was not detected at 12 months. Buerge et al. (2003) reported that HHCB was eliminated from lake water primarily via outflowing water and via losses to the atmosphere, with very little elimination occurring by photochemical degradation. Aschmann et al. (2001) determined that HHCB has a short atmospheric lifetime and would not undergo long-range atmospheric transport.

EC (2008a) identified half-lives for HHCB of 105 days in soil, based on results from a sludge-amended soil test, and 79 days for sediment. EC concluded that HHCB may be considered "inherently biodegradable" and did not meet the EC criteria for persistence (>120 days in soil and fresh- or estuarine water sediment; >180 days in marine sediment). In comparison, the OEHHA (2012) criteria for evidence of persistence for these environmental media are: >2 months in soil or sediment. Under the OEHHA criteria, there is evidence of persistence for HHCB.

Bioaccumulation:
Dietrich and Hitzfeld (2004) reported a range of experimental bioconcentration factors (BCFs) on a wet-weight basis: 620 (zebrafish), 862 (eel) and 1584 (bluegill sunfish). On a lipid weight basis, the BCF in eel was reported as 3504. Bioaccumulation factors (BAFs) on a wet weight basis ranged from 20 in rudd to 620 in zebrafish muscle (Dietrich and Hitzfiel, 2004). Gatermann et al. (2002) found that BAFs were dependent both on the lipid content of the fish and the extent of HHCB metabolism in the particular species. EC (2008a) concluded that the BCFs and BAFs did not meet the EU criterion for bioaccumulation (> 2000). OEHHA (2012) considers a BCF or BAF > 1000 or a log $K_{ow} \geq 4$ as evidence of potential bioaccumulation. The log K_{ow} of 5.9 and the range of BCFs shown above suggest a potential for HHCB to bioaccumulate in some species.

Past biomonitoring studies:
HHCB has been measured in blood, breast milk, adipose tissue and umbilical cord blood. It is the predominant synthetic musk in studies that have measured multiple synthetic musks (e.g., including other polycyclic musks and nitro musks). Few studies, however, have been conducted in the U.S. Selected studies are summarized below, organized by biological media. Units of measurement vary by publication. In this document, all values are reported in ng (e.g., ng/g lipid, ng/L). Detection frequency is defined as percent of samples greater than the limit of quantitation.

Whole blood

- Den Hond et al. (2013). Belgium (n=204), ages 14-15 years old. Samples collected in 2008- 2009.
    - Detection frequency: 100%
    - Geometric mean: 717 ng/L
    - Median: 754 ng/L
    - Range: 301-1539 ng/L
    - HHCB levels were significantly increased with increased self-reported use of personal care products and higher educational level of the adolescents.

Plasma

- Hu et al. (2010). 11 cities in China (n=204), 94 females, 110 males, at ages ranging from 17-75; median age 25.
    - Detection frequency: 91%
    - Median: 850 ng/L
    - Maximum concentration: 1630 ng/L
    - Women between the ages of 27 to 40 years had lower HHCB levels than younger and older women
    - A significant positive relationship was found between levels of HHCB and AHTN.

- Hutter et al. (2010). Austria (n=53). Women older than 50 years.
    - Detection frequency: 89%
    - Maximum concentration: 6900 ng/L
    - Higher HHCB [identified as “galaxolide”] concentrations were significantly associated with frequent use of perfumes, deodorants and shampoos.

- Hutter et al. (2005; 2009). Austria (n=100). Adults (55 female, 45 male), ages 19 to 43.
    - Detection frequency: 83%
    - Median: 420 ng/L
    - Maximum concentration: 4100 ng/L
    - Levels were significantly higher in women (580 ng/L compared to 260 ng/L in men)
    - Significantly higher levels were seen with more frequent use of body lotion and in the lower age group (19-25 years).

Serum:

- Kang et al. (2010). Korea. Samples collected from pregnant women, one day before delivery (n=20), in 2007. This study also measured breast milk and umbilical cord serum.
    - Detection frequency: 90%
    - Geometric mean: 380 ng/g lipid
    - Range: 170-1400 ng/g lipid
    - Significantly higher HHCB levels were found in serum and cord blood compared to breast milk.

- Kuklenyik et al. (2007). Atlanta, Georgia (GA). Methods development study which measured HHCB in seven anonymous adults. Samples collected in March 2004.
    - Detection frequency: 29% (2/7)
    - Mean: 1.04 ng/milliliter (mL) (wet weight)
    - Range: 0.38-1.70 ng/mL (wet weight)

Breast milk

- Kang et al. (2010) Korea (n=17). Samples collected 3-10 days after delivery, in 2007.
    - Detection frequency: 100%
    - Geometric mean: 180 ng/g lipid
    - Range: 55-515 ng/g lipid
    - HHCB levels in breast milk were significantly lower than in serum and cord blood, also measured in this study. An apparent increasing trend for higher HHCB levels with age was observed but parity did not affect HHCB levels.

- Ueno et al. (2009). Japan. Nursing mothers (n=5); 5 samples collected monthly from each donor in 2006-2008; 20 samples analyzed.
    - Detection frequency: 60%
    - Range: <50 – 440 ng/g lipid

- Reiner et al. (2007). Massachusetts (n=39). Samples collected in 2004.
    - Detection frequency: 97%
    - Mean: 220 ng/g lipid
    - Range: <5 to 917 ng/g lipid
    - No correlation was found between levels of HHCB and AHTN; the authors concluded that this suggests multiple sources of exposure.
    - Maternal age was not correlated with HHCB concentrations
    - Study found a trend of decreasing concentrations of HHCB with the number of children previously breast-fed, although it was not significant.

