7/94

Methyl styryl ketone
122-57-6

NTP NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Nomination Source: NCI

2. Recommendations: -Comparative toxicity studies with methyl vinyl ketone
-Metabolism
-Carcinogenicity

3. Rationale/Remarks: -Potential for widespread human exposure
-Nominated as a result of a class study of α,β-unsaturated ketones
-Flavoring and fragrance additive
-Natural product
-Environmental pollutant
-Mutagenic in Salmonella

4. Priority: -High for toxicity studies
-Moderate for carcinogenicity

5. Date of Nomination: July 1994

B. Interagency Committee for Chemical Evaluation and Coordination Review

1. Date of Review:

2. Recommendations:

3. Priority:

4. NTP Chemical Selection Principles:

5. Rationale/Remarks:

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122-57-6
Methyl styryl ketone

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

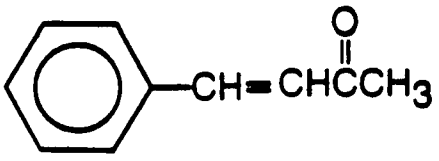
CAS Registry Number:	122-57-6
Chemical Abstracts Name:	3-Buten-2-one, 4-phenyl- (8CI, 9CI)
Synonyms and Trade Names:	Acetocinnamone; benzalacetone; benzylideneacetone; methyl 2-phenylvinyl ketone; methyl styryl ketone; methyl β-styryl ketone; 4-phenylbutenone; 4-phenyl-3-butene-2-one; 2-phenylvinyl methyl ketone; styryl methyl ketone; MSK
FEMA Number:	2881

Related isomers

CAS Registry Number:	937-53-1
Chemical Abstracts Name:	3-Buten-2-one, 4-phenyl-, (Z)- (8CI, 9CI)
Synonyms and Trade Names:	*cis*-4-Phenyl-3-buten-2-one; *cis*-benzalacetone; *cis*-benzylideneacetone; *cis*-methyl styryl ketone

CAS Registry Number:	1896-62-4
Chemical Abstracts Name:	3-Buten-2-one, 4-phenyl-, (E)- (8CI, 9CI)
Synonyms and Trade Names:	*trans*-4-Phenyl-3-buten-2-one; *trans*-benzalacetone; *trans*-benzylideneacetone; *trans*-methyl styryl ketone; TPBO

Structure, Molecular Formula, and Molecular Weight



$C_{10}H_{10}O$ Mol. wt.: 146.19

Chemical and Physical Properties

(from Aldrich Chemical Co., 1993, 1994; Budavari, 1989)

Description: White to yellow solid with a sweet, pungent, creamy, floral odor

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Boiling-point:	260-262° C
Melting-point:	39-42° C
Solubility:	Slightly soluble in water; soluble in acetone, benzene, chloroform, diethyl ether, and ethanol
Vapor pressure:	0.01 mm Hg at 25° C
Log P:	2.07 (Sangster, 1989)
Flash-point:	65° C
Reactivity:	Incompatible with strong oxidizing agents and strong acids; may decompose on exposure to light

Technical Products and Impurities: Methyl styryl ketone (MSK) (commonly known as benzylidene acetone and benzalacetone) is commercially available with a purity of 97% to greater than 99% (Givaudan-Roure Corp., 1993; Aldrich Chemical Co., 1994; Haarmann & Reimer Corp., undated). No information on impurities was found in the available literature. Suppliers market bulk quantities in tank trucks, 55-gal. drums, and 5-gal., 1 gal. and 1 lb. pails, as well as research quantities of 1 kg. (Kuney, 1993).

