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

[Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)- (9CI); 7-Acetyl-1,1,6,7-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalene; Amberonne; Iso-E Super¤]

[54464-57-2]

Review of Toxicological Literature

July 2001

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

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[54464-57-2]

Review of Toxicological Literature

Prepared for

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July 2001

EXECUTIVE SUMMARY

1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone, commonly referred to as Iso-E Super¤, is a synthetic terpenoid considered to be a petroleum-derived aroma chemical. Iso-E Super¤ has an odor threshold of 7.33 ppb and a substantivity of 45% on cotton-polyamide (90:10) fabrics treated with softener spiked with several raw fragrance materials. It has been analyzed by gas chromatography (GC) and identified with nuclear magnetic resonance (NMR), mass spectrometry (MS), and infrared spectrometry (IR).

Iso-E Super¤ is produced by International Flavors and Fragrances, Inc. A corresponding product is produced as Boisvelone¤ by Bush Boake Allen Inc. It is available as amberonne from subsidiaries of Makhteshim Agan and as methyl cyclomyrectone from Aedes Co. Iso-E Super¤ is produced commercially by Diels-Alder condensation of β-myrcene with 3-methyl-3-pentene-2-one in the presence of aluminum chloride to give a monocyclic intermediate that is cyclized in the presence of 85% phosphoric acid. Under the 1998 Inventory Update Rule, Bush Boake Allen Inc. and International Flavors and Fragrances Inc. both reported to EPA production/importation values of >10,000 pounds per year.

Iso-E Super¤ is used as a perfume ingredient, providing a sandalwood-like and cedar-like fragrance, in soap, shampoo, cologne, liquid detergent compounds, antimicrobial compounds, and malodor-reducing compounds. It is used in tobacco products to improve not only the aroma but also the flavor of tobacco and its smoke and to control the hardness of polyurethane foam.

For the general population, exposure to Iso-E Super¤ is via inhalation and the skin through the use of products (e.g., fragrances and perfumed personal care products) containing the chemical and via ingestion of water or food containing the chemical as a contaminant. In dermatological patients, two cases of an allergic reaction towards Iso-E Super¤ were observed on day 3 or 4 of application; however, this was not proved to be clinically relevant.

Trace analyses of Iso-E Super¤ in municipal wastewater and treated effluents have been conducted with GC-MS using selected ion monitoring. In an activated sludge and trickling filter wastewater treatment plant in the United States, Iso-E Super¤ influent concentrations were 3.470 and 3.250 g/L, respectively, and final effluent concentrations were 0.110 and 0.334 g/L, respectively. During activated sludge wastewater treatment, primary treatment produced 59% removal, while secondary treatment achieved 97% removal; during trickling filter wastewater treatment, the values were 43 and 90%, respectively.

A petition has been filed with the FDA asking that the fragrance Eternity by Calvin Klein, containing 11.7% Iso-E Super¤ in the fragrance portion of the formula, be declared "misbranded." It is listed in the TSCA Inventory under the 9CI name and in several comparable international lists under this name, the INCI (International Nomenclature for Cosmetic Ingredients) name 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8,-tetramethyl-2-naphthyl)ethan-1-one, and 1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-aceto-naphthalenone.

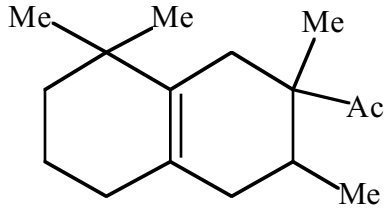
No data were available regarding chemical disposition, metabolism, or toxicokinetics; acute, short-term, subchronic, or chronic toxicity; synergistic or antagonistic activity; reproductive or teratological effects; carcinogenicity; genotoxicity; or immunotoxicity.

Several compounds were considered as structural analogues. Data are provided for the tetralin derivatives AHTN and AETT, which are also polycyclic synthetic musks. Both compounds have been detected in human adipose tissue and human milk. In one rat study, AHTN produced acute hepatic

damage but in another had no adverse effects when administered to lactating rats beginning the third week of pregnancy at doses producing levels in the milk ~1000 times those reported in human milk. Administered by gavage at 50 mg/kg/day on gestation days 7 through 17, AHTN produced clinical signs and reduced weight gain and feed consumption in dams but had no adverse effect on embryo-fetal viability, growth, or morphology. In female rats, AETT induced classic degenerative changes in the liver and effects on the nucleolus and was neurotoxic. Effects included demyelination, hyperirritability, limb weakness, and gait abnormality that became severe ataxia. AHTN gave negative results in several genotoxicity studies (e.g., the *Salmonella typhimurium/Escherichia coli* plate incorporation and liquid preincubation assays and *in vivo* mouse micronucleus assays).

CHEMICAL IDENTIFICATION

Chemical Name: 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone
CAS Registry Number: 54464-57-2



1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone ($C_{16}H_{26}O$), a synthetic terpenoid considered to be a petroleum-derived aroma chemical, is also called the following:

Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)- (9CI)
2-Acetonaphthone, [1,8]-octahydro-2,3,8,8-tetramethyl-
3-Acetyl-3,4,10,10-tetramethylbicyclo[4.4.0]dec-1(5)-ene
7-Acetyl-1,1,6,7-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalene
2-Acetyloctahydro-2,3,8,8-tetramethylnaphthalene
Amberonne
Ambralux
Boisvelone¤
Derambr ne
Iso-E Super¤
Methyl cyclomyrcetone
1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-acetonaphthalenone
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8,-tetramethyl-2-naphthyl)ethan-1-one
1-(2,3,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanone

The Chemical Abstracts 9th Collective Index (9CI) name, "Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-," is the regulatory name under the Toxic Substances Control Act (TSCA). This name, the INCI (International Nomenclature for Cosmetic Ingredients) name 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8,-tetramethyl-2-naphthyl)ethan-1-one, and the synonym 1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-acetonaphthalenone are used by several other countries in lists comparable to the TSCA List (CHEMLIST, 1999). The INCI name, developed by the European and American cosmetic industries, is used to identify each ingredient used in a cosmetic product (INCI, 1996, 1998). Makhetshim-Agan, which markets Iso-E Super¤, also refers to its product by the generic name amberonne. The name Iso-E Super is the only nonsystematic name listed in the Chemical Abstracts Service (CAS) Registry file and is the most prevalent name encountered in the published literature. The more common name Iso-E Super¤ will be used throughout this report.

The Chemical Abstracts Service Registry file does not assign any stereochemistry for the CASRN 54464-57-2. The Beilstein database assigns the *trans* stereochemistry to CASRNs 144651-56-9 and

59056-94-9 and the *cis* stereochemistry to CASRN 59056-93-8; all three CASRNs are sometimes used for Iso-E Super¤ (see Table 1 for structures). Boisvelone¤ may be another synonym for Iso-E Super¤, but CAS has assigned it the CASRN 234439-15-7. The NLM database ChemID gives Boisvelone¤ as a synonym for 54464-57-2.

Physical-Chemical Properties:

Property	Information	Reference
Molecular Weight	234.2	Agan Aroma & Fine Chemicals Ltd. (1999)
Physical State	colorless to a pale yellow liquid	Agan Aroma & Fine Chemicals Ltd. (1999)
Odor	amber, woody with "velvety undertones"	Agan Aroma & Fine Chemicals Ltd. (1999)
Boiling Point (°C)	110-117 at 1.0-1.5 Torr 124-135 at 2.1-2.9 Torr	Andreev et al. (1991); cited by BEILSTEIN (1999)
Flash Point (°C)	>100 closed cup	Agan Aroma & Fine Chemicals Ltd. (1999)
Specific Gravity (20 °C/4 °C)	0.960-0.970	Agan Aroma & Fine Chemicals Ltd. (1999)

The treatment of Iso-E Super¤ with orthophosphoric acid gives an oxatetracyclododecane in 95% yield (Andreev et al., 1991). On cotton-polyamide (90:10) fabrics treated with softener spiked with several raw fragrance materials, the odor threshold of Iso-E Super¤ was 7.33 ppb, and its substantivity or adherence to the fabric, which strongly correlated with hydrophobicity, was 45% (Widder, 1999).