- Kuklenyik et al. (2007). Atlanta, GA. Methods development study. Samples collected from 26 anonymous nursing mothers, in 2004.
    - Detected frequency: 27% (7/26)
    - Calculated range: 20.1-131.6 ng/g lipid. Authors assumed 1.74% lipid content in milk.

- Lignell et al. (2008). Sweden (n=101). Samples collected from primiparous mothers during the 3rd week after delivery, in 1996-2003.
    - Detection frequency: 100%
    - Median: 63.9 ng/g lipid
    - Range: 2.8-268 ng/g lipid
    - In a subset of mothers who were asked about perfume use (n=44), elevated concentrations of HHCB were found in women reporting high use of perfume and perfumed products during pregnancy.

- Duedahl-Olesen et al. (2005). Denmark (n=10). Samples collected from primiparous mothers 14-26 weeks after delivery, in 1999.
    - Detection frequency: 100%
    - Median: 147 ng/g lipid
    - Range: 38.0-422 ng/g lipid

- Rimkus and Wolf (1996). Germany. Samples collected from 4 nursing mothers; one mother provided two samples.
    - Detection frequency: 100%
    - Range: 16-108 ng/g lipid
    - One subject gave samples at 1 and 10 weeks. Levels were 108 ng/g lipid and 28 ng/g lipid, respectively.

Adipose tissue

- Moon et al. (2012). Korea (n=43). Samples collected from women (ranging in age from 40-70 years) undergoing laparoscopy surgery for myoma, in 2007-2008.
    - Detection frequency: 100%
    - Mean: 81 ng/g lipid
    - Range: 28-211 ng/g lipid
    - Study did not find a correlation between age and levels of total synthetic musks.

- Schiavone et al. (2010). Italy (n=12). Samples collected from surgical patients (9 male, 3 female), in 2005-2006.
    - Detection frequency: 92%
    - Mean: 361 ng/g lipid
    - Range: <5 – 1435 ng/g lipid

- Kannan et al. (2005). New York City (n=49). Samples collected from patients undergoing liposuction, in 2003-2004.
    - Detection frequency: 100%
    - In male subjects (n=12)
        - Median: 90.5 ng/g lipid
        - Range: 12 - 509 ng/g lipid
    - In female subjects (n=37)
        - Median: 180 ng/g lipid
        - Range: 18-798 ng/g lipid
    - Study found that levels of HHCB and AHTN (also measured in this study) did not increase with age and were higher in individuals aged 25-35 years.

- Rimkus and Wolf (1996). Germany (n=14). Samples collected from 8 women, 6 men, in 1993 and 1995.
    - Detection frequency: 100%
    - Range: 28-189 ng/g lipid

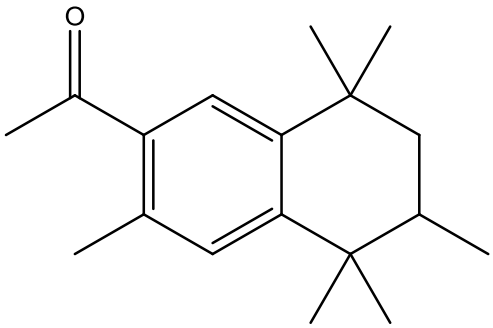
Umbilical cord blood

- Kang et al. (2010). Korea (n=20). Samples collected in 2007.
    - Detection frequency: 70%
    - Geometric mean: 710 ng/g lipid
    - Range: 670-2700 ng/g lipid

7-Acetyl-1,1,3,4,4,6-hexamethyltetrahydronaphthalene
AHTN

1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)ethanone

CASRN: 1506-02-1, 21145-77-7



Exposure or potential exposure to the public or specific subgroups:

AHTN has been found in personal care products such as perfumes, body lotions and creams, deodorants, and shampoos and conditioners. AHTN has also been detected in household items like furniture polish, laundry detergent and fabric softener. Reiner and Kannan (2006) analyzed 60 consumer products from the U.S. (New York) and found AHTN in a number of products, including many products that also contained HHCB. AHTN was found less often than HHCB and levels were, in most cases, lower than for HHCB. In one perfume sample the level of AHTN was 451 µg/g (compared to 1010 µg/g HHCB). In one sample of body cream, the AHTN concentration was 145 µg/g; in that same sample, HHCB levels were 2070 µg/g and HHCB-lactone was found to be 217 µg/g. In one deodorant sample, AHTN was 438 µg/g (HHCB levels were 2250 µg/g). Reiner and Kannan (2006) also found AHTN in samples of furniture polish (16.7 µg/g), laundry detergent (34.2 µg/g), fabric softener (47.1 µg/g), and stain remover (2.46 µg/g).

Production/import volume reported to the U.S. EPA was 10,000-500,000 lbs from 1986-1994 and 1-10 million lbs in 1998. There were no reports in 2002 or 2006 (U.S. EPA, 2002; 2006). Volume of use was listed as Confidential Business Information (CBI) in U.S. EPA's 2012 Chemical Data Reporting system (U.S. EPA, 2012a). IFRA-NA (2013) reported 2011 volume of use for North America as 100-150 metric tons (220,000-

330,000 lbs). AHTN is listed on Proctor and Gamble's website as a musk used in its products.

