

# Tetramethyl Acetyloctahydronaphthalenes

Materials for November 14, 2013 Meeting of the Scientific Guidance Panel (SGP)  
Biomonitoring California<sup>1</sup>

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", "Isocyclemon 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).

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<sup>1</sup> 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.

Tetramethyl acetyloctahydronaphthalenes

| Chemical                                                                                            | CASRN      | Chemical Structure | U.S.<br>Production/Import<br>Volume<br>(lbs)*                                                                                    |
|-----------------------------------------------------------------------------------------------------|------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone<br><br>OTNE<br>beta isomer | 54464-57-2 |                    | 2012: 1M – 10M<br>2006: 1M – 10M<br>2002: 1M – 10M<br>1998: 500K – 1M<br>1994: 500K – 1M<br>1990: 500K – 1M<br>1986: 10K – 500K  |
| 1-(1,2,3,4,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone<br><br>alpha isomer       | 68155-67-9 |                    | 2012: CBI**<br>2006: 1M – 10M<br>2002: 1M – 10M<br>1998: 500K – 1M<br>1994: 10K – 500K<br>1990: no reports<br>1986: no reports   |
| 1-(1,2,3,5,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone<br><br>gamma isomer       | 68155-66-8 |                    | 2012: CBI<br>2006: 1M – 10M<br>2002: 500K – 1M<br>1998: 500K – 1M<br>1994: 10K – 500K<br>1990: no reports<br>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<br>2006: 500K – 1M<br>2002: no reports<br>1998: no reports<br>1994: no reports<br>1990: no reports<br>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  $3.55 \pm 1.93$  micrograms per liter ( $\mu\text{g/L}$ ) 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  $7.3 \pm 1.4$   $\mu\text{g/dry gram}$  (Wilmington, DE) and  $30.7 \pm 3.7$   $\mu\text{g/dry gram}$  (Georgetown, DE). The levels of OTNE were comparable to the levels of two widely used polycyclic musks (HHCB<sup>2</sup> and AHTN<sup>3</sup>) (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<sub>1</sub> 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).

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<sup>2</sup> HHCB is 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran

<sup>3</sup> 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:  $1.5 \times 10^{-3}$  mm Hg (temperature not specified)

$1.7 \times 10^{-3}$  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<sup>4</sup> 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

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<sup>4</sup>Environmental Chemistry Laboratory (ECL) of the Department of Toxic Substances Control (DTSC)

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

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