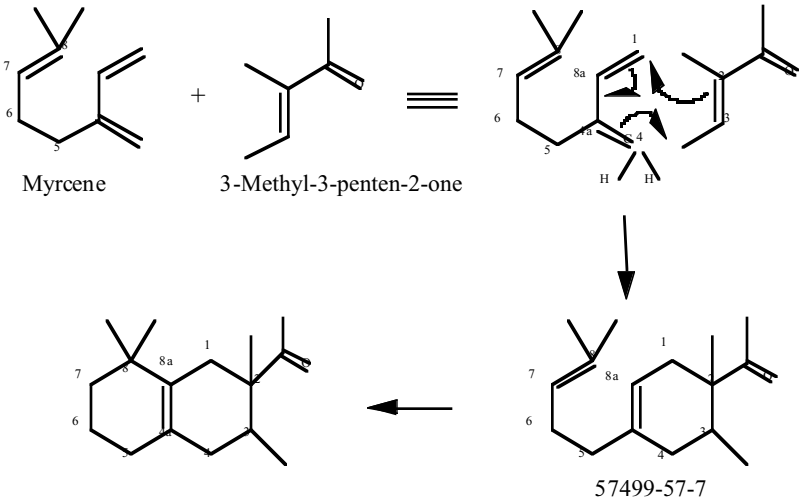
Chemical Analysis: Iso-E Super¤ has been analyzed by gas chromatography (GC) and identified with nuclear magnetic resonance (NMR), mass spectrometry (MS), and infrared spectrometry (IR) (Hall and Sanders, 1975a; BEILSTEIN, 1999). A minor (~5%) but very powerful constituent (5 pg/L [air]) of Iso-E Super¤, (–)-1-[(1*R**, 2*R**, 8a*S**)-1,2,3,5,6,7,8,8a-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one, was identified by NMR (Nussbaumer et al., 1999).

INDUSTRIAL INFORMATION/USES

Commercial Availability: Iso-E Super¤ is produced by International Flavors and Fragrances, Inc. (Ackroyd, 1999). A product corresponding to Iso-E Super¤ is produced as Boisvelone¤ by Bush Boake Allen Inc. (BBA), at manufacturing facilities in Gummidipoondi, India, and Widnes, England (Floreno, 1997). It is produced as amberonne by Agan Aroma and Fine Chemicals Ltd., a member of the Makhteshim-Agan Group headquartered in Israel (Agan Aroma & Fine Chemicals Ltd., 1999). Florachem, representing the subsidiary Makhteshim Agan of North America, supplies synthetic musks and other fragrance products, including amberonne (Florachem, 1999). The products are stored in Brunswick, New Jersey. The product known as ambralux has been produced at the All-Union Scientific Research Institute for Synthetic Natural Fragrances, Moscow, Russia (Andreev et al., 1992). The product known as methyl cyclomyrectone is available from Aedes Co. (CSCHEM, 1999).

Production Processes: Iso-E Super¤ is produced commercially by Diels-Alder condensation of β-myrcene with 3-methyl-3-pentene-2-one in the presence of aluminum chloride to give a monocyclic intermediate that is cyclized in the presence of 85% phosphoric acid (Hall and Sanders, 1974, 1975a [patent assignee: International Flavors and Fragrances, Inc., USA]; Bledsoe, 1997). Variations in reaction conditions have been published or patented by Andreev et al. (1990, 1992), Kakizawa and Takayama (1994; patent assignee: Takasago Perfumery Co, Ltd., Japan), and Yuan and Peng (1992).

The powerful minor constituent of Iso-E Super¤, (–)-1-[(1*R**, 2*R**, 8a*S**)-1,2,3,5,6,7,8,8a-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one, has been synthesized stereoselectively from α-ionone (Nussbaumer et al., 1991).



The immediate precursor is listed in Table 1 among the structurally related compounds with only one ring.

Production and Import Volumes: Under the 1998 Inventory Update Rule, Bush Boake Allen Inc. and International Flavors and Fragrances Inc. both reported to EPA production/importation values of >10,000 pounds per year (OPPT, 2000). BBA India planned on having an annual rated capacity of 800 metric tons for Boisvelone¤ plus geraniol derivatives (Floreno, 1997).

Uses: A search revealed more than 30 sources showing that Iso-E Super¤ has been and is used as a perfume ingredient, providing a sandalwood-like and cedarwood-like fragrance, in soap, shampoo, cologne, liquid detergent compounds, and malodor-reducing compounds, such as fabric freshening compounds, antiperspirants or deodorants, and air freshening compounds (e.g., Hall and Sanders, 1975a,b; Nogami and Mitsunaka, 1998 [patent assignee: The Procter and Gamble Co., USA]). In the fragrance Eternity by Calvin Klein, Iso-E Super¤ is 11.7% of the fragrance portion of the formula. It is used in tobacco products (at 100-2000 ppm) to improve not only the aroma but also the flavor of tobacco and its smoke, giving them sweet, spicy, sandalwood-like and cedarwood-like notes (Hall and Sanders, 1975a). Aroma chemicals such as Iso-E Super¤ have also been used to control the hardness of a polyurethane foam (Beck, 1995; patent assignee: International Flavors and Fragrances, Inc., USA). More recently, it has found application as a precursor for the delivery of organoleptic and antimicrobial compounds (Andersen and Frater, 2000; patent assignee: Givauden Roure [Int.] S.A., Switzerland).

POTENTIAL ENVIRONMENTAL EXPOSURE AND REGULATIONS

Environmental Occurrence and Persistence: Trace analyses of Iso-E Super¤ in municipal wastewater and effluents with GC-MS using selected ion monitoring had limits of quantitation of 35 ng/L for influent and 4 ng/L for effluent. When the method was applied to an activated sludge and trickling filter wastewater treatment plant in the United States, Iso-E Super¤ influent concentrations were 3.470 and

3.250 g/L, respectively, and final effluent concentrations were 0.110 and 0.334 g/L, respectively. During activated sludge wastewater treatment, primary treatment produced 59.2% removal, while secondary treatment achieved 96.8% removal; during trickling filter wastewater treatment, the values were 43.2 and 89.7%, respectively (Simonich et al., 2000).

Human Exposure: For the general population, exposure to Iso-E Super¤ is via inhalation and the skin through the use of products (e.g., fragrances and perfumed personal care products) containing the chemical and via ingestion of water or food containing the chemical as a contaminant.

Regulatory Status: The Environmental Health Network of California (EHN) has filed a petition (#99P-1340) with the Food and Drug Administration (FDA) asking that the fragrance Eternity be declared "misbranded," since it contains no warning label informing consumers that each ingredient in the product and the product itself have not been adequately tested for safety (21 CFR 740.10) (EHN, 1999; Bridges, 2000). Numerous letters in support of the petition have been filed (FDA, 1999). Iso-E Super¤ is listed in the TSCA Inventory under the 9CI name ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-.

Outside of the United States, Iso-E Super¤, along with two other isomers (CASRNs 68155-67-9 and 68155-66-8), is listed in the European Economic Community (EEC) Annex to Commission Decision 96/335/EC, which establishes an inventory and a common nomenclature for ingredients in cosmetic products (CHEMLIST, 1999; INCI, 1996, 1998). Its EINECS No. is 259-174-3. In Australia, Iso-E Super¤ is listed in the Australian Inventory of Chemical Substances (AICS), in Canada in the Domestic Substances List (DSL), and in Korea in the Existing Chemicals List (ECL) under the 9CI name, the INCI name 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8,-tetramethyl-2-naphthyl)ethan-1-one, and the synonym 1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-acetonaphthalenone (CHEMLIST, 1999).

