Potential Designated Chemicals

Selected Aroma Chemicals

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What are designated chemicals?

- Chemicals that can be considered for biomonitoring by the Program
- Consist of
  - Chemicals that are part of CDC's National Reports on Human Exposure to Environmental Chemicals program
  - Chemicals that the Scientific Guidance Panel has recommended be added to the list of designated chemicals

Background

November 2012 SGP Meeting:

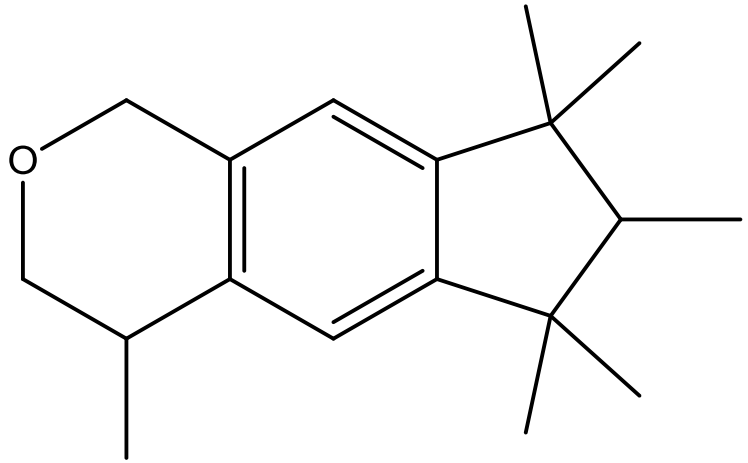
- Presentation on screening of four classes of synthetic musks and a structurally related aroma chemical (Iso E Super®)

- SGP requested documents to support consideration of these aroma chemicals as potential designated chemicals

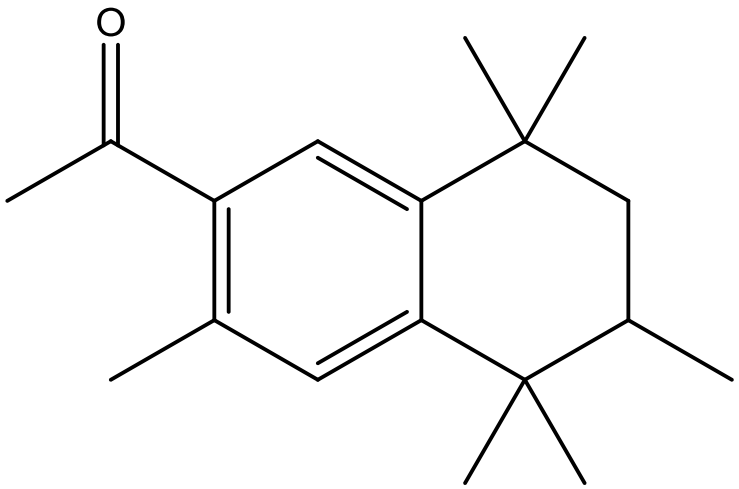
Implementing SGP recommendation

- Two classes for consideration today – structurally similar, common analytical method
  - Synthetic polycyclic musks
  - Tetramethyl acetyloctahydronaphthalenes
- Other classes not under consideration today –
  - Nitro musks – low or no current use
  - For future consideration
    - Macrocyclic musks
    - Alicyclic musks