AHTN was found in 100% of house dust samples from a Canadian study (n=49). Dust samples were collected by researchers ("fresh dust" or FD) and from personal home vacuum cleaners ("house dust" or HD). Maximum AHTN levels were 1.99 µg/g (FD) and 2.36 µg/g (HD). Median levels were 0.552 µg/g (FD) and 0.405 µg/g (HD) (Kubwabo et al., 2012). In Standard Reference Material (SRM) 2585 (household and motel dust samples from 1993-1994), AHTN levels (1.420±0.169 µg/g) are similar to levels of HHCB (1.220±0.143 µg/g dust) (Kubwabo et al., 2012). Fromme et al. (2004) found a median AHTN level of 0.9 µg/g in household dust samples from Berlin, Germany. AHTN was detected in 98.9% of house dust in China, at a median level of 0.0172 µg/g (Lu et al., 2011). Like HHCB, AHTN has been found in indoor air (Sofuoglu et al., 2010; Fromme et al., 2004).

The major environmental source of AHTN is from the discharge of wastewater treatment plant (WWTP) effluent. In a study of effluent-dominated rivers receiving discharge from WWTPs in five U.S. municipalities, AHTN was detected in fish caught at all sampled locations but levels were much lower in fish near municipalities with more advanced wastewater treatment (Ramirez et al., 2009). Mean tissue concentrations ranged from 60 ng/g to 240 ng/g, excluding one municipality for which a mean level was not calculated (only one detect [21 ng/g] in six composite fish samples).

According to Peck and Hornbuckle (2006), the primary removal process for AHTN during wastewater treatment is via adsorption to sludge (biosolids). Levels in biosolids measured by Difrancesco et al. (2004) in 2002 from two different WWTPs were reported as 8.1±1.6 µg/dry g and 17.7±2.2 µg/dry g.

Low levels of AHTN were also detected in a drinking water treatment plant in Iowa. At that plant, the removal efficiency was greater for AHTN compared to HHCB. For AHTN, average removal efficiency ranged from 79% in cold weather to 89% under warm weather conditions (Wombacher and Hornbuckle, 2009). AHTN was among the chemicals tentatively identified in run-off from agricultural crops treated with WWTP effluent in Ventura County, Southern California (Pedersen et al., 2005).

AHTN has been detected at low levels (approximately 1-2 ng/g wet weight) in marine mammals and other aquatic wildlife in U.S. waters (Kannan et al., 2005)

AHTN was found in oysters and mussels in the San Francisco Bay. In sampling in 2002 and 2003, median AHTN levels were 157 ng/g dry weight and 110.2 ng/g in oysters (n=5) and mussels (n=7), respectively. AHTN was not found in two sampled clams

(Hoenicke et al., 2007). In samples collected in 2009-2010 from the San Francisco Bay, AHTN was found in 24/39 mussels, with a maximum of 519 ng/g wet weight (reported in Klosterhaus et al., 2013).

Potential to biomonitor:

Physical and chemical properties (SRC, 2013):
Molecular weight: 258.41
Vapor pressure: 5.12×10^{-4} mm Hg
Water solubility: 1.25 mg/L at 25°C
Octanol/water partition coefficient (log K_{ow}): 5.7

Persistence:

DiFrancesco et al. (2004) monitored the decrease in AHTN levels over time in four different soils amended with sludge containing AHTN. AHTN was one of two fragrance chemicals (out of 22) still detected in soil after one year. Buerge et al. (2003) found that AHTN underwent rapid photochemical degradation in lake and distilled water. Photolysis was also found to be the predominant mode of elimination of AHTN from lake water in Zurich, Switzerland during summer months. Peck et al. (2008) reported that the ratio of HHCB/AHTN in Lake Ontario sediment was approximately 28, which they suggest is consistent with the greater photolysis of AHTN.

EC (2008b) concluded that AHTN may be considered “inherently biodegradable” and did not meet EC’s criteria for persistence. However, EC also indicated that AHTN has similar or longer half-lives compared to HHCB. As noted above, there is evidence of persistence for HHCB under OEHHA (2012) criteria.

Bioaccumulation:

Dietrich and Hitzfeld (2004) reported a range of experimental bioconcentration factors (BCFs) and bioaccumulation factors (BAFs), reported on a wet-weight basis. The reported BCFs were 600 in zebrafish, 597 in bluegill sunfish, and 1069 in eel. On a lipid weight basis, the BCF in eel was reported as 5017. Reported BAFs ranged from 40 to 670. Using lipid-based BAFs, Gatermann et al. (2002) found a wide range of values that were dependent both on lipid content of the fish and the extent of AHTN metabolism in the particular species. EC (2008b) reported that the range of BCFs and BAFs did not meet the EC criterion for bioaccumulation (>2000). OEHHA (2012) considers a BCF or BAF > 1000 or a log $K_{ow} \geq 4$ as evidence of potential bioaccumulation. The log K_{ow} of 5.7 and the range of BCFs shown above suggest a potential for AHTN to bioaccumulate in some species.

Past biomonitoring studies:
AHTN has been measured in blood, breast milk, adipose tissue and umbilical cord blood. Few studies, however, have been conducted in the U.S. Selected studies are summarized below, organized by biological media. Units of measurement vary by publication. In this document, all values are reported in ng (e.g., ng/g lipid, ng/L).

