Tetramethyl Acetyloctahydronaphthalenes

Materials for November 14, 2013 Meeting of the 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 "tetramethyl acetyloctahydronaphthalenes," which is the chemical group name for Iso E Super® and related isomers. The beta isomer, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone, is commonly referred to as OTNE. The National Toxicology Program (NTP, 2013) reported that the beta isomer is the major component (40-60%) of most commercial mixtures.

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

Tetramethyl acetyloctahydronaphthalenes are combined in various ratios to create fragrances described as woody, floral, or amber scented, commonly marketed under the name "Iso E Super®." Other names include "Timbersilk™", "Amberonne", "Isocyclemone E", "Iso Amber Super" (International Flavors and Fragrances [IFF], 2013; Good Scents Company Information System, 2013). Tetramethyl acetyloctahydronaphthalenes are also used as masking agents and skin conditioners (European Commission Cosmetic Ingredients database, 2013).

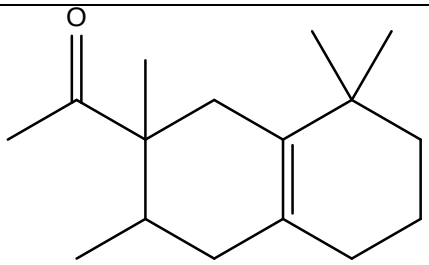
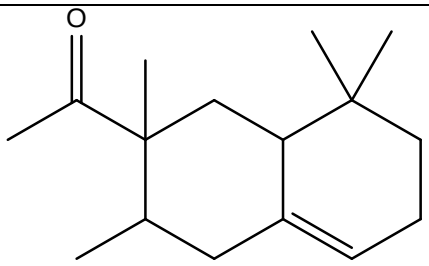
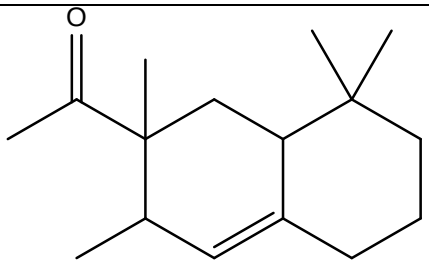
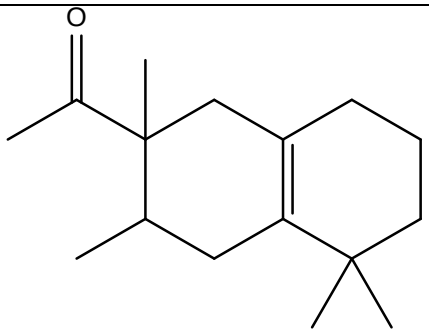
[1] California Environmental Contaminant Biomonitoring Program codified at Health and Safety Code section 105440 et seq.

The U.S. Environmental Protection Agency (U.S. EPA, 2012a, b) has identified four tetramethyl acetyloctahydronaphthalenes for risk assessment under the 2013-2014 Toxic Substances Control Act (TSCA) Work Plan. The International Fragrance Association (IFRA, 2009; 2013) has placed restrictions on the use of OTNE.

Exposure or potential exposure to the public or specific subgroups:

Exposure to tetramethyl acetyloctahydronaphthalenes occurs via dermal contact and inhalation during use of consumer products containing these compounds. These chemicals may also be found in dust, so exposure via ingestion is also possible (Kubwabo et al., 2012). Examples of products containing these aroma chemicals include cologne, perfume, soap, shampoo, body lotion, shower gels, air fresheners, detergent, household cleaners, and fabric softener (Kubwabo et al., 2012; NTP, 2001). Simonich et al. (2000; 2002) noted that the primary route of these materials into the environment is through the down-the-drain disposal of consumer products. NTP (2001) reported that Iso E Super® is used in tobacco products to improve the aroma and flavor of tobacco and its smoke and in the production of polyurethane foam to control hardness. Current information on these uses was not located.

U.S. production/import volume for four tetramethyl acetyloctahydronaphthalene isomers is shown in the table on the next page.