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BASIS OF NOMINATION TO THE CSWG

MSK was identified as one of several α,β-unsaturated ketones reviewed for the structural class study presented to the CSWG in December, 1992. MSK was suggested as a potential candidate for testing nomination based on multiplicity of producers/suppliers and industrial uses, human exposure as a synthetic flavoring agent, and reactivity in biological systems. As an interim step, MSK was selected for *in vitro* testing in the National Cancer Institute/Division of Cancer Etiology's Short-term Testing Program. When a positive result was subsequently reported in an Ames/*Salmonella* assay in strain TA100 with S9 activation, an individual summary sheet was requested to expand and update the information in the class study. The recent data added reinforce the original conclusions regarding the potential that the versatility and growing use of this chemical can result in low-level widespread exposures.

The fact that MSK is listed on the recently released list of tobacco additives used in cigarette manufacture further supports the recommendation of this chemical for chronic testing nomination (Anon., 1994a).

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

The Flavor and Extract Manufacturers' Association (FEMA) provided a copy of their FEMA Monograph on MSK. According to Dr. John Walker of the Interagency Testing Committee (ITC), no action has been recommended by this multi-agency group on MSK because of lack of documented annual production of greater than 100,000 pounds for this chemical in 1989 (Walker, 1994).

SELECTION STATUS

ACTION BY CSWG: 6/15/94

Studies Requested: Comparative toxicity and metabolism. Comparison with methyl vinyl ketone. Also interest in carcinogenicity testing if prechronic test results warrant.

Priority: High for preliminary tests; moderate for testing for carcinogenicity.

Comments: Positive in Ames assay; growing use which may result in low-level, widespread exposure. Use in fragrances may mean exposure through use of soaps in addition to its use as a food additive.

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EXPOSURE INFORMATION

Commercial Availability:

Production and Producers: Many preparations of MSK have been documented in the chemical literature as performed in both academic research institutions and industrial facilities (STN, 1994), including:

- a high yield Claisen-Schmidt condensation of benzaldehyde with acetone using activated barium hydroxide as catalyst (Edwards *et al.*, 1983)
- t-butyl hydroperoxide catalyzed oxidations of cinnamyl alcohol (Murahashi & Naota, 1993)
- reaction of cinnamic acid with 2 equivalents of methyl lithium (Edwards *et al.*, 1983)

MSK can also be prepared by condensing acetone and benzylidene by means of aqueous alkali (Opdyke, 1973; Budavari, 1989).

The following companies manufacture or supply/distribute MSK (Anon., 1993; Hunter, 1993; Kuney, 1993; Van, 1993).

Producers

Albright and Wilson, Ltd.
Aldrich Chemical Co.
BASF A.-G.
Eastman Kodak Co.
Givaudan-Roure Corp.
Haarmann & Reimer Corp.
ICI Americas, Inc.
International Chemicals Group
Mallinckrodt, Inc.
Penta Manufacturing Co.
Rhone-Poulenc, Inc.
Schweizerhall, Inc.
Shering A.-G.

Suppliers/Distributors

Allan Chemical Corp.

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Howard Hall, Div. of R.W. Greeff & Co.
Raschig Corp.
Rit-Chem Co.

No specific annual production levels for MSK were found in the available literature. However, it has been listed (as benzilidene acetone) as available for $4.50 per can or bottle in the *Chemical Marketing Reporter's* weekly list of prices for commodity chemicals (Anon, 1994b).

Imports: Import volumes in excess of 55,000 lbs were reported for 1993. Importers who reported these volumes included the Raschig Corp., the Enthone Co., and RIT Chemical Co. (DIALOG, 1994).

Use Pattern: MSK is a reactive carbonyl compound which is used in many different types of organic synthetic reactions. Numerous citations can be found in the chemical literature describing its uses, with examples as follows (STN, 1994):

- starting material/chemical intermediate in organic synthesis
- electroplating chemical/brightener used in electroplating baths for zinc, tin and copper and their alloys
- pharmaceutical intermediate in the preparation of drugs, including anticonvulsants, antivirals, antiinflammatories and disinfectants
- biochemical reagent in enzyme and other sulfhydryl-containing protein studies
- minor uses, including agricultural chemical intermediate and polymer additive
- investigational use as a UV-absorber and sunscreen ingredient/precursor

MSK has been in public use as a flavoring and fragrance additive in the United States since the 1920s. It has been used in the following commercial products at the following concentrations (ppm): soap (50-100); detergent (10-50); creams and lotions (50-100); and perfume (50-500) (Opdyke, 1973).