TOXICOLOGICAL DATA

Human Data: In dermatological patients, two cases of an allergic reaction towards Iso-E Super¤ were observed on day 3 or 4 of application (patch test); however, this was not proved to be clinically relevant. Fragrances for testing were selected from the top 25 constituents of perfumes, household products, and soaps (400 commercial products) sold in the United States ca. 1989 (Frosch et al., 1995).

Chemical Disposition, Metabolism, and Toxicokinetics: No data were available.

Acute Exposure: No data were available.

Short-Term and Subchronic Toxicity: No data were available.

Chronic Toxicity: No data were available.

Synergistic and Antagonistic Activity: No data were available.

Reproductive and Teratological Effects: No data were available.

Carcinogenicity: No data were available.

Initiation/Promotion Studies: No data were available.

Anticarcinogenicity: No data were available.

Genotoxicity: No data were available.

Cogenotoxicity: No data were available.

Antigenotoxicity: No data were available.

Immunotoxicity: No data were available.

STRUCTURE-ACTIVITY RELATIONSHIPS

Several compounds were considered as structural analogues (see Table 1 and Figure A-1 [in the Appendix]). The Appendix describes in detail the search strategy used to identify the structurally related compounds. The tetralin derivatives AHTN and AETT, which are also polycyclic synthetic musks, were selected for this discussion as being similar in structure and having considerable available toxicological studies. Their structures and synonyms are located in Table 1. (The literature availability for AHTN and AETT as well as for the benzopyran [indane] synthetic musks is depicted in Table 2.) This discussion is based primarily on abstracts of published literature so that when n.p. (not provided) is stated, it means the data were not in the abstract.

AHTN:

The subchronic toxicity and genotoxicity of AHTN have been reviewed by Ford (1998).

Environmental Releases and Exposure: Several substances from the group of the polycyclic musk fragrances are considered to have an ubiquitous distribution in surface waters. The pollution originates from their use in detergents and cosmetics, which enter surface waters via the wastewaters from municipal sewage treatment plants (Eschke et al., 1995b). The highest AHTN concentrations have been found in water from sewage plants (4.4 g/L), sludge from sewage plants (34 mg/kg dry matter), and fish from sewage ponds (58 mg/kg lipid) (Rimkus, 1999). Near a municipal wastewater treatment plant, the highest lipid concentrations of AHTN were observed in mussels, tench, and crucian carp (Ranke et al., 1999). In studies of the environmental risk assessment and fate of AHTN in the European Union, AHTN was found to be degraded to more polar metabolites in fish, in soil, and during sewage treatment (Balk and Ford, 1999a). Predicted no effect concentrations were 3.5 g/L for aquatic organisms, 0.32 mg/kg dry weight for soil organisms, and 10 mg/kg fresh weight for fish or worm-eating predators (Balk and Ford, 1999b). In the North Sea, concentrations of AHTN ranged from 0.08 to 2.6 ng/L (Bester et al., 1998). In Italy, AHTN was determined in freshwater fish samples; levels ranged from ≤4 to 105 ppb in fish mussel tissue (Draisci et al., 1998; cited by Daughton and Ternes, 1999). In the Swiss river Glatt, 75 ng/L AHTN

Table 1. Structurally Related Compounds

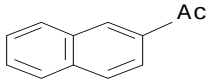
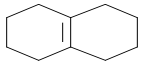
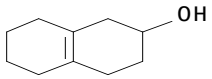
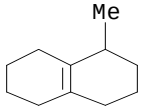
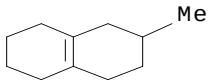
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Compounds with a fully unsaturated substructure				
Methyl β-naphthyl ketone	93-08-3	2«-Acetonaphthone (6CI, 8CI); β-Acetonaphthone; 2-Acetylnaphthalene; β-Acetylnaphthalene; Ethanone, 1-(2-naphthalenyl)- (9CI); β-Naphthyl methyl ketone; 1-(2-Naphthalenyl)ethanone; 1-(2-Naphthyl)ethanone; 2-Naphthyl methyl ketone; Methyl 2-naphthyl ketone		This is listed in the TSCA Inventory[1-B,C,D,G]. It is a common fragrance material in laundry products and cleaners (FPIN, 2000) with the fragrance of orange blossoms (Aldrich, 2000). Honda et al. (1991) reported that 700 mg/kg i.p. induced pulmonary damage in mice.
Simple δ9,10-octalin and derivatives in which CAS listed names containing the fragment "octalin"				
9,10-Octalin	493-03-8	9,10-Dehydrodecalin; Naphthalene, 1,2,3,4,5,6,7,8-octahydro- (6CI, 7CI, 8CI, 9CI); 9-Octalin; δ-9-Octalin; δ-9,10-Octalin		The double bond is considered to be between carbons 4a and 8a when named as a naphthalene derivative.
2-Hydroxy-δ9,10-octalin	5689-10-1	2-Naphthalenol, 1,2,3,4,5,6,7,8-octahydro- (9CI); 2-Naphthol, 1,2,3,4,5,6,7,8-octahydro- (7CI, 8CI)		
1-Methyl-δ9,10-octalin	99623-78-6	Naphthalene, 1,2,3,4,5,6,7,8-octahydro-1-methyl- (9CI)		
2-Methyl-δ9,10-octalin	99623-79-7	Naphthalene, 1,2,3,4,5,6,7,8-octahydro-2-methyl- (9CI)		

Table 1. Structurally Related Compounds (Continued)

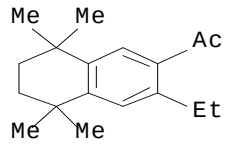
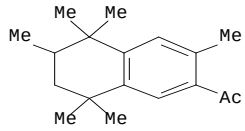
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Tetralins[b] (Tetrahydronaphthalene dervatives)  Tetralin¤ (CASRN 119-64-2)				
AETT; Versalide¤	88-29-9	2«-Acetonaphthone, 3«-ethyl-5«,6«,7«,8«-tetrahydro-5«,5«,8«,8«-tetramethyl- (7CI, 8CI); 7-Acetyl-6-ethyl-1,1,4,4-tetramethyltetralin; Ethanone, 1-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)- (9CI); 3«-Ethyl-5«,6«,7«,8«-tetrahydro-5«,5«,8«,8«-tetramethyl-2«-acetonaphthone; Musk 36A; 1,1,4,4-Tetramethyl-6-ethyl-7-acetyl-1,2,3,4-tetrahydronaphthalene; 1,1,4,4-Tetramethyl-6-ethyl-7-acetyltetralin; Versalide (6CI)		AETT is listed in the TSCA Inventory[2]. Neurotoxic — See Table 2 for available toxicity information. There is a structural similarity with Iso-E Super¤ with respect to substitution at C2 (an acetyl group) and C8 (two methyl groups). The structure of the cyclohexene ring in tetralin is analogous to that of cyclohexene itself wherein the ethylenic carbons and the two adjacent allylic carbon atoms are in a plane (Eliel, 1962). Presumably, both of the 9,10-octalin rings in Iso-E Super¤ would be similarly constrained with six carbons in the same plane. Versalide¤ is the subject of *Merck Index*, 12th ed., Monograph 10101. It is a product of Givaudin-Delawanna.
AHTN*; Tonalide	21145-77-7	2«-Acetonaphthone, 5«,6«,7«,8«-tetrahydro-3«,5«,5«,6«,8«,8«-hexamethyl- (8CI); AHMT; Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)- (9CI); Musk tonalid; Tonalid		This has the same 8CI and 9CI names and structure as Fixolide (entry below with CASRN 1506-02-1). Both CASRNs are used in indexing recent literature abstracted by CAS. Tonalide is a common fragrance chemical used in laundry products and cleaners (FPIN, 2000). There is a structural similarity with Iso-E Super¤ with respect to substitution at C2 (an acetyl group) and C8 (two methyl groups). A mirror held at the top of this structure reveals the same similarity to Iso-E Super¤ as described for AETT. This is listed in the TSCA Inventory[1-A,B,D]. Neurotoxic — See Table 2 for available toxicity information.