Chemical	CASRN	Chemical Structure	U.S. Production/Import Volume (lbs)*
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone OTNE beta isomer	54464-57-2		2012: 1M – 10M 2006: 1M – 10M 2002: 1M – 10M 1998: 500K – 1M 1994: 500K – 1M 1990: 500K – 1M 1986: 10K – 500K
1-(1,2,3,4,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone alpha isomer	68155-67-9		2012: CBI** 2006: 1M – 10M 2002: 1M – 10M 1998: 500K – 1M 1994: 10K – 500K 1990: no reports 1986: no reports
1-(1,2,3,5,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone gamma isomer	68155-66-8		2012: CBI 2006: 1M –10M 2002: 500K – 1M 1998: 500K – 1M 1994: 10K – 500K 1990: no reports 1986: no reports
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)ethanone	54464-59-4		2012: CBI 2006: 500K –1M 2002: no reports 1998: no reports 1994: no reports 1990: no reports 1986: no reports

*U.S. Environmental Protection Agency (U.S. EPA) (2002, 2006, 2012c)
**CBI = Confidential Business Information

Tetramethyl acetyloctahydronaphthalenes have been detected in wastewater and sludge (U.S.) and in house dust (Canada). Simonich et al. (2002) found an average level of 3.55 ± 1.93 micrograms per liter (μg/L) for OTNE in influent samples collected from 12 U.S. wastewater treatment plants (including one in Lodi, California) between

1997 and 2000. The authors reported that the percent removal of OTNE from different types of treatment plants varied with treatment plant design, ranging from approximately 29% to over 99%. DiFrancesco et al. (2004) measured OTNE in sludge collected in 2002 from two municipal wastewater treatment plants in Delaware [DE], reporting levels of 7.3 ±1.4 μg/dry gram (Wilmington, DE) and 30.7 ± 3.7 μg/dry gram (Georgetown, DE). The levels of OTNE were comparable to the levels of two widely used polycyclic musks (HHCB[2] and AHTN[3]) (DiFrancesco et al., 2004).

Kubwabo et al. (2012) reported that OTNE was the third most predominant aroma chemical, after HHCB and AHTN, detected in Canadian dust samples (household vacuum dust [abbreviated as HD]; and "fresh dust" [FD], collected from the homes by the researchers). Authors detected OTNE in 82% of the HD samples (n=49) and 94% of the FD samples (n=49). The median value for OTNE in HD samples was 212 nanograms per gram (ng/g) and in FD samples was 252 ng/g.

Known or suspected health effects:

Few toxicological data for tetramethyl acetyloctahydronaphthalenes are publicly available.

Politano et al. (2009) studied the developmental toxicity of OTNE. Pregnant Sprague-Dawley rats (25/group) received gavage doses of 0 (water), 96, 240, or 480 milligrams per kilogram of body weight per day (mg/kg-d) on days 7 through 17 of gestation. The authors identified a maternal no observed adverse effect level (NOAEL) of 240 mg/kg-d, based on significant reductions in body weight gain in the 480 mg/kg-d dose group. They identified a developmental NOAEL of 240 mg/kg-d, based on a non-statistically significant reduction in mean fetal body weight at 480 mg/kg-d. Politano et al. (2009) concluded that OTNE was not a developmental toxicant under the conditions of the study.

NTP (2013) completed a short-term toxicity study (dermal application) and an immunotoxicity study on OTNE, but reports are not available on-line. Results of the genetic toxicity studies were negative, with the exception of one equivocal finding in the micronucleus assay in female B6C3F$_1$ mice (NTP, 2013).

Tetramethyl acetyloctahydronaphthalenes are structurally similar to the synthetic polycyclic musk AHTN, which has shown some indications of endocrine activity in several studies (Bitsch et al., 2002; Mori et al., 2007; Schreurs et al., 2002; 2005).

[2] HHCB is 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran
[3] AHTN is 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene

Potential to biomonitor:

Physical and chemical properties

Molecular weight: 258.41 (all isomers)

For OTNE (beta isomer) or Iso E Super®
(as reported by Simonich et al., 2000; ECHA, 2013):
Vapor pressure: 1.5×10^{-3} mm Hg (temperature not specified)
1.7×10^{-3} mm Hg at 23°C
Water solubility: 2.68 mg/L at 20°C
Octanol/water partition coefficient (log K_{ow}): 5.7; 5.6 at 30°C

Persistence and bioaccumulation:
Chen et al. (2009) studied the degradation of OTNE in sludge samples taken from a reed bed water treatment plant. The authors reported that OTNE concentrations were decreased to 42% in the top layer, 53% in the middle layer, and 70% in the bottom layer. Estimated tentative half-lives ranged from 239 – 630 days, depending on the layer. DiFrancesco et al. (2004) monitored the decrease in OTNE levels over time in four different soils amended with sludge containing OTNE. At three months, OTNE was one of seven fragrance chemicals (out of a total of 22 fragrances) present above the quantification limit. OTNE was not detected at 12 months. Ozaki et al. (2011) studied the photodegradation of OTNE in dry loamy sand (a type of soil) under artificial sunlight and reported a half-life of 7 days. Aschmann et al. (2001) concluded that OTNE has a short atmospheric lifetime and is not likely to undergo long-range transport. Assessments compiled by ECHA (2013) concluded that OTNE (or Iso E Super®) is not persistent based on EC criteria. Experimental half-lives available from ECHA (2013) are also below the OEHHA (2012) criteria for persistence.