Whole blood

- Den Hond et al. (2013). Belgium (n=204), ages 14-15 years old. Samples collected in 2008- 2009.
  - Detection frequency: 92.2%
  - Geometric mean: 118 ng/L
  - Median: 127 ng/L
  - Range: 20-307 ng/L
  - Blood AHTN was significantly increased with increased use of personal care products and higher educational level of the adolescents.

Plasma

- Hu et al. (2010). 11 cities in China (n=204). Adults (94 females, 110 males), at ages ranging from 17-75; median age 25.
  - Detection frequency: 77%
  - Median: 530 ng/L
  - Maximum concentration: 1290 ng/L
  - A significant positive relationship was found between levels of HHCB and AHTN.

- Hutter et al. (2010). Austria (n=53). Women older than 50 years.
  - Detection frequency: 19%
  - Maximum concentration: 290 ng/L

- Hutter et al. (2005; 2009). Austria (n=100). Adults (55 females; 45 males), ages 19-43 years.
  - Detection frequency: 16%
  - Maximum concentration: 800 ng/L
  - Study found that younger age and use of lotion and perfume were positively correlated with higher levels of polycyclic musks as a group.

Serum

- Kang et al. (2010). Korea. Samples collected from pregnant women, one day before delivery (n=20), in 2007. This study also measured AHTN in breast milk and umbilical cord serum.

  - Detection frequency: 35%
  - Geometric mean: 17 ng/g lipid
  - Range: <17-140 ng/g lipid

Breast Milk

- Kang et al. (2010) Korea (n=17). Samples collected 3-10 days after delivery, in 2007.
  - Detection frequency: 65%
  - Geometric mean: 24 ng /g lipid
  - Range: 15-91 ng g/g lipid

- Ueno et al. (2009). Japan. Five nursing mothers; 5 samples collected monthly from each donor, in 2006-2008; 20 samples analyzed.
  - Detection frequency: 30%
  - Range: <50-190 ng/g lipid

- Kuklenyik et al. (2007). Atlanta, GA. Methods development study. Samples collected from 26 anonymous nursing mothers, in 2004.
  - Detected frequency: 19% (5/26)
  - Calculated range: 26.4-41.4 ng/g lipid. Authors assumed 1.74% lipid content in milk.

- Reiner et al. (2007). Massachusetts (n=39). Samples collected in 2004.
  - Mean: 46.8 ng/g lipid
  - Range: <5-144 ng/g lipid
  - Maternal age was not correlated with levels of AHTN
  - Study found a trend of decreasing AHTN levels with the number of children previously breast-fed, although the correlation was not significant.

- Lignell et al. (2008). Sweden (n=101). Samples collected from primiparous mothers during the 3rd week after delivery, in 1996-2003.
  - Detection frequency: 74%
  - Median: 10.4 ng/g lipid
  - Range: <3.0-53.0 ng/g lipid
  - Study found that women who reported use of perfumed laundry detergent had elevated concentrations of AHTN.

- Duedahl-Olesen et al. (2005). Denmark (n=10). Samples collected from primiparous mothers 14-26 weeks after delivery, in 1999.
    - Detection frequency: 100%
    - Median: 17.5 ng/g lipid
    - Range: 5.58-37.9 ng/g lipid

- Rimkus and Wolf (1996). Germany. Samples from 4 nursing mothers; one mother provided two samples.
    - Detection frequency: 100%
    - Range: 11- 58 ng/g lipid

Adipose tissue

- Moon et al. (2012). Korea. Samples collected from 43 female patients (age range, 40-70 years) undergoing laparoscopy surgery for myoma, in 2007-2008.
    - Detection frequency: 81%
    - Mean: 12 ng/g lipid
    - Range: <2.0-51 ng/g lipid
    - Study did not find a correlation between age and levels of total synthetic musks.

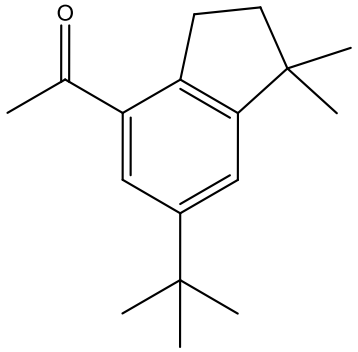
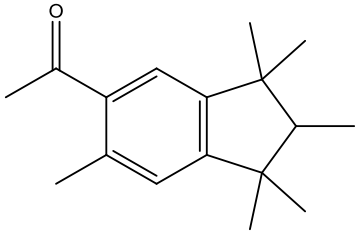
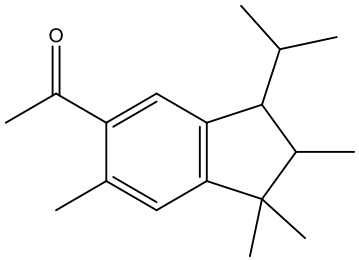
- Schiavone et al. (2010). Italy (n=12). Samples collected from surgical patients (9 male, 3 female), in 2005-2006.
    - Detection frequency: 83%
    - Mean: 132 ng/g lipid
    - Range: <5-931 ng/g lipid