Table 1. Structurally Related Compounds (Continued)

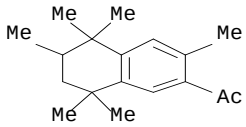
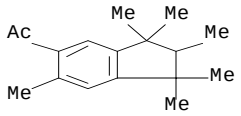
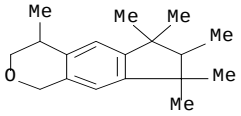
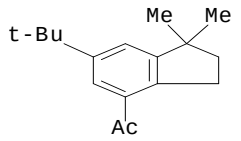
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Fixolide	1506-02-1	2«-Acetonaphthone, 5«,6«,7«,8«-tetrahydro-3«,5«,5«,6«,8«,8«-hexamethyl- (6CI, 7CI, 8CI); 6-Acetyl-1,1,2,4,4,7-hexamethyltetralin; 6-Acetyl-1,2,3,4-tetrahydro-1,1,2,4,4,7-hexamethylnaphthalene; 7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene; 7-Acetyl-1,1,3,4,4,6-hexamethyltetralin; 7-Acetyl-1,2,3,4-tetrahydro-1,1,3,4,4,6-hexamethylnaphthalene; Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)- (9CI); Tentarome		Although AHMT was among the synonyms of AHTN (above entry with CASRN 21145-77-7), no name corresponded to the acronym. Several systematic names for fixolide would have AHMT as acronyms. Furthermore, note the additional and missing synonyms compared to those given for AHTN. There is a structural similarity with Iso-E Super® with respect to substitution at C2 (an acetyl group) and C8 (two methyl groups). A mirror held at the top of this structure reveals the same similarity to Iso-E Super® as described for AETT. This is listed in the TSCA Inventory[1-E,F,G]. Neurotoxic — See Table 2 for available toxicity information.
Indanes[b] (Benzopyran derivatives)		Benzopyran		
Phantolide*	15323-35-0	6-Acetyl-1,1,2,3,3,5-hexamethylindan; 6-Acetyl-1,1,2,3,3,5-hexamethylindane; AHDI; Ethanone, 1-(2,3-dihydro-1,1,2,3,3,6-hexamethyl-1*H*-inden-5-yl)- (9CI); Ketone, 1,1,2,3,3,6-hexamethyl-5-indanyl methyl (6CI, 8CI); Musk phantolid; Phantolid		This is listed in the TSCA Inventory[2]. A mirror held to the side of this structure (on the reader's right) shows a placement of dimethyl and acetyl substituents at the top of the two rings similar to that of Iso-E Super®.
Galaxolide	1222-05-5	Abbalide; Cyclopenta[*g*]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl- (7CI, 8CI, 9CI); Galaxolide 50; 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran; HHCB; Pearlide		This is listed in the TSCA Inventory[1-A,D,F]. Galoxolide 50% is a common fragrance chemical used in laundry products and cleaners (FPIN, 2000).
Celestolide	13171-00-1	4-Acetyl-6-tert-butyl-1,1-dimethylindane; Esperone; Ethanone, 1-[6-(1,1-dimethylethyl)-2,3-dihydro-1,1-dimethyl-1*H*-inden-4-yl]- (9CI); Ketone, 6-tert-butyl-1,1-dimethyl-4-indanyl methyl (6CI, 7CI, 8CI)		This is listed in the TSCA Inventory[1-B,D].

Table 1. Structurally Related Compounds (Continued)

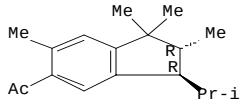
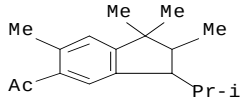
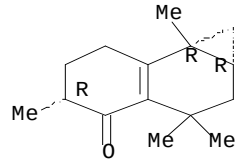
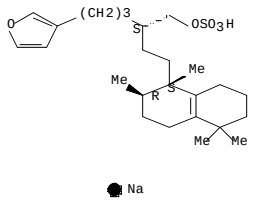
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Traseolide	68857-95-4	ATII; Ethanone, 1-[(2*R*,3*R*)-2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1*H*-inden-5-yl]-, rel- (9CI); Ethanone, 1-[2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1*H*-inden-5-yl]-, *trans*-		See next entry.
5-Acetyl-3-isoproyl-1,1,2,6-tetramethylindane	68140-48-7	Ethanone, 1-[2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1*H*-inden-5-yl]- (9CI)		This compound has the same structure as traseolide (above entry with CASRN 68857-95-4) but without the stereochemistry. This is listed in the TSCA Inventory[1-G].
Natural products with a 9,10-octalin substructure				
Africanone	90851-05-1	4*H*-Cyclopropa[*a*]naphthalen-4-one, 1,1a,2,3,5,6,7,7b-octahydro-3,3,5,7b-tetramethyl-, (1a*R*,5*R*,7b*R*)- (9CI); 4*H*-Cyclopropa[*a*]naphthalen-4-one, 1,1a,2,3,5,6,7,7b-octahydro-3,3,5,7b-tetramethyl-, [1a*R*-(1aα,5β,7bα)]-; Lippifoli-1(6)-en-5-one		This is a sesquiterpene ketone isolated from the flowering plant *Lippia integrifolia*. No toxicity data sources were identified.
Halisulfate 3	116302-40-0	3-Furanpentanol, β-[2-[(1*S*,2*R*)-1,2,3,4,5,6,7,8-octahydro-1,2,5,5-tetramethyl-1-naphthalenyl]ethyl]-, hydrogen sulfate, sodium salt, (β*S*)- (9CI); 3-Furanpentanol, β-[2-(1,2,3,4,5,6,7,8-octahydro-1,2,5,5-tetramethyl-1-naphthalenyl)ethyl]-, hydrogen sulfate, sodium salt, [1*S*-[1α(*R**),2β]]-		This is a sesterterpene sulfate from a sponge. No toxicity data sources were identified.

Table 1. Structurally Related Compounds (Continued)

