SUMMARY OF DATA FOR CHEMICAL SELECTION

Fenchone

1195-79-5 (alpha), 7787-20-4 (*l*-), 4695-62-9 (*d*-)

BASIS OF NOMINATION TO THE CSWG

The nomination of fenchone to the CSWG is based on widespread low-level consumer exposure, potential exposure of workers, scientific interest, and lack of toxicity data. Fenchone is an ingredient in several seasonings and flavorants, and it is also found in the workplace. What is more important, it typifies a group of bicyclic terpenes and camphors that are widely distributed in nature. As a class, these substances have such limited toxicological data that the human health consequences of exposure cannot be characterized. As a representative of a group of natural products, fenchone is likely to remain untested without the involvement of the National Toxicology Program (NTP).

SELECTION STATUS

ACTION BY CSWG: 12/10/97

Studies requested:

- *In vitro* cytogenetics

- *In vivo* micronucleus

- Mouse lymphoma assay of *d*-fenchone (NCI Short-Term Test Program)

Priority: Moderate

Rationale/Remarks:

- Defer for carcinogenicity pending results of NTP camphor study

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Ms. Joellen Putnam, Scientific Project Manager, Flavor and Extract Manufacturers'Association (FEMA), provided a copy of the FEMA mongraph on *d*-fenchone and *l*-fenchone.

Dr. Dan Benz, Center for Food Safety and Applied Nutrition (CFSAN), FDA, and Dr. Ed Matthews, formerly with CFSAN, provided information on *d*- and *l*-fenchone from FDA's Priority-Based Assessment of Food Additives (PAFA) database.

CHEMICAL IDENTIFICATION

alpha-Fenchone

CAS Registry Number: 1195-79-5

Chemical Abstracts Service Name: Bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl- (9CI); 2-norbornanone, 1,3,3-trimethyl- (8CI)

Synonyms and Trade Names: alpha-Fenchone; fenchone; AI3-00736; 1,3,3-trimethyl- 2-norcamphanone

l-Fenchone

CAS Registry Number: 7787-20-4

Chemical Abstracts Service Name: Bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl-, (1R)- (9CI); 2-norbornanone, 1,3,3-trimethyl-, (1R,4S)-(-)- (8CI)

Synonyms and Trade Names: L-Fenchone

d-Fenchone

CAS Registry Number: 4695-62-9

Chemical Abstracts Service Name: Bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl-, (1S)- (9CI); 2-norbornanone, 1,3,3-trimethyl-, (1S,4R)-(-)- (8CI)

Synonyms and Trade Names: (+)-Fenchone; (1R)-1,3,3-trimethylbicyclo(2.2.1) heptan-2-one; *d*-1,3,3-trimethyl-2-norbornanone; *d*- 1,3,3-trimethyl-2-norcamphanone; D(+)- fenchone; D-fenchone

Structural Class: Bridged ring ketone; bicycloheptanone

Structure, Molecular Formula and Molecular Weight:

$C_{10}H_{16}O$ Mol. wt.: 152.24

Chemical and Physical Properties:

alpha-Fenchone

Description: Colorless oily liquid with a camphor-like odor (Lewis, 1993; Citrus and Allied Essences, Ltd., 1997)

Boiling Point: 193%C (Lewis, 1993)

Melting Point: 6%C (Polarome International, Inc., undated a)

Flash Point: 140%F (Citrus and Allied Essences, Ltd., 1997)

Density: 0.9465 @ 19%C (Lewis, 1993)

Solubility: Soluble in alcohol and in ether, insoluble in water (Lewis, 1993; Citrus and Allied Essences, Ltd., undated)

Stability: Stable (Citrus and Allied Essences, Ltd., 1997)

Reactivity: Combustible (Lewis, 1993)

l-Fenchone

Boiling Point: 192-194%C (Aldrich Chemical Co., Inc., 1996)

Melting Point: 5%C (Aldrich Chemical Co., Inc., 1996)

Flash Point: 52%C (Aldrich Chemical Co., Inc., 1996)