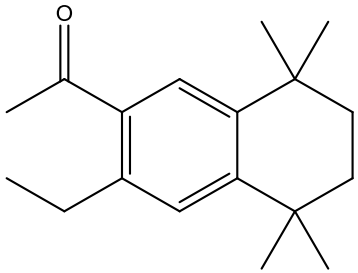
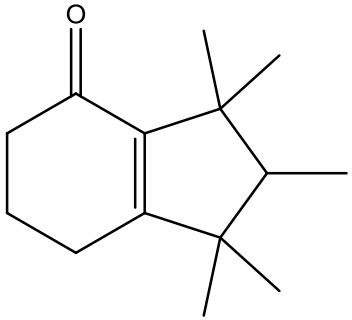
- Kannan et al. (2005). New York City (n=49). Samples from patients who underwent liposuction, in 2003-2004.
    - Detection frequency: 86%
    - In male subjects (n=12)
        - Median: 31.5 ng/g lipid
        - Range: <8-110 ng/g lipid
    - In female subjects (n=37)
        - Median: 38.7 ng/g lipid
        - Range: <8-134 ng/g lipid
    - Study found that levels of AHTN and HHCB did not increase with age and were higher in individuals aged 25-35 years.

- Rimkus and Wolf (1996). Germany (n=14). Samples collected from 8 women, 6 men, in 1993 and 1995.
    - Detection frequency: 100%
    - Range: 8-33 ng/g lipid

Umbilical cord serum

- Kang et al. (2010). Korea (n=20). Samples collected in 2007.
    - Detection frequency: 15%
    - Geometric mean: 430 ng/g lipid
    - Range: <670-2700 ng/g lipid

Other Synthetic Polycyclic Musks	Structure	Indication of Use
ADBI (4-Acetyl-1,1-dimethyl-6-*tert*-butylindan) Celestolide® CASRN 13171-00-1 1-[6-(1,1-Dimethylethyl)-2,3-dihydro-1,1-dimethyl-1*H*-inden-4-yl]ethanone		Production/import volume: 10-500K from 1986 to 2002 (U.S. EPA, 2002); no records after 2002 (U.S. EPA, 2006; 2012a) Available on-line (see for example: http://shop.perfumersapprentice.com/p-6026-celestolide-crystals-i.aspx) Detected in mussels collected from the San Francisco Bay (5/39 [13%]; maximum concentration 93 ng/g dry weight) (as reported by Klosterhaus et al., 2013).
AHMI (6-Acetyl-1,1,2,3,3,5-hexamethylindane) Phantolide® CASRN 15323-35-0 1-(2,3-Dihydro-1,1,2,3,3,6-hexamethyl-1*H*-inden-5-yl)ethanone		Production/import volume: no records (U.S. EPA, 2002; 2006; 2012a) Suppliers identified (see for example: http://www.thegoodscentscompany.com/data/rw1000831.html)
ATII (5-Acetyl-1,1,2,6-tetramethyl-3-isopropylindan) Traseolide® CASRN 68140-48-7 1-[2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1*H*-inden-5-yl]ethanone		Production/import volume: 10-500K lbs (1986-2002) (U.S. EPA, 2002); no records after 2002 (U.S. EPA, 2006; 2012a) Suppliers identified (see for example: http://www.thegoodscentscompany.com/data/rw1023772.html)

Other Synthetic Polycyclic Musks	Structure	Indication of Use
AETT (Acetylethyltetramethyltetralin) Versalide® CASRN 88-29-9 1-(3-Ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethanone		Production/import volume: no records (U.S. EPA, 2002; 2006; 2012a) Use prohibited by IFRA (2013). Detected in mussels collected from the San Francisco Bay (3/39 [8%]; maximum concentration 56 ng/g dry weight) (as reported by Klosterhaus et al., 2013).
DPMI (6,7-Dihydro-1,1,2,3,3-pentamethyl-4[5H]indanone) Cashmeran® CASRN 33704-61-9 1,2,3,5,6,7-Hexahydro-1,1,2,3,3-pentamethyl-4*H*-inden-4-one		Production/import volume: 10-500K lbs (1986-2002) (U.S. EPA, 2002); no records in 2006 (U.S. EPA, 2006); CBI in 2012 (2012a) Supplier identified (see for example http://yaoshitanye.en.alibaba.com/product/701657917-215381462/1_2_3_5_6_7_hexahydro_1_1_2_3_3_pentamethyl_4H_inden_4_one.html)

References Consulted (not all references are cited in this document):

Anderson, P, Denslow, N, Drewes, J, Olivieri, A et al. (2012). Monitoring strategies for chemicals of emerging concern (CECs) in California's aquatic ecosystems - recommendations of a science advisory panel. Technical report 692. Southern California Coastal Water Research Project, Costa Mesa, CA.

Aschmann S, Arey J, Atkinson R, Simonich S (2001). Atmospheric lifetimes and fates of selected fragrance materials and volatile model compounds. *Environ Sci Technol* 35:3595-3600.

Benotti M, Trenholm R, Vanderford B, Halady J (2009). Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. *Environ Sci Technol 43:597-603.*

Bitsch N, Dudas C, Korner W, Failing K et al. (2002). Estrogenic activity of musk fragrances detected by the E-Screen assay using human MCF-7 cells. *Arch Environ Contam Toxicol* 43:257-264.

Buerge I, Buser H-R, Muller M, Poiger T (2003). Behavior of the polycyclic musks HHCB and AHTN in lakes, two potential anthropogenic markers for domestic wastewater in surface waters. *Environ Sci Technol* 37:5635-5644.