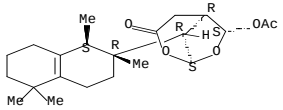
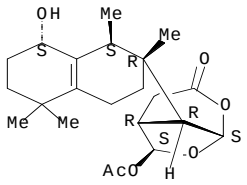
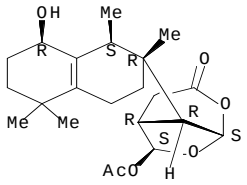
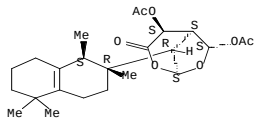
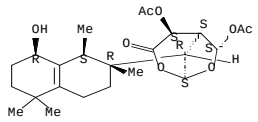
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Shahamin F	116079-56-2	2,7-Dioxabicyclo[3.2.1]octan-3-one, 6-(acetyloxy)-8-[(1*R*,2*S*)-1,2,3,4,5,6,7,8-octahydro-1,2,5,5-tetramethyl-2-naphthalenyl]-, (1*R*,5*S*,6*R*,8*S*)-rel-(-)- (9CI); 2,7-Dioxabicyclo[3.2.1]octan-3-one, 6-(acetyloxy)-8-(1,2,3,4,5,6,7,8-octahydro-1,2,5,5-tetramethyl-2-naphthalenyl)-, [1α,5α,6α,8*S**(1*R**,2*S**)]-(-)-		These are diterpenes from nudibranchs of the genus *Chromodoris* and from marine sponges of the genuses *Chelonaplysilla*, *Dendrilla*, and *Dysidea*. No toxicity data sources were identified.
Shahamin G	116079-57-3	2,7-Dioxabicyclo[3.2.1]octan-3-one, 6-(acetyloxy)-8-[(1*R*,2*S*,8*R*)-1,2,3,4,5,6,7,8-octahydro-8-hydroxy-1,2,5,5-tetramethyl-2-naphthalenyl]-, (1*R*,5*S*,6*R*,8*S*)-rel- (9CI); 2,7-Dioxabicyclo[3.2.1]octan-3-one, 6-(acetyloxy)-8-(1,2,3,4,5,6,7,8-octahydro-8-hydroxy-1,2,5,5-tetramethyl-2-naphthalenyl)-, [1α,5α,6α,8*S**(1*R**,2*S**,8*R**)]-		
Shahamin H	116179-73-8	2,7-Dioxabicyclo[3.2.1]octan-3-one, 6-(acetyloxy)-8-[(1*R*,2*S*,8*S*)-1,2,3,4,5,6,7,8-octahydro-8-hydroxy-1,2,5,5-tetramethyl-2-naphthalenyl]-, (1*R*,5*S*,6*R*,8*S*)-rel- (9CI); 2,7-Dioxabicyclo[3.2.1]octan-3-one, 6-(acetyloxy)-8-(1,2,3,4,5,6,7,8-octahydro-8-hydroxy-1,2,5,5-tetramethyl-2-naphthalenyl)-, [1α,5α,6α,8*S**(1*R**,2*S**,8*S**)]-		
Shahamin I	116079-58-4	2,7-Dioxabicyclo[3.2.1]octan-3-one, 4,6-bis(acetyloxy)-8-[(1*R*,2*S*)-1,2,3,4,5,6,7,8-octahydro-1,2,5,5-tetramethyl-2-naphthalenyl]-, (1*R*,4*R*,5*R*,6*R*,8*S*)-rel-(-)- (9CI); 2,7-Dioxabicyclo[3.2.1]octan-3-one, 4,6-bis(acetyloxy)-8-(1,2,3,4,5,6,7,8-octahydro-1,2,5,5-tetramethyl-2-naphthalenyl)-, [1α,4β,5α,6α,8*S**(1*R**,2*S**)]-(-)-		
Shahamin J	116102-40-0	2,7-Dioxabicyclo[3.2.1]octan-3-one, 4,6-bis(acetyloxy)-8-[(1*R*,2*S*,8*S*)-1,2,3,4,5,6,7,8-octahydro-8-hydroxy-1,2,5,5-tetramethyl-2-naphthalenyl]-, (1*R*,4*R*,5*R*,6*R*,8*S*)-rel- (9CI); 2,7-Dioxabicyclo[3.2.1]octan-3-one, 4,6-bis(acetyloxy)-8-(1,2,3,4,5,6,7,8-octahydro-8-hydroxy-1,2,5,5-tetramethyl-2-naphthalenyl)-, [1α,4β,5α,6α,8*S**(1*R**,2*S**,8*S**)]-		

Table 1. Structurally Related Compounds (Continued)

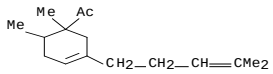
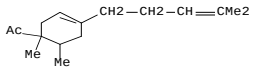
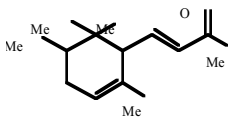
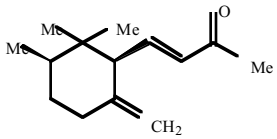
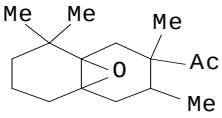
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Compounds with only one ring				
Ethanone, 1-[1,6-dimethyl-3-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]- (9CI)	54464-54-9			CAS indexed as a Diels-Alder reaction product with myrcene moiety uncyclized in the CA File record for Hall and Sanders (1974). Cyclization would place the dimethyl carbon at C5 instead of C8. See structure V in Figure A-1. This is listed in the TSCA Inventory[1-D].
Ethanone, 1-[1,6-dimethyl-4-(4-methyl-3-pentenyl)-3-cyclohexen-1-yl]- (9CI)	57499-57-7			This is the uncyclized Iso-E Super® reaction-product precursor indexed in CA file records for Andreev et al. (1990) and Hall and Sanders (1975a). This is listed in the TSCA Inventory[1-D].
α-Irone*		4-(2,5,6,6-Tetramethyl-2-cyclohexen-1-yl)-3-butene-2-one		This exists in *dl-cis*, *dl-trans*, *d-cis*, and *d-trans* forms.
γ-Irone	79-68-5	4-(2,2,3-Trimethyl-6-methylenecyclohexyl)-3-buten-2-one		
Other analogues				
Ethanone, 1-(octahydro-2,3,8,8-tetramethyl-4*a*,8*a*-epoxynaphthalen-2-yl)- (9CI)	139701-69-2	4a,8a-Epoxynaphthalene, ethanone derivative		This is a derivative of Iso-E Super® with an epoxy group replacing the double bond. It is prepared from Iso-E Super® by heating with peracetic acid in the presence of sodium carbonate as described in U.S. Patent 5,077,273 assigned to Intl. Flavors & Fragrances, Inc. in 1991. The odor is described as "sweet, woody and patchouli undertones" (Sprecker et al., 1991). No toxicity information was available.

Table 1. Structurally Related Compounds (Continued)

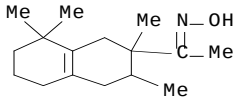
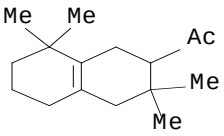
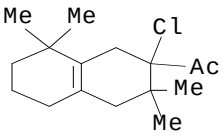
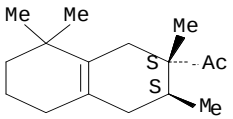
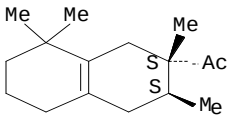
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-, oxime (9CI)	57499-58-8			This is an oxime of Iso-E Super®. Another oxime was mentioned in the key to Figure A-1. (See 54464-58-3 below.) No toxicity information was available.
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-3,3,8,8-tetramethyl-2-naphthalenyl)- (9CI)	94201-32-8	2«-Acetonaphthone, 1«,2«,3«,4«,5«,6«,7«,8«-octahydro-3«,3«,8«,8«-tetramethyl- (6CI)		This is a 9,10-octalin analogue not in Figure A-1 but mentioned in the key.
Ethanone, 1-(2-chloro-1,2,3,4,5,6,7,8-octahydro-3,3,8,8-tetramethyl-2-naphthalenyl)- (9CI)	66362-90-1			This is a 9,10-octalin analogue in which a chlorine atom replaced the C2 methyl group of Iso-E Super®. No toxicity information was available.
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-, *trans*-(-)- (9CI)	144651-56-9			This is structure II in Figure A-1. Beilstein database lists as a CASRN sometimes used for Iso-E Super®. See comment in key to Figure A-1.
Ethanone, 1-[(2*R*,3*R*)-1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl]-, rel- (9CI)	59056-94-9	Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-, *trans*-		This structure is the same as that above with CASRN 144651-56-9. Beilstein database lists as a CASRN sometimes used for Iso-E Super®.