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MSK has the following reported food uses with associated use levels (ppm): baked goods, 5.2; soft candy, 4.4; gelatin/pudding, 1.6; alcoholic beverages, 1.3; frozen dairy, 1.2; nonalcoholic beverages, 0.9; hard candy, 0.1; and fats and oils, 0.02. Levels of use as a flavoring agent have been (kg): 1970, 100; 1975, 70; 1982, 60; and 1987, 17 (FEMA, 1994). MSK has recently been identified as a tobacco flavoring additive present in cigarettes, but the level of use was not reported (Anon., 1994).

Environmental Occurrence: MSK has been reported to occur naturally in the essential oils from flowers, such as *Campsis grandiflora* (trumpet flower); and *Scutellaria baicalensis*. It has also been identified as a volatile constituent of *Amomum globosum*, which is used in traditional Chinese herbal medicines (Fukuhara *et al.*, 1987; Yaozu *et al.*, 1987; Ueyama *et al.*, 1989).

MSK has been identified as one of the organic compounds in waste gases resulting from the removal of coating materials during the recycling of used beverage containers. With other captive pyrolysis products, it is further broken down by subsequent incineration (Roussel & Gaboury, 1987). MSK has also been identified as one of a number of organic compounds adsorbed on granular activated carbon filters used in water treatment plants (Millington et al., 1983) and tentatively identified as an ozonation product of model humic substance, p-hydroxybenzaldehyde (Matsuda *et al*, 1992). Furthermore, MSK is one of a number of lipophilic organic compounds identified as water pollutants and measured for bioaccumulation in blue crabs in the southern Chesapeake Bay (Hale, 1988). MSK has also been identified in mixed wastewater effluents from a chemical-pharmaceutical plant and evaluated for acute ecotoxicological effects (Brorson *et al.*, 1994).

Human Exposure: In the United States, the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 estimated that 5,458 US workers were potentially exposed to MSK including 2,178 female workers (Aldrich Chemical Co., 1994; RTECS, 1994). The estimate of number of workers is based on a survey of US companies and did not involve measurements of actual exposures. However, occupational

exposure to MSK may occur through direct contact during its production, storage, transport, and formulation in commercial products.

Although MSK is known to occur naturally, its extensive presence in consumed products is mainly as a synthetic flavoring agent. There is potential for widespread consumer exposure in food and other products in which MSK is used as a flavoring or fragrance agent. According to data provided to the CSWG by the FDA, MSK as a food additive has an estimated human exposure level of 61.6 pounds per year (Matthews, 1992). MSK has been identified as a tobacco additive in information compiled and released recently by the Philip Morris Co. on behalf of the 6 major US tobacco manufacturers (Anon., 1994a). Because of the number of consumer adverse reaction reports associated with exposure to this chemical, the FDA has published a method for the liquid chromatographic-fluorometric determination of MSK as a fragrance material in perfumes and essences (Yates & Wenninger, 1988).

Regulatory Status: MSK was given Generally Recognized As Safe (GRAS) status in 1965 and is approved by the US Food and Drug Administration (1993) for food use as a synthetic flavoring substance (21 CFR 172.515) (FEMA, 1994). The American Conference of Governmental Industrial Hygienists (ACGIH) has not established a Threshold Limit Value (TLV), the National Institute for Occupational Safety and Health (NIOSH) has not established a Recommended Exposure Level (REL), and the US Occupational Safety and Health Administration (OSHA) has not established a Permissible Exposure Level (PEL) for MSK in the work environment (ACGIH, 1993; NIOSH, 1992; OSHA, 1993). This substance is listed by EPA on the TSCA Inventory.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: There is limited information in the published literature on the effects of MSK on humans. No epidemiological or case reports associating this chemical with a carcinogenic effect in humans were identified.