Polycyclic musks- example structures



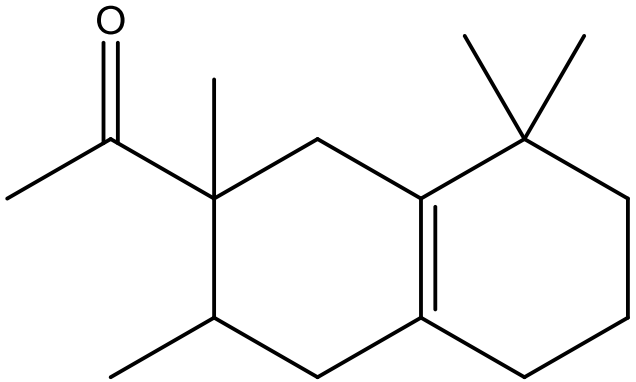
HHCB*
Galaxolide®



AHTN**
Tonalide®

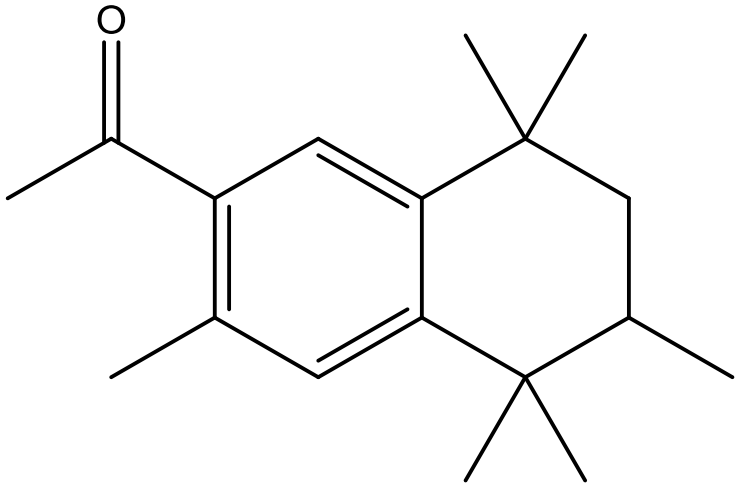
*HHCB: 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran
**AHTN: 7-Acetyl-1,1,3,4,4,6-hexamethyltetrahydronaphthalene

Tetramethyl acetyloctahydronaphthalenes



OTNE*
(beta isomer, Iso-E Super®)

OTNE is structurally similar to some polycyclic musks



AHTN

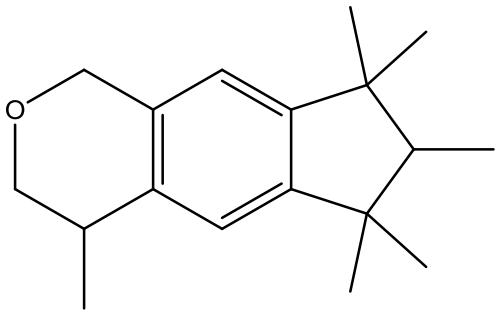
*OTNE: 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone

Criteria for Panel to recommend designated chemicals

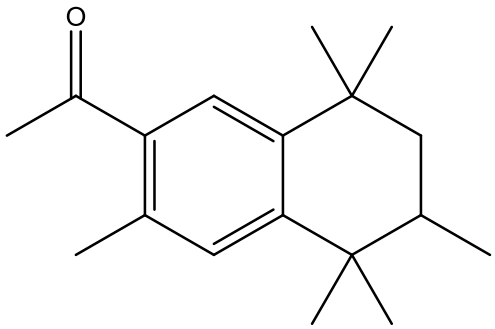
- **Exposure or potential exposure** to the public or specific subgroups
- The **known or suspected health effects** based on peer-reviewed scientific studies
- The **need to assess the efficacy of public health actions** to reduce exposure
- The **availability of a biomonitoring analytical method** with adequate accuracy, precision, sensitivity, specificity, and speed
- The **availability of adequate biospecimen samples**
- The **incremental analytical cost** to perform the biomonitoring analysis for the chemical

Polycyclic musks

- Widely used in personal care products and some cleaning products
- Replacements for nitro musks (e.g., musk xylene)
- Highlighting two – HHCB and AHTN – which have been commercially most important