Table 1. Structurally Related Compounds (Continued)

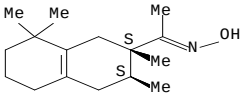
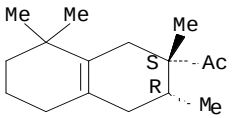
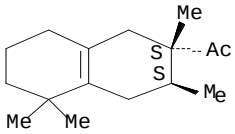
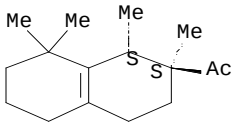
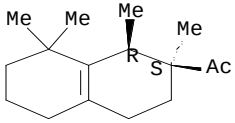
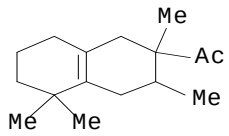
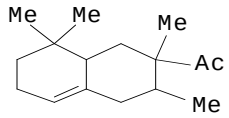
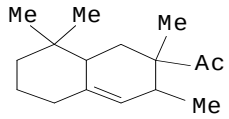
Compound	CASRN	Synonym(s)	Structure[a]	Comments
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-, oxime, *trans*- (9CI)	54464-58-3			This is the oxime of the compound above with CASRN 59056-94-9. This CASRN was used by CAS to index the oxime of Iso-E Super® in the CA record for Hall and Sanders (1974) mentioned in the key to Figure A-1.
Ethanone, 1-[(2*R*,3*S*)-1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl]-, rel- (9CI)	59056-93-8	Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-, *cis*-		This is an enantiomer of the compound with CASRN 59056-94-9. Beilstein lists this CASRN as sometimes being used for Iso-E Super®. This is listed in the TSCA Inventory[2]. No toxicity information was available.
Ethanone, 1-[(2*R*,3*R*)-1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl]-, rel- (9CI)	260792-33-4			This is an analogue of structure III in Figure A-1. (III is a stereoisomer of Iso-E Super®.) No toxicity information was available.
Ethanone, 1-[(1*R*,2*R*)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (9CI)	260792-30-1			This is another structure III analogue without toxicity information.
Ethanone, 1-[(1*R*,2*S*)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl]-, rel- (9CI)	185429-83-8	Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethyl-2-naphthalenyl)-, *cis*-		This is an analogue of structure IV in Figure A-1. This is listed in the TSCA Inventory[2].

Table 1. Structurally Related Compounds (Continued)

Compound	CASRN	Synonym(s)	Structure[a]	Comments
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-(9CI)	54464-59-4			This is structure V in Figure A-1. This is listed in the TSCA Inventory[2].
Structural analogs without double bond at C4a-C8a bridging the two rings				
Ethanone, 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-(9CI)	68155-67-9			This is listed in the TSCA Inventory[1-D].
Ethanone, 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-(9CI)	68155-66-8			This is listed in the TSCA Inventory[1-D]

* Acetyl group attachment relative to C8-dimethyl is similar to that of Iso-E Super®.

[a] Source: Registry (2000); [b] The tetralin and indane derivatives are synthetic polycyclic musks that account for two-thirds of world-wide musk production. Their environmental occurrence and wide use have been reviewed by C.G. Daughton (U.S. EPA) and T.A. Ternes in their review of pharmaceuticals and personal care products in the environment in Environ. Health Perspect. 107(Suppl. 6), Dec. 1999. ILS, Inc., has compiled abstracts of numerous articles indexed by Chemical Abstracts (CA File) and several biomedical databases. See Table 2. The compilation was submitted to Dr. Masten with this report.

[1]Production/importation was reported to be >10,000 pounds per year. Data were reported by the following companies: A-Bush Boake Allen Inc.; B-Givaudan Roure Corporation; C-Haarmann and Reimer; D-International Flavors and Fragrances Inc.; E-PFW Aroma Chemicals USA; F-The Procter and Gamble Company; and G-Quest International Fragrances Company.

[2]Production/importation was reported to be <10,000 pounds per year or confidential business information. Source: OPPT (2000)

Table 2. Summary of Literature Availability for Tetralin and Indane Derivatives

Toxicity	Tetralin Derivatives		Indane (Benzopyran) Derivatives			
	AHTN	AETT; Versalide	Galaxolide ; HHCB	Celestolide	ATII; Traseolide	Phantolide
03 acute toxicity	1	3				
04 environmental occurrence/biota	14	1	13	5	3	1
05/11 review	3	2	3	1	1	1
06 repeated dose			2			
07 carcinogenesis						
08 immunotoxicity (includes phototoxicity)	1	2	1		1	2
09 genotoxicity	5	3	2	4	4	4
10 reproductive toxicity	2		3			
12 ADME, occurrence in human tissues	5	4	5	1	2	
16 epidemiology						
17 cell effects	1	1				
19 neurotoxicity		8	1			
20 endocrine modulation	1		1			
22 synergism/antagonism						
23 membrane effects; lipid peroxidation						
25 ecotoxicology	3	2	1			
28 enzyme effects		1				
29 CVS						
30 blood, etc.						

was measured, while in the fatty tissue of bream and perch from the Ruhr River in Germany, concentrations were 2.5 to 4.6 ppm and in surface waters in Berlin, Germany, and vicinity, maximum concentrations were >10 g/L (Eschke et al., 1995a; M ller et al., 1996; Heberer et al., 1999; all cited by Daughton and Ternes, 1999). In densely populated areas, Canadian aquatic fauna samples (i.e., lobster, winter flounder, American eel, lake trout, clams and mussels) had high concentrations of AHTN (Gatermann et al., 1999). In suspended particulate matter from the Elbe River in Germany, concentrations of AHTN ranged from 194 to 770 ppb, while in water samples, levels were 24 to 88 ppb (Winkler et al., 1998; cited by Daughton and Ternes, 1999). AHTN was a major polycyclic musk in domestic and industrial sludges; concentrations up to 12 mg/kg dry matter polycyclic musks were found (Herren and Berset, 2000). AHTN also accumulates in surface water and fish (Steinberg et al., 1999).

Trace analyses of AHTN in municipal wastewater and effluents with GC-MS using selected ion monitoring had limits of quantitation of 2 ng/L for influent and 3 ng/L for effluent. When the method was applied to an activated sludge and trickling filter wastewater treatment plant in the

United States, AHTN influent concentrations were 10.700 and 10.000 g/L, respectively, and final effluent concentrations were 1.180 and 1.660 g/L, respectively. During activated sludge wastewater treatment, primary treatment produced 34.7% removal, while secondary treatment achieved 89.0% removal; during trickling filter wastewater treatment, the values were 29.7 and 83.4%, respectively (Simonich et al., 2000).

Human Data: AHTN has been detected in human adipose tissue and human milk (Eschke et al., 1995a). Residue levels for AHTN ranged from 8 to 58 g/kg fat (Rimkus and Wolf, 1996).

ADME: In skin, significant amounts of AHTN were diffused, most of which was further absorbed, but a significant amount was also lost to surface dressing by diffusion and/or desquamation. In three male volunteers, application of ring ^{14}C-labeled AHTN in alcoholic solutions at concentrations approximating that found in a typical cologne-type product without occlusion resulted in an absorbed dose of ~1% (based on excretion mainly in urine). During the next five days, 14.5% of AHTN was recovered from the skin in the dressings over the site of application; a mean of 24% was evaporated. In rats, dermal application of the radiolabeled AHTN at doses of 4.5 mg/kg under occlusion resulted in an absorbed dose of ~19% (Ford et al., 1999).

Acute Toxicity: In rats, a single high dose (n.p.) produced acute hepatic damage, which was characterized by single cell necrosis, inflammation, swelling of liver parenchymal cells, the presence of cytoplasmic condensations in the hepatocytes, disorganization of the rough endoplasmic reticulum and mitochondria, and focal cytolysis (Steinberg et al., 1999).