Skin irritation and sensitization from MSK have been reported in humans with dermatoses or allergies. When tested at a 2% concentration in petrolatum, MSK produced no irritation in a 48-hour closed patch test in 25 human subjects. However, several studies reported positive patch test results when MSK was tested at 2% in subjects with dermatoses or a history of perfume allergies. Positive reaction incidences from these studies were 2/394, 1/58, 1/56, 3/322, and 3/21. MSK has been shown to be a contact sensitizer in humans. At a 2% concentration, two tests reported sensitization effects in 12/25 and 1/182 subjects, respectively. At a concentration of 5%, sensitization was seen in 4/182 subjects and a 0.5% concentration produced positive reactions in 2/4 bakers with dermatitis (Opdyke, 1973; Ishihara, 1981 as cited in FEMA, 1994; Itoh, 1986 as cited in FEMA, 1994; Kligman, 1972 as cited in FEMA, 1994; Malten, 1979 as cited in FEMA, 1994; Meynadier, 1986 as cited in FEMA, 1994; Nishimura, 1984 as cited in FEMA, 1994).

Animal Data: No 2-year bioassay studies associating MSK with carcinogenicity in mammalian species were found in the available literature. Toxicity information identified was limited to the following acute studies.

In rats, the acute oral LD_{50} has been reported at >5 g/kg (Opdyke, 1973). In a more recent study from US EPA (1991), the oral LD_{50}s for male and female rats have been reported as 2,031 and 3,536 mg/kg, respectively. In rabbits the acute dermal LD_{50} is >3 g/kg and in mice the acute intraperitoneal and intravenous LD_{50}s are 1,210 mg/kg and 112 mg/kg, respectively (RTECS, 1994).

Male and female rats given single oral doses of MSK at 1,250, 2,500, and 5,000 mg/kg exhibited treatment-related effects which included diffuse necrosis and hemorrhage in the glandular gastric

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mucosa at 5,000 mg/kg and enlarged kidneys and liver in one mid-dose male rat which survived the 14-day observation period. It was concluded that MSK may be toxic to the male rat kidney as evidenced by vacuolization and histological changes suggestive of epithelial regeneration. The liver changes were interpreted as an adaptive response related to xenobiotic metabolism and not a toxic response. No treatment-related changes were observed at necropsy for animals in the 1,250 mg/kg group (USEPA, 1991).

MSK was mildly irritating to intact or abraded rabbit skin at 1, 2 or 3 g/kg and at 0.5 g per animal for 4 hours resulted in slight erythema. No irritation occurred when applied at 2% to guinea pig skin; however, three sensitization studies in guinea pigs reported positive results at topical doses of 1 and 2% or an intradermal dose of 0.1% (Levenstein, 1972 as cited in FEMA, 1994; Prince, 1973 as cited in FEMA, 1994; USEPA, 1991; Sharp, 1978; Brulos *et al.*, 1977).

Short-term Tests: In the Ames *Salmonella typhimurium* assay carried out for the Short-term Testing Program of the National Cancer Institute/Division of Cancer Etiology, MSK was mutagenic in strain TA100 when tested with metabolic activation at 33-3,333 μg/plate. It was not mutagenic in strain TA98 under the same test conditions (NCI, 1994). MSK was tested in the mouse lymphoma L5178Y TK+/- assay both with and without rat liver S9 activation. MSK gave negative results when tested at a concentration of 50-10 μg/ml without activation but was positive at 50-10 μg/ml with activation (NCI, 1994).