Christian MS, Parker RM, Hoberman AM, Diener RM, Api AM (1999). Developmental toxicity studies of four fragrances in rats. *Toxicol Lett* 111:169-174.

Correia P, Cruz A, Santos L, Alves A (2013). Human dermal exposure to galaxolide from personal care products. *Int J Cosmet Sci* 35: 299–309.

Den Hond E, Paulussen M, Geens T, Bruckers L et al. (2013). Biomarkers of human exposure to personal care products: Results from the Flemish Environment and Health Study (FLEHS 2007-2011). *Sci Tot Environ* 463-464:102-110.

Dietrich D, Hitzfeld B (2004). Bioaccumulation and ecotoxicity of synthetic musks in the environment. First published in The Handbook of Environmental Chemistry 3. pp. 233-244.

DiFrancesco A, Chiu P, Standley L, Allen H, Salvito D (2004). Dissipation of fragrance materials in sludge-amended soils. *Environ Sci Technol* 38:194-201.

Dodson R, Nishioka M, Standley L, Perovich L, et al. (2012). Endocrine disruptors and asthma-associated chemicals in consumer products. *Environ Health Persp* 120: 935-943.

Duedahl-Olesen L, Cederberg T, Pedersen K, Hojgard A (2005). Synthetic musk fragrances in trout from Danish fish farms and human milk. *Chemosphere* 61:422-431.

European Commission (EC, 2008a). European Union risk assessment report for 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-a-2-benzopyran (1,3,4,6,7,8,-hexahydro-4,6,6,7,8,8-hexamethylin-den[5,6-C]pyran-HHCB), CAS No. 1222-05-5, EINECS No. 214-916-9. Risk Assessment. Final Approved Version. The Netherlands. European Commission. Office for Official Publications of the European Communities, Luxembourg. Available at: http://echa.europa.eu/documents/10162/947def3b-bbbf-473b-bc19-3bda7a8da910

European Commission (EC, 2008b). European Union Risk Assessment Report. 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (AHTN). CAS No: 1506-02-1 or 21145-77-7, EINECS No: 216-133-4 or 244-240-6, Risk Assessment. Final Approved Version. The Netherlands. European Commission. Office for Official Publications of the European Communities, Luxembourg. Available at: http://echa.europa.eu/documents/10162/26e223a9-eda9-4e79-8c4d-650d2a3c1124

European Commission (EC, 2002). Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers concerning Hexahydrohexamethylcyclopenta(2-benzopyran) (HHCB) adopted by the SCCNFP during the 21st plenary meeting of 17 September 2002. European Commission. Available at: http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out179_en.pdf

Epel D, Luckenbach T, Stevenson C, Macmanus-Spencer L et al. (2008). Efflux transporters: Newly appreciated roles in protection against pollutants: Cellular "bouncers" help keep toxicants out of cells, but anthropogenic chemicals can circumvent or overwhelm this defense. *Environ Sci Technol* 42: 3914-3920.

Fromme T, Lahrz T, Poloty M Gebhart H et al. (2004). Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Germany). *Indoor Air* 14:188-195.

Gatermann R, Biselli S, Huhnerfuss H, Rimkus G (2002). 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 42: 437-446.

Human and environmental risk assessment on ingredients of household cleaning products (HERA, 2004). HERA risk assessment of HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-y-2-benzopyran and related isomers) (CAS no. 1222-05-5). Version 2.0. October 2004. Available at: http://www.heraproject.com/files/29-HH-04-pcm%20HHCB%20HERA%20Human%20Health%20DISCL%20ed2.pdf

Hoenicke R, Oros D, Oram J, Taberski K (2007). Adapting an ambient monitoring program to the challenge of managing emerging pollutants in the San Francisco Estuary. *Environ Res* 105:132-144.

Hu Z, Shi Y, Niu H, Cai Y et al. (2010). Occurrence of synthetic musk fragrances in human blood from 11 cities in China. *Environ Toxicol Chem* 29:1877-1882.

Hutter H-P, Wallner P, Moshammer H, Hartl W et al. (2005). Blood concentrations of polycyclic musks in healthy young adults. *Chemosphere* 59:487-492.

Hutter H-P, Wallner P, Moshammer H, Hartl W et al. (2009). Synthetic musks in blood of healthy young adults: Relationship to cosmetics use. *Sci Total Environ* 407:4821-4825.

Hutter H-P, Wallner P, Harl W, Uhl M et al. (2010). Higher blood concentrations of synthetic musks in women above fifty years than in younger women. *Int J Hyg Environ Health* 213:124-130.

International Fragrance Association (IFRA). (2013). IFRA Standard 47th Amendment. Available online: http://www.ifraorg.org/en-us/standards#.UmhVbFN34mA. Accessed October 2013.

International Fragrance Association – North America (IFRA-NA, 2013). Letter from Megan Ekstrom (IFRA-NA) to Sara Hoover (OEHHA). Re: Submission of Documents Related to Musks. June 3, 2013.

Kallenborn R, Gatermann R, Rimkus G (1999). Synthetic musks in environmental samples: indicator compounds with relevant properties for environmental monitoring. *J Environ Monit* 1:70N-74N.

Kang C, Lee JH, Kim SK et al. (2010). Polybrominated diphenyl ethers and synthetic musks in umbilical cord serum, maternal serum and breast milk from Seoul, South Korea. *Chemosphere* 80:116-122.