Reproductive Toxicity: A modified version of the ICH Guideline on Detection of Toxicity to Reproduction for Medicinal Products was used to assess potential neonatal adverse effects of AHTN. AHTN was administered to lactating rats beginning the third week of pregnancy at doses producing levels in the milk ~1000 times those reported in human milk. No adverse effects were seen (Ford and Bottomley, 1997 abstr.). When Sprague-Dawley rats were given AHTN (5, 15, 50 mg/kg/day) by gavage on gestation days 7 through 17, the maternal NOAEL was 5 mg/kg/day and the developmental NOAEL was 50 mg/kg/day. At the high dose, clinical signs and reduced weight gain and feed consumption were seen in the dams while no adverse effect on embryo-fetal viability, growth, or morphology was observed, indicating "that under conditions of normal use, the tested fragrances do not pose a risk to human conceptuses" (Christian et al., 1999).

Genotoxicity: AHTN did not have any significant potential to act as a genotoxic carcinogen (Api and San, 1999). Negative results were obtained in several tests (including the *Salmonella typhimurium/Escherichia coli* plate incorporation and liquid preincubation assays, *in vitro* unscheduled DNA synthesis assays in primary rat hepatocytes, *in vivo* mouse micronucleus assays, micronucleus tests using human lymphocytes and the hepatoma cell line Hep G2, and *E. coli* PQ37 genotoxicity assay [SOS chromotest]) (Api and San, 1999; Kevekordes et al., 1997; Mersch-Sundermann et al., 1998a,b). Only in the *in vitro* cytogenetics assay in Chinese hamster

ovary cells in the presence of metabolic activation were structural aberrations observed with AHTN (Api and San, 1999).

Other Data: AHTN exhibited very weak estrogenic activity (ERα- and ERβ-dependent gene transcription assays with human embryonal kidney 293 cells) but no uterotrophic activity (uterine weight assay in juvenile Balb/c mice at a dietary exposure of 50 ppm, a level which caused increased liver weight) (Seinen et al., 1999).

AETT:

Environmental Releases and Exposure: AETT was among those pollutants monitored in surface water and fish in Germany [whether it was found was not clear from the abstract] (Eschke et al., 1995b).

Human Data: In a German study, AETT was among those compounds determined in human adipose tissue samples and human milk samples [AETT concentrations were not given in the abstract] (Rimkus and Wolf, 1996).

ADME: During *in vitro* cultured skin permeation studies, AETT was metabolized (1.9% of absorbed ^{14}C-labeled AETT was seen in two unknown peaks) in the skin but to a significantly less extent than in the liver (Bronaugh et al., 1989).

General Toxicity: In rat liver mitochondria respiring with succinate, oligomycin, or glutamate plus malate as substrate, AETT (10-50 g/mL) caused uncoupling of oxidative phosphorylation *in vitro* (Cammer, 1980). Oral administration of AETT (dose n.p.) to Sprague-Dawley female rats induced classic degenerative changes in the liver and effects on the nucleolus (Pennisi et al., 1984).

Neurotoxicity: AETT is neurotoxic in animals (Eiermann, 1980). Topical administration (dose n.p.) produced demyelination in rats (Spencer et al., 1978a,b). Repeated exposure to AETT (dose n.p.) produced hyperirritability and limb weakness in rats. The brain, spinal cord, and peripheral nerves showed progressive neuronal ceroid degeneration and myelin bubbling (Spencer et al., 1979). In Sprague-Dawley rats fed ~50 mg/kg/day of AETT dissolved in ethanol, myelin was damaged, but Schwann cell somal functions were not significantly affected (Sterman and Spencer, 1981). Percutaneous administration of high doses (n.p.) to rats caused a gait abnormality that became severe ataxia. Microscopically, significant cerebellar changes and widespread accumulation of ceroid-like pigmentation in the neuronal cytoplasm were seen (Akasaki et al., 1990). In Wistar rats, i.p. administration of AETT (dose n.p.) for three months produced a significant increase in neuronal ceroid lipofuscin and a significant impairment of learning ability (Furuhashi et al., 1994).

DATABASES SEARCHED

Online Databases

Chemical Information System Files
SANSS (Structure and Nomenclature Search System)

DIALOG Files
CEH (Chemical Economics Handbook)
DIOGENES

STN International Files

AGRICOLA	CANCERLIT	CSCHEM	PROMT
BEILSTEIN	CHEMINFORMRX	EMBASE	Registry
BIOSIS	CHEMLIST	MEDLINE	RTECS
CA	CIN	NIOSHTIC	TOXLINE

TOXLINE includes the following subfiles (which do not always have all the records in the standalone versions):

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC¤	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

In-House Databases

Current Contents on Diskette¤
The Merck Index, 1996, on CD-ROM

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APPENDIX: Structural Analogues of Iso-E Super¤ [54464-57-2]

Structural analogues to Iso-E Super¤ that appeared in the Iso-E Super¤ literature on synthesis for use as a fragrance in tobacco products are presented in Figure A-1. Very limited information was available for the compounds. In Figure A-1, compounds I, V, VI, VII, and X are listed on the TSCA Inventory. [In Table 1, those which are covered by TSCA are noted under "Comments."]

On November 14, 2000, searches for additional structural analogues were performed in the CAS Registry file that combined name fragments found in systematic chemical names for Iso-E Super¤. Use of octahydro linked (L) to tetramethyl linked to naphthalen? gave 3223 records (set A); use of octalin produced 20 records (set B); use of octahydro(L)tetramethyl(L)acetonaphthone, 3 records (set C); use of octahydro(L)tetramethyl(L)ethanone, 27 records (set D); and use of octahydro(L)tetramethylnaphthalen?(L)ethan(L)one, 1 record (set E). The combination of sets C, D, and E comprised 29 records (set F), one of which was Iso-E Super¤.

The small sets were printed and examined. Subtracting the small sets B and F (a total of 27 unique compounds) from set A gave 3196 records (set G), 10 of which were in the TSCA Inventory. These 10 (set H) were printed and examined. All were terpenoid compounds. None had a double bond between C-4a and C-8a (also called C-9 and C-10), and most had methyl and/or methylene (-CH_2-) groups attached to C-4a or C-8a. None had an acetyl group substituent anywhere. Two did not have all four methyl groups attached to rings. Five had common names (numbers in curly braces are records in Chemical Abstracts [CA file]) [(-)-thujopsanone, 25966-79-4 {15}; isolongifolene epoxide, 26619-69-2 {12}; (-)-α-eudesmol, 473-16-5 {344}; (-)-patchouli alcohol, 5986-55-0 {135}; and (-)-thujopsene, 470-40-6 {201}]. The latter four compounds had records in the biomedical databases. These were not retrieved because of the lack of close similarity to the Iso-E Super¤ structure. Set D largely corresponded to the compounds presented in Figure A-1 plus additional compounds indexed in the CA records for the references cited in the Key to Figure A-1. [Figure A-1 had been based on the CA and Registry records retrieved in the October 1999 preliminary search package. Note: Errors in the Key to Figure A-1 that appeared in the October 1999 version have been corrected.]

No substructure searches have been performed since no clear pattern of substitution on the rings emerged in the structures retrieved using name fragments. More than 25,000 octahydronaphthalene (octalin) derivatives have been registered. More that 3,000 (set A) of them have four methyl groups, not necessarily all on the octalin ring structure. It is likely that allowance for more or fewer methyl groups, short-chain homologous alkyl groups (Et, Pr, Bu), and oxidized derivatives in a substructure search would retrieve thousands of additional candidates.

