M92-0019

ETHYL VINYL KETONE

CAS Number: 1629-58-9

NTP Nomination History and Review

NCI Summary of Data for Chemical Selection

C92006

Ethyl vinyl ketone
1629-58-9

NTP NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute

2. Recommendation: -Carcinogenicity
   -Mechanistic studies

3. Rationale/Remarks: -Natural and synthetic flavoring substance
   -Important synthetic intermediate
   -Present in orange essence, the most widely used natural flavoring agent
   -Significant human exposure from foods and beverages
   -Interest in toxicity of α,β-unsaturated ketones chemical class
   -Positive mutagenicity data
   -Lack of chronic toxicity data
   -Suspicion of carcinogenicity

4. Priority: High

5. Date of Nomination: 1/92

B. Chemical Evaluation Committee Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. NTP Chemical Selection Principles:
5. Rationale/Remarks:

C. Board of Scientific Counselors Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. Rationale/Remarks:

D. Executive Committee Review

1. Date of Review:
2. Decision:

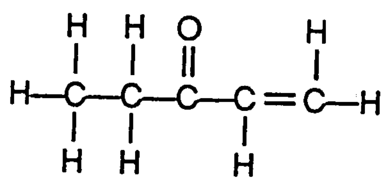
1629-58-9
Ethyl vinyl ketone

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION:

CAS Registry Number:	1629-58-9
Chemical Abstracts Name:	1-Penten-3-one
Synonyms:	Ethyl vinyl ketone; EVK; propionylethylene; vinyl ethyl ketone
Trade Names:	FEMA Compound 3382; Rotichrom GC

Structure, Molecular Formula, and Molecular Weight:



C_5H_8O Mol. wt.: 84.13

Chemical and Physical Properties: (Weast 1989, unless otherwise noted)

Description:	Flammable volatile liquid with pungent aroma (Janssen Chimica, 1990; Aldrich Chemical Co., 1991)
Melting Point:	102°C at 740 mm Hg
Solubility:	Soluble in alcohol, ether, acetone, benzene
Density:	0.8468 g/ml at 20°C/4°C
Stability:	Uninhibited monomer may polymerize on exposure to heat or light (Janssen Chimica, 1990; Fluka Chemical Corp., 1990)
Reactivity:	May react with oxidizing or reducing agents

Prepared for NCI by Technical Resources, Inc. under Contract No. NO1-CP-56019 (11/91, rev. 1/92)

Technical Products and Impurities: Ethyl vinyl ketone (EVK) is commercially available in analytical grade with purities ranging from 95% to >98% and is stabilized with 0.05% hydroquinone or 0.1% 2,6-di-tert-butyl-p-cresol (Aldrich Chemical Co., 1990; Janssen Chimica, 1990; Fluka Chemical Corp., 1990; Pfaltz & Bauer, 1990).

BASIS OF NOMINATION OF THE CSWG

Ethyl vinyl ketone (EVK) is a secondary conjugated carbonyl compound from the subclass of aliphatic α,β-unsaturated ketones (α,β-UKs) which has a wide distribution in the environment, particularly in foods. Consumption in foods and beverages represents a broad human exposure which is complementary to the predominantly industrial and environmental pollutant exposures found with methyl vinyl ketone. The limited available test data on this compound include demonstrations of positive mutagenicity and the formation of DNA-damaging adducts which have led one research group (Eder *et al.*, 1991) to conclude that EVK may pose a mutagenic and carcinogenic risk to humans.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

The Food and Drug Administration's Center for Food Science and Applied Nutrition (CFSAN) provided a summary of the information on EVK which is stored in their Priority-based Assessment of Food Additives (PAFA) database.

SELECTION STATUS

ACTION BY CSWG: 12/13/91

Studies Requested: Nominated for carcinogenicity bioassay and mechanistic studies.

Priority: High

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Comments: The Interagency Testing Committee has classified chemicals containing the closely related substructure α,β-unsaturated aldehydes as a group of chemicals likely to be associated with adverse health and ecological effects.

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EXPOSURE INFORMATION

Commercial Availability

Production and Producers: Numerous methods have been reported in the literature for the synthesis of vinyl ketones, but some had problems with low yields or starting materials not readily available. The Exxon Chemical Company's Plastics Technology Division reported an improved commercial route for the synthesis of EVK and other vinyl ketones. EVK was prepared from the corresponding carboxylic acid, propionic acid, with vinyl lithium using 1,2-dimethoxyethane (DME) as solvent (Floyd, 1974). Chapman *et al.* (1990) reported generating EVK *in situ* from 1-chloropentan-3-one for further reaction to produce pharmaceutical intermediates. Aristech Chemical Corp. was issued a patent in 1991 for the synthesis of EVK by a catalyzed vinylation of the corresponding ketone with paraformaldehyde (Pugach & Salek, 1991).