OEHHA (2012) considers a bioconcentration factor (BCF) > 1000 or a log $K_{ow} \geq 4$ as evidence of potential bioaccumulation. The log K_{ow} of 5.6-5.7 suggests a potential for OTNE to bioaccumulate. However, experimental BCFs available from ECHA (2013) are below 1000. Assessments compiled by ECHA (2013) concluded that OTNE (or Iso E Super®) is not bioaccumulative.

Pharmacokinetics and metabolism:

The European Chemicals Agency (ECHA, 2013) summarized a 2001 unpublished study that detected radiolabeled OTNE in breast milk and plasma samples from rats following oral gavage administration of 2 or 20 mg/kg-d. ECHA provided the study authors' conclusion: "During the 4-24 hours post dosing, plasma radioactivity concentrations at the low and high doses declined by 26-80% and 32-72%, respectively. Radioactivity in milk decreased by >79% at both dose levels by 24 hours post dose indicating a more rapid decline than that of plasma. At the high dose, total radioactivity in plasma and milk was 8-19 times greater than at the low dose. OTNE appeared to be completely metabolised since no detectable levels were found in milk samples taken at 4 and 8 hours."

Guy (2010) reported an experimental dermal absorption value of 15% for OTNE, citing unpublished reports from the Research Institute for Fragrance Materials (RIFM).

Past biomonitoring studies:

Yin et al. (2012) measured OTNE in breast milk collected from 110 mothers (age 19-39) in southwestern China in 2009. OTNE was detected in 34% of the human milk samples; however, concentrations were below the method quantification limit [MQL] of <1.5 ng/g lipid. No other biomonitoring studies were located.

Need to assess efficacy of public health action

Measuring tetramethyl acetyloctahydronaphthalenes would help Biomonitoring California determine whether these chemicals are found in California residents and at what levels, and help track changes in exposure over time.

Availability of analytical methods:

Analytical methods have been published for simultaneous measurement of OTNE (beta isomer) and other synthetic musks (including polycyclic musks HHCB and AHTN) in breast milk using gas chromatography tandem mass spectrometry (GC-MS/MS) (Yin et al., 2012, Wang et al., 2011). Methods could be adapted or developed for the group of tetramethyl acetyloctahydronaphthalenes. The Program laboratory[4] would likely analyze serum samples with GC-MS/MS instrumentation, using electron ionization (EI) and multiple reaction monitoring (MRM). With regard to incremental analytical cost, it

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

appears that tetramethyl acetyloctahydronaphthalenes could be bundled with synthetic polycyclic musks.

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

Agan Aroma and Fine Chemicals Ltd. (2000). MSDS for Amberonne. Available at: http://www.agan-aroma.com/p-amberonne.asp.

Aschmann S, Arey J, Atkinson R, et al. (2001). Atmospheric lifetimes and fates of selected fragrance materials and volatile model compounds. *Environ Sci Technol* 36:3595-3600.

Bester K, Klasmeier J, Kupper T (2008). Emissions of OTNE (Iso-E-super) – Mass flows in sewage treatment plants. *Chemosphere* 71:2003-2010.

Bester K, Hüffmeyer N, Schaub J, et al. (2008). Surface water concentrations of the fragrance compound OTNE in Germany – A comparison between data from measurements and models. *Chemosphere* 73:1366-1372.

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.

Bothe F, Dettmer K, Engewald W (2003). Determination of perfume oil in household products by headspace solid-phase microextraction and fast capillary gas chromotagraphy. *Chromatographia* 57:S119-206.

Chen X, Pauly U, Rehfus S, et al. (2009). Personal care compounds in a reed bed sludge treatment system. *Chemosphere* 76:1094–1101.

Chen X and Bester K (2009). Determination of organic micro-pollutants such as personal care products, plasticizers and flame retardants in sludge. *Anal Bioanal Chem* 395:1877-1884.

DiFrancesco A, Chiu P, Standley L, et al. (2004). Dissipation of fragrance materials in sludge-amended soils. *Enviro Sci Technol* 38:194-201.

European Chemicals Agency (ECHA, 2013). Chemical file for “Reaction Mass of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one and 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one and 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one”. Other names: Iso E Super®, OTNE, 2-acetoxy-2,3,8,8-tetramethyloctahydronaphthalene, Amberonne, Boisvelone, Isocyclemone E, Orbitone, Iso Gamma Super®. Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-a001d05a-8c59-0cab-e044-

00144f67d031/DISS-a001d05a-8c59-0cab-e044-00144f67d031_DISS-a001d05a-8c59-0cab-e044-00144f67d031.html. Accessed October 2013.