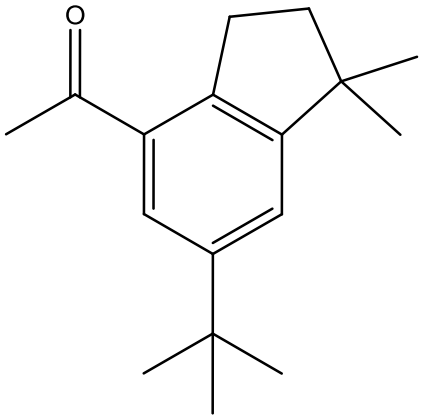


HHCB

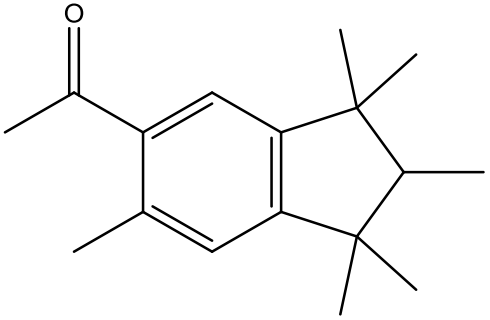


AHTN

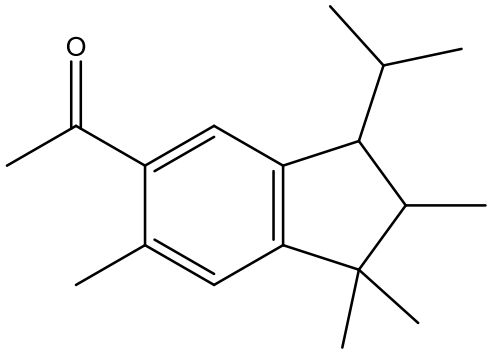
Other polycyclic musks



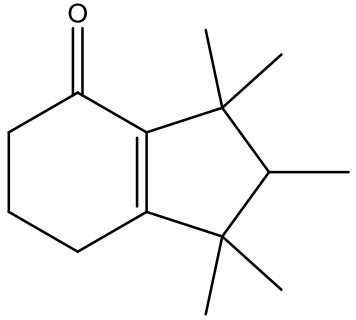
ADBI[1]



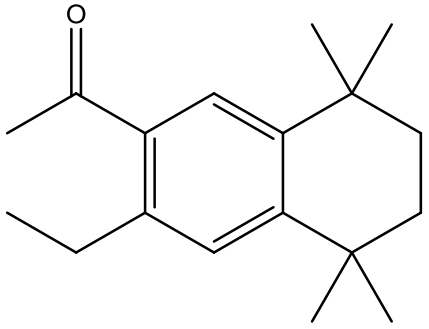
AHMI[2]



ATII[3]



DPMI[4]



AETT[5]

[1] ADBI: (4-Acetyl-1,1-dimethyl-6-*tert*-butylindan)
[2] AHMI: 6-Acetyl-1,1,2,3,3,5-hexamethylindane
[3] ATII : 5-Acetyl-1,1,2,6-tetramethyl-3-isopropylindan
[4] DPMI: 6,7-Dihydro-1,1,2,3,3-pentamethyl-4[5*H*]indanone
[5] AETT: Acetylethyltetramethyltetralin

Polycyclic musks

U.S. Production/Import Volume (pounds)						
	1986	1994	1998	2002	2006	2012
HHCB	500K-1M	1-10M	1-10M	1-10M	1-10M	3.1 M
AHTN	10-500K	10-500K	1-10M	NR	NR	CBI *220-330K
DPMI	10-500K	10-500K	10-500K	10-500K	NR	CBI

Table notes:
Source: U.S. EPA (2002;2006; 2012) unless otherwise noted
NR=not reported; volume is less than U.S. EPA reporting threshold
CBI= Reported as Confidential Business Information
*AHTN volume of use in North America, reported as 220-330K lbs in 2011 (IFRA-NA)

Polycyclic musks
Use and exposure

Personal care products

- Perfumes/fragrances
- Body lotions/body creams
- Deodorants/antiperspirants
- Shower gels/shaving cream
- Shampoo/conditioner products
- Hand soaps/bar soaps

Reiner and Kannan (2006)
Dodson et al. (2012)

Polycyclic musks
Use and exposure

Household products

- Carpet cleaner
- Furniture polish
- Dish soap
- Laundry detergent
- Stain remover
- Fabric softener
- Liquid bleach
- Disinfecting wipes

Reiner and Kannan (2006)
Dodson et al. (2012)

Polycyclic musks: Example levels in personal care products

- HHCB
  - Body splash 4,990 µg/g
  - Body lotion 3,740 µg/g
  - Deodorant 2,250 µg/g
  - Shaving cream 1,230 µg/g
- AHTN
  - Perfume 451 µg/g
  - Deodorant 438 µg/g
  - Body cream 145 µg/g