Two companies reported manufacture of this chemical to EPA's TSCA plant and production database (TSCAPP, 1991). International Flavors and Fragrances, Inc., Union Beach, NJ, reported manufacturing this compound at an annual level of up to 1,000 lbs; and EM Laboratories, Inc., of Elmsford, NY, reported importing an undisclosed amount of EVK. Two companies which specialize in flavor and aroma chemicals and supply EVK, according to their catalogs, are Aldrich Chemical Co. (1991) and Oxford Chemical, Ltd. (1987). In addition, EVK is available from the following chemical companies: Aldrich Chemical Co. Inc., Atomergic Chemicals Corp., Pfaltz and Bauer, Inc., Lancaster Synthesis, Ltd., Janssen Chimica, and Fluka Chemical Corp. Manufacture of EVK as a synthetic food additive accounted for total sales of 10 lb per year, according to a National Academy of Sciences survey conducted in 1987 for the Food and Drug Administration (FDA, 1991).

The annual world production of orange essence, of which EVK is a low-level constituent, was reported in 1984 to be 15-20 million lbs (Moshonas & Shaw, 1990a). Flavor compounding and the flavor-enhancer market is a growth market. Rogers and Fischetti (1980) reported a projected doubling of sales from 1976 to 1985. Thirty-five (35) companies offer orange oil for sale to the drug and cosmetics industries, 25 sell orange peel extracts, and 23 sell orange flower oil (Davis, 1991).

Use Pattern: EVK, an alkylating agent and Michael acceptor, is used as a reagent in organic synthesis and polymerization monomer. Some specific uses in the chemical process industry are summarized as follows:

- reagent/chemical intermediate in organic synthesis (Floyd, 1974; Matsuda, 1987)
- starting materials to produce pharmaceutical intermediates used, for example, for the synthesis of hypolipidemic agents (anticholesteremics) (Chapman *et al.*, 1990)
- reagent for annulation reactions for terpene ring construction (Gawley, 1976; Jung, 1976; Sato *et al.*, 1990)
- reagent which forms the dimer, 4-methylene-3,7-nonandione, and homopolymers - products useful in themselves as chemical intermediates (Basavaiah *et al.*, 1987)
- monomer in copolymerization with methylmethacrylate, vinyl acetate and styrene (Otsu & Tanaka, 1975; Sastre *et al.*, 1977)
- yield improver in alkaline pulping of cellulose (Karpunin *et al.*, 1990).

The principal use of EVK, however, is as a natural and synthetic flavoring substance (De Vincenzi *et al.*, 1987). EVK is a constituent of the processed natural flavoring agent in orange aqueous essence and oils for flavor and aroma enhancement especially of frozen orange juice concentrates. The largest single category of flavorings available to the flavor compounder is the essential oils. Natural citrus fruit oils are processed to yield the essential oils mainly by distillation processes in use since the middle ages. Distilled oils are classified as a concentrated flavoring source (Furia, 1975). According to Moshonas and Shaw (1984), cited in Moshonas and Shaw (1990a), orange essence is the world's most widely used natural flavoring fraction.

Human Exposure: Human exposure to mutagenic α,β-unsaturated carbonyl compounds, including EVK, is said to be widespread by a variety of exogenous and endogenous routes (Chung *et al.*, 1988). According to Ruth (1986), the odor threshold concentration for olfactory recognition of EVK has been reported between 0.4 and 6.9 $\mu g/m^3$ in various literature citations.

The major route of exposure to EVK is ingestion through its widespread occurrence in foods and beverages. Although exposure levels in foods are very low, they may be frequent and nearly universal because of EVK's presence in orange juice and other commonly consumed products. EVK was first reported as a constituent of Valencia orange essence oil in 1971 by Coleman and Shaw and subsequently identified as a volatile component of aqueous orange essence (Moshonas & Shaw, 1973). Flavor enhancement of orange juice products, especially concentrates for reconstitution, involves addition of processed aqueous essence and essence oils. Moshonas and Shaw (1990a) compared commercial aqueous orange essence with several experimental concentrated orange essences for flavor, aroma and compositional differences. They reported that EVK was a constituent in all samples of concentrated aqueous orange essences. They reported that essence oils are known to be the source of oxidation products which form on storage and may have a deleterious effect on flavor, and that commercially available orange flavoring materials currently in use are oil-rich. Processed aqueous orange essence and essence oils produced in Brazil were found to have a significantly higher EVK concentration (approx. 3 times higher) than similar products produced in the U.S. (Moshonas & Shaw, 1990b). Rogers and Fischetti (1980), in a study of flavor compounding, reported that an artificial citrus fruit flavoring for chewing gum contained 37 wt % of orange oil. According to FDA, average exposure across the U.S. population resulting from a market disappearance level of 10 lbs per year of synthetic EVK flavoring additive amounts to 0.000014 mg/kg body weight/day/person (FDA, 1991).