Kannan K, Reiner J, Yun S, Perrotta E et al. (2005). Polycyclic musk fragrances in higher trophic level aquatic organisms and humans from the United States. *Chemosphere* 61:693-700.

Kinney C, Furlong E, Zaugg S, Burkhard M et al. (2006). Survey of organic wastewater contaminants in biosolids destined for land application. *Environ Sci Technol* 40:7207-7215.

Klosterhaus S, Yee D, Sedlak M, Wong A, Sutton R (2013). Contaminants of emerging concern in San Francisco Bay: Summary of occurrence data and identification of data gaps. RMP Contribution 698. San Francisco Estuary Institute, Richmond CA. 121 pp. Available at: http://www.sfei.org/documents/contaminants-emerging-concern-san-francisco-bay-summary-occurrence-data-and-identification

Kubwabo C, Fan X, Rasmussen P, Wu F (2012). Determination of synthetic musk compounds in indoor house dust by gas chromatography-ion trap mass spectrometry. *Anal Bioanal Chem* 404:467-477.

Kuklenyik Z, Bryant X, Needham, L, Calafat A (2007). SPE/SPME-GC/MS approach for measuring musk compounds in serum and breast milk. *J Chromatogr B* 858:177-183.

Li Z, Yin N, Liu Q, Wang C et al. (2013). Effects of polycyclic musks HHCB and AHTN on steroidogenesis in H295R cells. *Chemosphere* 90:1227-1235.

Lignell S, Darnerud P, Aune M, Cnattingius S et al. (2008). Temporal trends of synthetic musk compounds in mother's milk and associations with personal use of perfumed products. *Environ Sci Technol* 42:6743-6748.

Llompart M, Celeiro M, Lamas J, Sanchez-Prado L (2013). Analysis of plasticizers and synthetic musks in cosmetic and personal care products by matrix solid-phase dispersion gas chromatography-mass spectrometry. *J Chromatogr A* 1293:10-19.

Lu Y, Yuan T, Wang W, Kannan K (2011). Concentrations and assessment of exposures to siloxanes and synthetic musks in personal care products from China. *Environ Pollut* 159:3522-3528.

Lu Y, Yuan T, Yun S, Wang W, Kannan K (2011). Occurrence of synthetic musks in indoor dust from China and implications for human exposure. *Arch Environ Contam Toxicol* 60:182-189.

Luckenbach T, Epel D (2005). Nitromusk and polycyclic musk compounds as long-term inhibitors of cellular xenobiotic defense systems mediated by multidrug transporters. *Environ Health Perspect* 113:17-24.

Moon H-B, Lee K-H, Lee Y, Kannan K (2012). Occurrence and accumulation patterns of polycyclic aromatic hydrocarbons and synthetic musk compounds in adipose tissues of Korean females. *Chemosphere* 86:485-490.

Mori T, Iida M, Ishibashi H, Kohra S et al. (2007). Hormonal activity of polycyclic musks evaluated by reporter gene assay. *Environ Sci* 14:195-202.

Nakata H (2005). Occurrence of synthetic musk fragrances in marine mammals and sharks in Japanese coastal waters. *Environ Sci Technol* 39:3430-3434.

Nakata H, Shinohara R-I, Nakazawa Y, Isobe T et al. (2012). Asia-Pacific mussel watch for emerging pollutants: Distribution of synthetic musks and benzotriazole UV stabilizers in Asian and US coastal waters. *Mar Pollut Bull* 64:2211-2218.

OEHHA (2012). Title 22, California Code of Regulations. Chapter 54. Green Chemistry Hazard Traits for California's Toxics Information Clearinghouse. Available at: http://oehha.ca.gov/multimedia/green/pdf/GC_Regtext011912.pdf

Osemwengie L, Gerstenberger S. (2004). Levels of synthetic musk compounds in municipal wastewater for potential estimation of biota in receiving waters. *J Environ Monit* 6:533-539.

Peck A, Hornbuckle K (2006). Environmental sources, occurrence, and effects of synthetic musk fragrances. *J Environ Monit* 8:874-879.

Peck A, Hornbuckle K (2004). Synthetic musk fragrances in Lake Michigan. *Environ Sci Technol* 38: 367-382.

Peck A, Linebaugh E, Hornbuckle K (2006). Synthetic musk fragrances in Lake Erie and Lake Ontario sediment cores. *Environ Sci Technol* 40:5629-5635.

Pedersen J, Soliman M, Suffet I (2005). Human pharmaceuticals, hormones, and personal care product ingredients in runoff from agricultural fields irrigated with treated wastewater. *J Agr Food Chem* 53:1625-1632.

Proctor & Gamble (2013). Musk ingredients. Available at: http://www.pgbeautygroomingscience.com/musk-ingredients.php. Accessed October 2013.

Ramierz A, Brain R, Usenko S, Mottaleb M et al. (2009). Occurrence of pharmaceuticals and personal care products in fish: Results of a national pilot study in the United States. *Environ Toxicol Chem* 28:2587-2597.

Reiner J, Kannan K (2006). A survey of polycyclic musks in selected household commodities from the United States. *Chemosphere* 62:867-863.

Reiner J, Wong C, Arcaro K, Kannan K (2007). Synthetic musk fragrances in human milk from the United States. *Environ Sci Technol* 41:3815-3820.