Density: 0.948 @ 18%C/4%C (Aldrich Chemical Co., Inc., 1996)

d-Fenchone

Description: Oily liquid with a camphor-like odor (Budavari, 1996)

Boiling Point: 193.5%C (Budavari, 1996)

Melting Point: 6.1%C (Budavari, 1996)

Density: 0.948 @ 18%C/4%C (Budavari, 1996)

Solubility: Practically insoluble in water (pH saturated solution 6.82); very soluble in absolute alcohol and ether (Buadavari, 1996)

Technical Products and Impurities: Fenchone and *l*-fenchone are available at 98+% purity (Aldrich Chemical Co., Inc., 1996; Polarome International, Inc., undated b).

EXPOSURE INFORMATION

Production and Producers: Fenchone is isolated from cedar leaf oil (Thuja oil) or prepared by various synthetic methods (Opdyke, 1976).

Fenchone, *l*-fenchone, and *d*-fenchone are listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1997a,b).

No data were reported for fenchone, *l*-fenchone, or *d*-fenchone by the United States International Trade Commission (USITC) in the ten most recent volumes of *Synthetic Organic Chemicals, US Production and Sales* for the years 1983-1993, and no other quantitative information on annual production was found in the available literature.

According to recent chemical catalogs and directories, fenchone is manufactured and/or distributed by Haldin International Inc. (McCoy, 1997).

Use Pattern: Fenchone has been used as a flavor and fragrance ingredient since the 1930s (Opdyke, 1976). The typical concentration is 0.02% in soap products, 0.002% in detergents, 0.005% in lotions, 0.05% in perfumes, 0.25 ppm in candy and baked goods, 0.13-80 ppm in nonalcoholic beverages, and 5.0 ppm in alcoholic beverages (Citrus and Allied Essences, Ltd., undated). *d*-Fenchone is also used as a flavoring in foods and is used in perfumes (Budavari, 1989).

FEMA (1997a,b) reports no known uses for *l*-fenchone as a flavoring and that *d*-fenchone is used as a flavoring in food at the following levels (ppm): baked goods, 9.86 (13.02 max.); frozen dairy, 3.15 (5.35 max.); soft candy, 7.25 (9.99 max.); gelatin pudding, 3.21 (5.44 max.); non-alcoholic beverages, 1.08 (3.10 max.); and alcoholic beverages, 0.10 (5.00 max.).

The use of *d*-fenchone in flavorings in the U.S. was 264 lbs in 1970, 11 lbs in 1975, 39.6 lbs in 1982, 6.6 lbs in 1987, and 114.4 lbs in 1995 (FEMA, 1997b). Opdyke (1976) reported that the use of fenchone in fragrances in the U.S. was approximately 1,000 lbs per year (Opdyke, 1976).

Fennel, in which fenchone occurs, has anise-like flavor characteristics and is used as a top note or blender in liqueurs and salad dressings (Furia, 1959).

Human Exposure: There is potential for exposure to fenchone in occupational, consumer, and environmental settings by inhalation, ingestion, and dermal contact. *d*-Fenchone is found in 8 direct food additives and *l*-fenchone in 3. In 1994, the annual consumption was estimated to be 1.585 million lbs for fennel, 37,166 lbs for sweet fennel, and 6,550 lbs for the oil of sweet fennel (FDA, 1994).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 12,992 workers, including 6,693 female workers, were potentially exposed to fenchone in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NLM, 1997b).

Fenchone is released into teas prepared from whole and powdered or crushed fruits of the fennel plant *Foeniciulum officinale* (Fehr, 1982).

Environmental Occurrence: Fenchone is a constituent of many essentials oils, including those of *Thuja plicata*, *T. occidentalis*, *T. standishii*, Russian anise, fennel, a few Artemisia varieties (*A. frigida*, *A. verlotorum* and *A. santolinaefolia*), *Lavandula stoechas* and *L. burmannii*. The highest levels (12-19%) are found in fennel oil (Opdyke, 1976). *d*- Fenchone has been detected in the essential oils of wild, bitter, and sweet fennel plants and seeds, and *l*-fenchone in the oils of wormwood, tansy, and cedar leaf (Ravid *et al*., 1992). Fenchone is present in concentration of 0.2-4% in sweet fennel oil and 4-24% in bitter fennel oil (Lawrence, 1995).