EVK is described as the selected character impact item in horseradish, i.e., when tasted and/or smelled is reminiscent of that food flavor (Rogers & Fischetti, 1980). In addition to aqueous orange essence and orange oil, some other recently reported detections of this chemical in edible products include:

- fresh tomato and tomato paste aroma volatile (Buttery *et al.*, 1987; 1990)
- Pacific, but not Atlantic, oysters aroma volatiles (Josephson *et al.*, 1985)
- aroma volatiles of grapes, guava fruit, and kiwi fruit (Schreier *et al.*, 1976; Idstein & Schreier, 1985; Bartley & Schwede, 1989)
- apple juice stored for 2 years in inner protected aluminum and tin cans at 4-20°C (Bloeck *et al.*, 1986)
- volatile compound in cooked potatoes (potato chips) (De Vincenzi *et al.*, 1987)
- key flavor component of soybeans and reverted soybean oils; flavor volatile with beany, green grassy odor of defatted soy flour contributing to objectionable flavor of soy protein products (Hsieh *et al.*, 1981).
- volatile of freeze dried chive and blended endive (Deininger *et al.*, 1990; Kallio *et al.*, 1990)
- aroma volatile of black tea infusions (Mick & Schreier, 1984).

Frankel *et al.* (1987) have identified EVK as a volatile decomposition product of methyl linolenate hydroperoxides at a level of 0.6% weight in total volatiles. Volatile oxidation products of these polyunsaturated fats and vegetable oils contained in foods have been linked to flavor deterioration but little is known of their potential role in decreasing the safety of foods or association, if any, with cellular damage.

Murray *et al.* (1976) reported that, based on a model system, autoxidation of the fatty acid, linolenic acid, was the origin of volatile extracts of moderately off-flavored frozen green peas (shell concentrate) and that EVK was the aliphatic monocarbonyl compound arising from linolenic acid in a model system. The metallic fishy odor volatile of tainted (oxidized) butterfat was demonstrated to contain EVK by Swoboda and Peers (1977); and EVK was identified in cold stored oxidized whitefish, but not fresh whitefish, odor volatiles by Josephson *et al.* (1984). A trace of EVK was found in cooked ground beef which had been freeze-dried, defatted and rehydrated before cooking (MacLeod & Ames, 1987).

Environmental Occurrence: Pettersson *et al.* (1982) identified EVK as a ketone component of the semi-volatile fraction of cigarette/tobacco smoke. Pellizzari *et al.* (1982) have proposed using mother's milk as an indicator of ambient environmental pollutant levels; they reported that EVK was present in 4 out of 12 human milk samples from 4 urban areas. According to Garrido *et al.* (1988), EVK occurs and accumulates to toxic levels as a metabolite from the alcohol dehydrogenase mediated reduction of 1-pentene-3-ol in *Drosophila melanogaster*.

EVK has been detected by Jüttner (1984) as a volatile substance present in shallow, unsaturated, eutrophic lake water liberated by *Cyanobacteria*. Such low molecular weight volatile organic compounds have been linked to odor and taste problems associated with water purification and fish breeding.

Regulatory Status: EVK is offered for sale as a generally recognized as safe (GRAS) compound. The FDA's CSFAN lists EVK by name only in its PAFA database. No citations or references to regulatory guidelines were included for this chemical as of September 1991 (FDA, 1991).

FDA has regulative authority over substances in which EVK has been identified as a low level constituent. Canned fruit juices covered in the Code of Federal Regulations include frozen concentrated orange juice (21 CFR 146.146), canned concentrated orange juice (21 CFR 146.150), and orange juice for manufacturing (21 CFR 146.151). Essential oils, oleoresins and natural extractives (including distillates) are GRAS for their intended uses in foods (21 CFR 182.20). Isolated soy protein is GRAS for its occurrence as a substance migrating to food from paper and paperboard products used in food and food packaging (21 CFR 182.90).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports associating EVK with a cancer risk in humans were found in the published literature [see Search Resource List]. Available information indicates that EVK has not been tested for carcinogenicity or evaluated by the IARC. No citations were found in PHS-149 or CCRIS, and this compound is not known to be on test or scheduled for testing for chronic effects at this time. Eder *et al.* (1990) have studied EVK for reactions with nucleosides and 5'-mononucleotides and for genotoxicity in the SOS Chromotest. Based on their observation of its genotoxicity, these researchers postulated that this chemical poses a mutagenic and carcinogenic risk to mankind.