Rimkus G, Wolf M (1996). Polycyclic musk fragrances in human adipose tissue and human milk. *Chemosphere* 33:2033-2043.

Rimkus G. (1999). Polycyclic musk fragrances in the aquatic environment. *Toxicol Lett* 111:37-56.

Roosens L, Covaci A, Neels H (2007). Concentrations of synthetic musk compounds in personal care and sanitation products and human exposure profiles through dermal application. *Chemosphere* 69:1540-1547.

Schiavone A, Kannan K, Horii Y, Focardi S, Corsolini S (2010). Polybrominated diphenyl ethers, polychlorinated naphthalenes and polycyclic musks in human fat from Italy: Comparison to polychlorinated biphenyls and organochlorine pesticides. *Environ Pollut* 158:599-606.

Schlumpf M, Kypke K, Wittassek M, Angerer J et al. (2010). Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: Correlation of UV filters with use of cosmetics. *Chemosphere* 81:1171-1183.

Schnell S, Martin-Skilton R, Fernandes D, Porte C (2009). The interference of nitro- and polycyclic musks with endogenous and xenobiotic metabolizing enzymes in carp: an in vitro study. *Environ Sci Technol* 43:9458-9464.

Schreurs R, Legler J, Artola-Garciano, Sinnige T (2004). *In vitro* and *in vivo* antiestrogenic effects of polycyclic musks in zebrafish. *Environ Sci Technol* 38:997-1002.

Schreurs R, Quaedackers M, Seinen W, van der Burg B (2002). Transcriptional activation of Estrogen Receptor ERα and ERβ by polycyclic musks is cell type dependent. *Toxicol Appl Pharmacol* 183:1-9.

Schreurs R, Sonneveld E, Jansen J, Seinen, W, van der Burg B (2005). Interaction of polycyclic musks and UV filters with the estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR) in reporter gene bioassays. *Toxicol Sci* 83:264-272.

Seinen W, Lemmen J, Pieters R, Vergruggen E, van der Burg (1999). AHTN and HHCB show weak estrogenic – but no uterotrophic activity. *Toxicol Lett* 111:161-168.

Shi J, Li M, Jiao Z, Zhang J et al. (2013). Microarray analysis of gene expression in mouse (Strain 129) embryonic stem cells after typical synthetic musk exposure. *Bull Environ Contam Toxicol* 90:17-21.

Simmons D, Marlatt V, Trudeau V, Sherry J, Metcalfe C (2010). Interaction of Galaxolide with the human and trout estrogen receptor-α. *Sci Total Environ* 408:6158-6164.

Sofuoglu A, Kiymet N, Kavcar P, Sofuoglu S (2010). Polycyclic and nitro musks in indoor air: a primary school classroom and a women's sport center. *Indoor Air* 20:515-522.

SRC (Syracuse Research Corporation) (2013). PhysProp Database. Available at: http://esc.srcinc.com/fatepointer/search.asp. Accessed October 2013.

Ueno D, Moribe M, Inoue K, Somey T et al. (2009). Synthetic musk fragrances in human breast milk and adipose tissue from Japan. In *Interdisciplinary Studies on Environmental Chemistry – Environmental Research in Asia.* Eds. Obayashi Y, Isobe T, Subramanian, Suzuki S, Tanabe S. pp. 247-252.

U.S. Environmental Protection Agency (U.S. EPA, 2002). Non-Confidential Inventory Update Reporting Production Volume Information. Toxic Substances Control Act (TSCA) Inventory. Available at: http://www.epa.gov/cdr/tools/data/2002-vol.html

U.S. EPA (2006). Non-Confidential 2006 Inventory Update Reporting Company/Chemical Records. Toxic Substances Control Act (TSCA) Inventory. Available at: http://cfpub.epa.gov/iursearch/index.cfm

U.S. EPA (2012a). 2012 Chemical Data Reporting (CDR) Results. Available at: http://www.epa.gov/cdr/pubs/guidance/cdr_factsheets.html

U.S. EPA (2012b). Endocrine Disruptor Screening Program. Universe of Chemicals. Jointly developed by the Office of Chemical Safety & Pollution Prevention, the Office of Water, and the Office of Research and Development. Available at: http://www.epa.gov/endo/pubs/edsp_chemical_universe_list_11_12.pdf

U.S. EPA (2012c). EPA Fragrance Ingredient List. Available at: http://www.epa.gov/opprd001/inerts/fmaingredient.pdf.

van der Burg B, Schreurs R, van der Linden S, Seinen W et al. (2008). Endocrine effects of polycyclic musks: do we smell a rat? *Int J Androl* 31:188-193.

Wombacher W, Hornbuckle K (2009). Synthetic musk fragrances in a conventional drinking water treatment plant with lime softening. *J Environ Eng (New York)* 135:1192.

Wang H, Zhang J, Gao F, Yang Y et al. (2011) Simultaneous analysis of synthetic musks and triclosan in human breast milk by gas chromatography tandem mass spectrometry. *J Chromatogr B* 879:1861-1869.

Yin J, Wang H, Zhang J, Zhou N, et al. (2012). The occurrence of synthetic musks in human breast milk in Sichuan, China. *Chemosphere* 87:1018-1023.

Zhang X, Liang G, Zeng X, Zhou J, et al. (2011) Levels of synthetic musk fragrances in human milk from three cities in the Yangtze River Delta in Eastern China. *J Environ Sci* 23:983-990.