Reiner and Kannan (2006)

Polycyclic musks: Example levels in consumer products

Personal care products

- Bar soap >100–1000 µg/g (HHCB); >1–100 µg/g (AHTN)
- Hand soap >1–100 µg/g (HHCB, DPMI)

Household cleaning products

- Dish liquid >100–1000 µg/g (HHCB)
- Carpet cleaner >100–1000 µg/g (HHCB)
- Laundry detergent >1–100 µg/g (HHCB, AHTN)
- Dryer sheets >1–100 µg/g (HHCB, AHTN)
- Polish/wax >1– 100 µg/g (HHCB, DPMI)
- Air freshener >1–100 µg/g (HHCB)

Dodson et al. (2012)

Polycyclic musks
Levels in house dust

Samples collected as part of the Canadian House Dust Study, 2007–2010 (n=49)

Household vacuum cleaner dust			
	Detection frequency (%)	**Median** (ng/g)	**Range** (ng/g)
HHCB	100	992	36–31,100
AHTN	100	405	91–2,360

Kubwabo et al. (2012)

Polycyclic musks Environmental occurrence in U.S.

- Main environmental source is effluent from wastewater treatment plants (WWTPs)
  - HHCB and AHTN detected in:
    - fish caught in WWTP effluent waters (sampled in 2006)
    - sewage sludge (biosolids)
    - some drinking water
    - run-off from agricultural fields irrigated with treated wastewater (California)

Polycyclic musks Detections in biota

- Bivalves in San Francisco Bay
  - HHCB, AHTN, ADBI, AETT detected in 2002-2003 sampling
  - HHCB, AHTN, ADBI, AETT detected in mussels in 2009-2010 sampling
- Fish
  - Levels dependent on location, and on metabolism and lipid content of fish
- Marine mammals
  - Finless porpoises (Japan): Level in one porpoise was comparable to level in its fetus

Polycyclic musks
Known or suspected health effects

- Indications of endocrine activity
  - *In vitro*
    - Weak estrogenicity
    - Inhibition of estrogen, androgen, and progesterone activity
    - Decreased progesterone and cortisol synthesis
  - *In vivo*
    - Anti-estrogenicity (transgenic zebrafish, trout)
- Other *in vitro* biological activity
    - AHTN caused changes in the activation of certain signaling pathways (mouse embryonic stem cells)
    - Several polycyclic musks inhibited efflux transporters (mussel gill tissue)

Properties of polycyclic musks

- Lipophilic chemicals

Polycyclic musk	Log K_{ow}
HHCB	5.9*
AHTN	5.7*
ADBI	5.4**
AHMI	5.8**
DPMI	4.5**
AETT	6.4 (*est*)*

- Potential to bioaccumulate in some species
- Some indications of persistence (e.g., experimental studies in soils amended with sludge)

*SRC (2013)
**Cited in Rimkus et al. (1999)

Polycyclic musks
Biomonitoring studies

- Multiple studies in blood, breast milk, adipose tissue (HHCB and AHTN)
- Several studies reported levels increased with use of personal care products
- Most studies from Europe and Asia
- Few studies from the U.S.

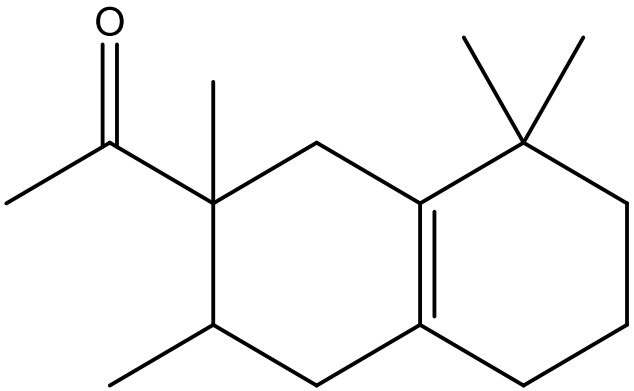
Polycyclic musks Biomonitoring studies

Breast milk – Massachusetts (n=39)