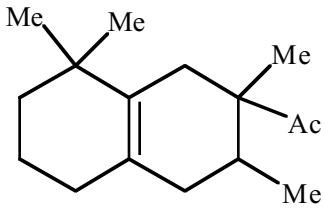
Commercial Products: Among the structural analogues, those appearing in the TSCA Inventory (compounds I, V, VI, VII, and X in Figure A-1 and those noted in Table 1) were readily identified by combining set G with the set of substances identified in the Registry file as being on the TSCA List.

Natural Products: On November 16, set G (minus set H) was further reduced by restricting to those 120 compounds having CASRNs that had been indexed in the natural products database NAPRALERT. All but 20 had a substituent at 8a, which precludes a double bond in the desired position. Seven of the remaining 20 natural products had C-4a to C-8a double bonds and are depicted in Table 1. No toxicity data sources were identified.

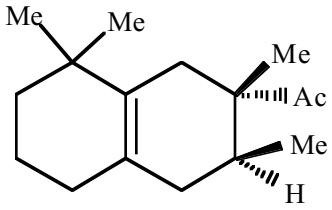
Polycyclic Musks: The δ9,10-octalin substructure of Iso-E Super¤ requires that six of the ten carbons in the ring system be coplanar. In tetralin, which is undergoing NTP studies, the structure is even more rigid, with eight ring carbons in the same plane. Two methyl-substituted tetralin-derived fragrance compounds were identified and included in Table 1. The indexing of the examined abstracts for these tetralin-derived fragrances, AETT and AHTN (also called tonalide and fixolide), also included benzopyran (indan) analogues. The indan derivatives included phantolide, galaxolide (HHCB), celestolide, and traseolide (ATII). All of these fragrances (included in the group polycyclic synthetic musks) have been reported as occurring in environmental media or biota, and all had records in the biomedical databases (see Table 2).

Two hexamethyltetralin derivatives were identified that are used as fragrances. The compounds are 1,1,2,4,4,6-hexamethyltetralin (82881-97-8) and 1,1,3,4,4,6-hexamethyltetralin (2084-69-7). Neither had references in the biomedical databases. Preparations are described in U.S. patents assigned to Union Camp Corp., USA, and International Flavors and Fragrances, Inc., USA, and in several Japanese patents.

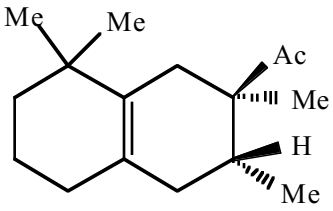
Figure A-1. 54464-57-2 and Related Compounds Indexed in Chemical Abstracts Database Records of Patents and Articles on Iso-E Super¤ Production and Use



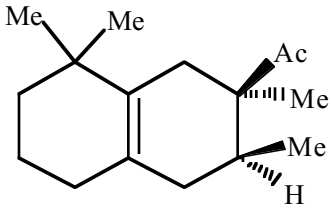
(I)
54464-57-2



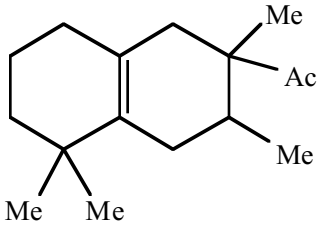
(II)
144651-56-9



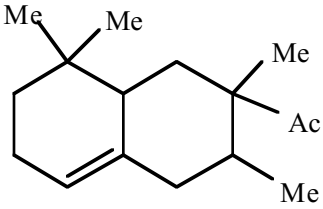
(III)
"54464-57-2"



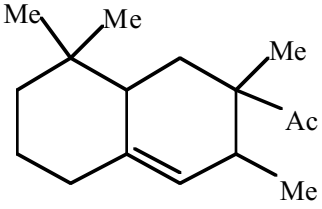
(IV)



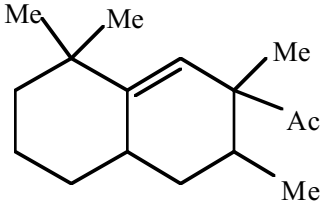
(V)
54464-59-4



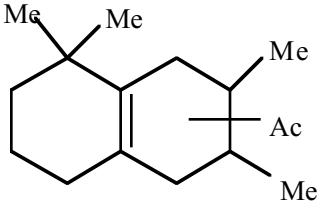
(VI)
68155-67-9



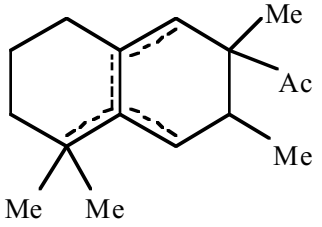
(VII)
68155-66-8



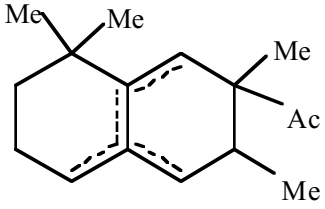
(VIII)



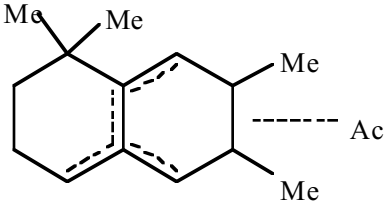
(IX)



(X)
68311-19-3



(XI)
145206-68-4



(XII)
168112-58-1

Key to Structures I - XII

(I) 54464-57-2 — Reaction from myrcene gives mixture of compounds having this general structure [Hall and Sanders (1975a), Andreev et al. (1990, 1991)]. No stereochemistry in Registry record.

(II) 14461-56-9 — Structure assigned in Yuan and Peng (1992) Chem. Abstr. (CA) record and in Registry record. Described as major component of Iso-E Super¤ in synthesis from myrcene. Isolated via hydrazinecarboxamide derivative (144651-60-5). Although the desired isomer was isolated via oxime (54464-58-3) by Hall and Sanders (1974), CA record gives 54464-57-2 as CASRN of desired isomer.

(III) 54464-57-2 — Said to be desired component isolated via oxime or distillation [Hall and Sanders (1975a) (p. 26)].

(IV) Not found in literature. Another possible isomer when stereochemistry is not specified.

(V) 54464-59-4 — No stereochemistry in Registry [Hall and Sanders (1974)]. Sprecker et al. (1991) show structure, but no CASRN is assigned to it.

(VI) 68155-67-9 — Hall and Sanders (1975a) (p. 16) and Kakizawa and Takayama (1994). Registry record does not show relative stereochemistry.

(VII) 68155-66-8 — No stereochemistry in Registry record. Kakizawa and Takayama (1994) and Hall and Sanders (1975a) (p. 16).

(VIII) See example V (p. 18) in Hall and Sanders (1975a).

(IX) See example VII in Hall and Sanders (1975a). Includes 2,3,5,5-tetramethyl-2-acetyl isomers.

(X) 68311-19-3 — Registry record shows this structure without stereochemistry and without the double bond it needs to have the given molecular formula of $C_{16}H_{26}O$ (as shown in Registry record, would be $C_{16}H_{28}O$). Only CA record indexed with this CASRN is Yuan and Peng (1992).

(XI) 145206-68-4 — Registry record shows this structure without stereochemistry and without the double bond it needs to have the given molecular formula of $C_{16}H_{26}O$ (as shown in Registry record, would be $C_{16}H_{28}O$). Only CA record indexed with this CASRN is Yuan and Peng (1992).

(XII) 168112-58-1 — Registry record is missing double bond for given molecular formula $C_{16}H_{26}O$. No specification for acetyl group location. Koch et al. (1975) is only CA record indexed with this CASRN.

Related Fragrance Compounds

94201-32-8 No methyl on C-2. Two methyls on C-3 (CA54:17355d, CA55:18686h).

108978-05-8 No methyl on C-2. Two methyls on C-3. Double bond between C-4a and C-5 (CA52:2822e).

108982-45-2 Methyl on C-1 instead of C-3 (CA54:2500h).