Fenchone has been identified in soil extract and water samples (<0.1-200 &g/l) from an abandoned waste site of a former pine-tar manufacturer (McCreary *et al*., 1983); in landfill leachate (36 &g/l) in Florida (Hallbourg *et al*., 1992); in water samples from Spirit Lake and Coldwater Creek following the 1980 eruption of Mount St. Helens in Washington, presumably from pyrolysis of plant material (Pereira *et al*., 1982); and in biogenic emissions (Atlas *et al*., 1993; Guenther *et al*., 1994).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of fenchone or its stereoisomers. Fenchone and its steroisomers were not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) and biological exposure index (BEI) are made.

d-Fenchone was given GRAS status in 1965 and is approved by the FDA for food use (21 CFR 121.1164) (Opdyke, 1976; FEMA, 1997b).

The possible acceptable daily intake (PADI) for *d*-fenchone is 1.66 mg (FEMA, 1997b)

.EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological or case reports investigating the association of exposure to fenchone or its stereoisomers and cancer risk in humans were identified in the available literature.

Tested at 4% in petrolatum, fenchone did not produce irritation after a 48-hour closed-patch test or sensitizaton in a maximization test on human subjects (Opdyke, 1976).

Animal Data: Fenchone applied full strength to intact or abraded rabbit skin for 24 hours under occlusion was mildly irritating. The oral LD_{50} of *d*-fenchone in rats was 6160 mg/kg, and the dermal $LD_{50}$of fenchone in rabbits exceeded 5 g/kg (NLM, 1997b; Opdyke, 1976).

No 2-year carcinogenicity studies of fenchone or its stereoisomers were identified in the available literature.

Short-Term Tests: No *in vitro* or *in vivo* studies evaluating fenchone or its stereoisomers for mutagenic effects were identified in the available literature.

Metabolism: Following oral administration of *d*-fenchone to rabbits, urinary metabolites were identified as 8-, 9-, and 10-hydroxyfenchone (Miyazawa & Kameoka, 1987, 1988a,b).

Metabolism studies with dogs conducted in the early 1900s showed that urinary metabolites of *d*-fenchone were 4- and 5-hydroxyfenchone and pi-apofenchone-3- carboxylic acid (Williams, 1959).

Absorption of fenchone on the intact shaved abdominal skin of mice was moderately rapid (45 minutes) (Opdyke, 1976).

Structure Activity Relationships: Fenchone is a natural product structurally related to borneol, camphene, and camphor. All four of these compounds contain the bicycloheptane moiety. Fenchone and camphor are heptanones and differ significantly from borneol and camphene. There is no information at all on borneol or camphene to aid in a structural analysis of fenchone. The limited data on camphor is of interest.

The hydroxylation of camphor is known to occur through the mono-oxygenase, Cytochrome P-450cam (P450 CIA 1) (Di Primo *et al*., 1990). P450cam binds camphor through van der Waals contacts and the formation of a single hydrogen bond between tyrosine 96 and the ketone group of camphor. It would be anticipated that fenchone would be metabolized in the same manner.

It has also been suggested that camphor is a potential radiosensitizing agent in cancer radiotherapy (Goel & Roa, 1988). Whether this information is relevant to fenchone is not known.

An OSHA Permissible Exposure Limit for camphor of 2 mg/m^3 is based on an ACGIH Threshold Limit Value first proposed in 1963. According to the ACGIH (1991), the basis for the TLV was an evaluation of six employees in a synthetic camphor processing plant. The ACGIH is soliciting additional data on the adverse health hazards posed by exposure to camphor. Camphor is presently in chronic toxicity tests by the NTP (NTP, 1997). An Ames *Salmonella* assay of *d*-camphor was negative (Dr. S, Matthews, personal communication to the CSWG, December 10, 1997).

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