- HHCB: detection frequency: 97%
  - Mean: 220 ng/g lipid
  - Range: <5 – 917 ng/g lipid
- AHTN: detection frequency: 56%
  - Mean: 46.8 ng/g lipid
  - Range: <5-144 ng/g lipid

Reiner et al. (2007)

Tetramethyl acetyloctahydronaphthalenes



OTNE*
(beta isomer, Iso-E Super®)

- Woody, floral, or amber fragrances
- Widely used in personal care products and some cleaning products

*OTNE: 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone

Tetramethyl acetyloctahydronaphthalenes

U.S. Production/Import Volume (pounds)						
	1986	1994	1998	2002	2006	2012
54464-57-2 (beta isomer)	10K-500K	500K-1M	500K-1M	1M-10M	1M -10M	1M -10M
68155-67-9 (alpha isomer)	NR	10K-500K	500K-1M	1M-10M	1M-10M	CBI
68155-66-8 (gamma isomer)	NR	10K-500K	500K-1M	500K-1M	1M-10M	CBI
54464-59-4 ("4th" isomer)	NR	NR	NR	NR	500K-1M	CBI

Source: U.S. EPA (2002;2006;2012)
NR=not reported; volume less than U.S. EPA reporting threshold
CBI= Reported as Confidential Business Information

Tetramethyl acetyloctahydronaphthalenes

Uses and exposure: Examples

- Personal care products
  - Perfume/cologne
  - Soap/shower gels/shampoo
  - Body lotion/skin conditioner

- Cleaning products
  - Air freshener
  - Laundry detergent
  - Fabric softener

Levels of OTNE in house dust

Samples collected as part of the Canadian House Dust Study, 2007–2010 (n=49)

Household vacuum cleaner dust			
	Detection frequency (%)	**Median** (ng/g)	**Range** (ng/g)
OTNE	82	212	nd – 5,620
Compared to polycyclic musks			
HHCB	100	992	36 – 31,100
AHTN	100	405	91 – 2,360

nd = not detected

Kubwabo et al. (2012)

Tetramethyl acetyloctahydronaphthalenes
Environmental occurrence

- Main environmental source is effluent from wastewater treatment plants (WWTPs)
- OTNE detected in:
  - Influent and effluent wastewater
  - Sewage sludge
    - Levels comparable to the polycyclic musks HHCB and AHTN

Tetramethyl acetyloctahydronaphthalenes
Bioaccumulation and persistence

- Bioaccumulation
  - Lipophilic: log K_{ow} >5
  - Experimental BCFs (Bioconcentration Factors) do not suggest bioaccumulation (below 1000)

- Persistence
  - Few published studies
  - No evidence of persistence based on available data

Tetramethyl acetyloctahydronaphthalenes
Known or suspected health effects

- Few toxicological data for tetramethyl acetyloctahydronaphthalenes are publicly available
- Structurally similar to AHTN, which has shown some potential for endocrine and other biological activity

Summary – Polycyclic musks

- High levels in personal care and household cleaning products
- Potential to bioaccumulate in some species
- Potential for endocrine and other biological activity
- Detected in:
  - Various environmental samples, including house dust
  - Human blood, breast milk, adipose tissue samples

Summary – Tetramethyl acetyloctahydronaphthalenes

- OTNE – high production volume chemical
- Detected in dust, wastewater treatment plant influent and effluent, biosolids
- Structurally similar to AHTN

Laboratory analysis

- Methods for analysis of some of these chemicals available in the literature
- Laboratory would develop methods to measure polycyclic musks and tetramethyl acetyloctahydronaphthalenes in serum samples
- Analysis could likely be bundled

Need to assess efficacy of public health actions

- Widespread use of these aroma chemicals in California and in the U.S.

- Biomonitoring would:
  - Determine whether these chemicals are found in California residents and at what levels
  - Track levels over time

Options for the Panel

- Designate: “synthetic polycyclic musks” as a class
- Designate: “tetramethyl acetyloctahydronaphthalenes” as a class
- Postpone decision
- Decide against designating