EVK is a extremely strong irritant to eyes and mucous membranes, especially the respiratory tract, and its smell is more intense and unpleasant than that of methyl vinyl ketone (MVK) (Deininger *et al.*, 1990). Contact of eyes or skin with the liquid or inhalation of vapors should be avoided. Sax and Lewis (1989) state that this chemical is poisonous by the intravenous route.

Animal Data: No chronic carcinogenicity studies of EVK in animals were found in PHS-149 or in the published literature. This chemical has not been studied in a 2-year bioassay by the NTP nor evaluated by the IARC. Available information indicates that EVK is not currently on test or scheduled to be tested in a chronic/carcinogenicity mammalian bioassay [see Search Resource List].

The only acute toxicity data found in the literature for EVK is the following, reported in RTECS (1991):

intravenous mouse LD_{50}:56 mg/kg

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EVK has been reported by Talalay *et al.* (1988) to be an excellent substrate for induction of glutathione-S-transferase, based on studies with Hepa 1c1c7 murine hepatoma cells. They postulated that such phase II enzyme inducers may have potential chemoprotective properties.

Short-term Tests: Deininger *et al.* (1990) tested EVK for mutagenicity/genotoxicity in two bacterial test systems. It was clearly but weakly genotoxic in the SOS Chromotest using *E. coli* strain PQ37 producing an SOS inducing potency of 0.027 without S-9. Addition of S-9 to the incubation mixture did not result in an increase of genotoxicity.

In the Ames/*Salmonella* assay using strain TA100, EVK was mutagenic with S-9 producing a 3-fold increase of 1293 revertants per μmole (rev/μmole). Bacterial toxicity became evident at the 2.0 μmole level. It was also mutagenic without S-9 causing 748 rev/μmole at 0.5 μmoles followed by bacterial toxicity detectable at the 0.6 μmole level. Addition of 100 μg/ml, but not 50 or 20 μg/ml, of SKF 525 (an inhibitor of microsomal monooxygenases) to the S-9 led to a disappearance of the mutagenic response; but addition of 100 μg/ml of 1,1,1-trichloropropene-2,3-oxide (TCPO, an inhibitor of epoxide hydrolase) led to an increase of mutagenic activity from 385 to 960 rev/μmole (Deininger *et al.*, 1990).

Metabolism: Ketones are known to undergo metabolic transformations to the corresponding alcohols, epoxides and various other metabolites. Conversion in mammals to the relatively less toxic alcohols is reported to proceed slowly (Pilotti *et al.*, 1975). According to Deininger *et al.* (1990), EVK can be expected to form DNA adducts directly or to react as the epoxide after metabolic activation. Compounds with ketone functionality are known to react reversibly with glutathione (GSH). α,β-UKs that are sufficiently electrophilic have been reported to react non-enzymatically with GSH to form a product identical to that which results by way of the metabolic pathway catalyzed by glutathione-S-transferases. This metabolic conversion of α,β-UKs involves reactivity toward sulfhydryl groups with addition of GSH to the ß-carbon; it takes place in various tissues but especially in the liver

(Portoghese *et al.*, 1989). α,β-UKs are considered classic substrates for this reversible Michael 1,4-addition reaction in which the whole GSH molecule is added to the substrate to form conjugates. According to Monks *et al.* (1990), this detoxifying metabolic reaction of the electrophilic substrate with GSH may be more complicated than previously thought. GSH conjugation may not always be the endpoint; reformation of reactive species may occur with significant implications relative to effects at sites distant from the site of initial exposure and/or initial conjugation.

Structure/Activity Relationships: The Interagency Testing Committee (ITC) has classified chemicals containing the closely related substructure, α,β-unsaturated aldehydes, as a group of chemicals likely to be associated with adverse health and ecological effects. Their concern for potential health effects resulting from exposures to this class of chemicals includes oncogenicity, mutagenicity and membrane irritation. For comparative test results on related compounds, please refer to the analogs described in the accompanying summary sheet on methyl vinyl ketone.

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SEARCH RESOURCE LIST

DIALOG	NLM	CIS	STN INTL
Chem. Ind. Notes (19)	CCRIS	TSCAPP	CA/CAOLD
NIOSH/OSHA (161)	EMICBACK	TSCATS	REGISTRY
Heibron (303)	HSDB		
Fine Chemicals Database (360)	RTECS		
CA Search (399)	TOXLINE		

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