European Commission (EC, 2013). Cosmetic Ingredients database (CosIng). Available at: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40504. Accessed October 2013.

Good Scents Company Information System. (2013). Patchouli ethanone. Available at: www.thegoodscentscompany.com/data/rw1020612.html. Accessed October 2013.

Guy R (2010). Predicting the rate and extent of fragrance chemical absorption into and through the skin. *Chem Res Toxicol* 23:864-870.

International Flavors and Fragrances (IFF, 2013). Iso E Super®. Available at: http://fragranceingredients.iff.com/materials/materials.aspx. Accessed October 2013.

International Flavors and Fragrances (IFF, 2013). Timbersilk™ Available at: http://fragranceingredients.iff.com/materials/materials.aspx. Accessed October 2013.

International Fragrance Association (IFRA, 2007). Available at: http://www.ifraorg.org/ Accessed October 2013.

IFRA (2009). IFRA Standard for OTNE (1-(1,2,3,4,5,6,7,8 Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone). 43rd Amendment. Available at: http://www.ifraorg.org/en-us/standards-library/s/OTNE#.UmGCdlN34mA. Accessed October 2013.

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

Klaschka U, Carsten von der Ohe P, Bschorer A, et al. (2013). Occurrences and potential risks of 16 fragrances in five German sewage treatment plants and their receiving waters. *Environ Sci Pollut Res* 20:2456-2471.

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

Mitjans D and Ventura F (2005). Determination of fragrances at ng/L levels using CLSA and GC/MS detection. *Water Sci Technol* 52(10-11):145-150.

Mitjans D and Ventura F (2004). Determination of musk and other fragrances at ng/L levels using CLSA (closed loop stripping analysis) and GC/MS detection. *Water Sci Technol* 52(5):119-123.

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.

National Toxicology Program (NTP, 2001). Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-Tetramethyl-2-Naphthalenyl)- (Iso-E Super [reg]; OTNE) Nomination Background: Review of Toxicological Literature. Available at: http://ntp.niehs.nih.gov/?objectid=BDCCAEF8-123F-7908-7BC26977A3ABF242 (click on Nomination Background to get pdf).

NTP (2013). Testing Status of Agents at NTP: Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-Tetramethyl-2-Naphthalenyl)- (Iso-E Super [reg]; OTNE). Last updated October 14, 2013. Available at http://ntp.niehs.nih.gov/?objectid=BDCCAEF8-123F-7908-7BC26977A3ABF242 Accessed October 2013.

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. Accessed October 2013.

Ozaki N, Bester K, Moldrup P, et al. (2011). Photodegradation of the synthetic fragrance OTNE and the bactericide triclosan adsorbed on dried loamy sand - Results from models and experiments. *Chemosphere* 83(11):1475-1479.

Politano V, Letiza C, Christian M, et al. (2009). Evaluation of the developmental toxicity of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) ethanone (OTNE) in rats. *Int J Toxicol* 28(3):213-218.

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.

Simonich SL, Begley WM, Debaere G, et al. (2000). Trace analysis of fragrance materials in wastewater and treated wastewater. *Environ Sci Technol* 34:959–965.

Simonich SL, Federle TW, Eckhoff WS, et al. (2002). Removal of fragrance materials during U.S. and European wastewater treatment. *Environ Sci Technol* 36:2839–2847.

United States 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 Accessed October 2013.

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. Accessed October 2013.

U.S. EPA (2012a). TSCA Work Plan Chemicals: Methods Document. Available at: http://www.epa.gov/oppt/existingchemicals/pubs/wpmethods.pdf. Accessed October 2013.

U.S. EPA (2012b). Work Plan Chemicals for Assessment during 2013-2014. Available at: http://www.epa.gov/oppt/existingchemicals/pubs/workplanlist.html. Accessed October 2013.

U.S. EPA (2012c). Non-Confidential 2012 Chemical Data Reporting (CDR). Toxic Substances Control Act (TSCA) Inventory. Available at: http://www.epa.gov/oppt/cdr/index.html. Accessed October 2013.

U.S. EPA (2012d). EPA Fragrance Ingredient List. Available at: http://www.epa.gov/opprd001/inerts/fmaingredient.pdf. Accessed October 2013.

U.S. EPA (2012e). 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.

Wang H, Zhang J, Gao F, 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, et al. (2012). The occurrence of synthetic musks in human breast milk in Sichuan, China. *Chemosphere* 87(9):1018-1023.