When tested at 10-3000 μg/plate with metabolic activation, *trans*-methyl styryl ketone also produced a positive mutagenic response in strain TA100 (Prival *et al.*, 1982). The mutagenicity of *trans*-methyl styryl ketone showed a great dependence on pH. At pH values below 6.7 there was no significant mutagenicity in strain TA100; however, the number of revertants increased steadily as the pH was raised from 6.7 to 8.0 (Popkin & Prival, 1985). Aqueous chlorination, under conditions of pH and reactant concentrations that would be relevant to waste water and drinking water chlorination, did not convert MSK to a mutagenic species for TA100 when tested in the Ames assay without activation (Cheh, 1986).

MSK was not mutagenic in *E. coli* WP2; however, it did cause a slight decrease (20-30%) in the number of revertants induced in this strain by 4-nitroquinoline-1-oxide or UV irradiation. MSK also demonstrated antimutagenic effects on mutagenicity induced by 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) in *S. typhimurium* strain TA98 (Ohta *et al.*, 1983; Edenharder *et al.*, 1993).

Metabolism: Very little information was found in the published literature on the metabolism of MSK. Generally, when ketones are absorbed into the bloodstream, they may be eliminated unchanged in the expired air, reduced to secondary alcohols, or oxidized to hydroxyketones, diketones, and carbon dioxide by a variety of metabolic pathways. Recent studies indicate that carbonyl reduction, α and ω-1 oxidation, decarboxylation and transamination play important roles in the metabolism of aliphatic ketones. Nakayama *et al.* (1982) reported that MSK was reduced by an NAD(P)H-dependent aldehyde reductase present in the cytosol of guinea pig lung. In addition, aromatic and aliphatic ketones may be conjugated with glucuronic acid, sulfuric acid, or glutathione prior to excretion in the urine. Glucuronic and sulfuric acid conjugations usually occur after a ketone is reduced to a secondary alcohol or oxidized to a carboxylic acid. Of the various conjugation mechanisms that occur, glucuronic acid conjugation appears to be the predominant pathway. Furthermore, the ethylenic double bond can undergo addition reactions that may result in adduct formation (Krasavage *et al.*, 1981; Sandmeyer, 1981).

Other Biological Effects: MSK is an electrophilic substrate and Michael reaction acceptor which has been shown to induce enzymes, including glutathione S-transferases (GST) and quinone reductase (QR) in humans and other mammals (Smith *et al.*, 1985; Spencer *et al.*, 1991). In an *in vitro* study using rat liver supernatant fractions, 1 millimolar concentration of MSK induced enzyme-catalyzed conjugation; activity (μmol of sulfhydryl lost/min/g of tissue) was 1.7 (Boyland, 1967 as cited in FEMA, 1994). Such inductions of detoxication (phase 2) enzymes by diverse chemical agents including Michael acceptors are proposed to result from enhanced transcription, mechanistically related on a cellular level to toxic and neoplastic effects of carcinogens (Prestera *et al.*, 1993).

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Insecticidal activity has been attributed to MSK. A Japanese patent was issued for use of MSK as a mothproofing agent for wool fabric, which was formulated containing 1 part MSK to 9 parts naphthalene. Furthermore, MSK has been shown to have a synergistic effect on several organophosphorus or carbamate insecticides. Simultaneous administration of MSK enhanced the toxicity of the insecticides to houseflies (Welling & De Vries, 1985).

Structure Activity Relationships: MSK is an aryl substituted, unsaturated aliphatic ketone. Several structurally related conjugated ketone analogs were identified; however, little information was found in the published literature associating these analogs with a mutagenic or carcinogenic effect. However, methyl vinyl ketone gave a positive result for mutagenicity in an Ames/*Salmonella* assay and has been nominated by the CSWG and selected for a 2-year bioassay in the NTP (NTP, 1994).

Cinnamaldehyde has been studied for evidence of mutagenic or carcinogenic potency in a variety of assays. This chemical was reported by the NTP to have tested negative in a micronucleus test and to have been submitted for testing for subchronic toxicity by gavage; its *trans*-isomer, on the other hand, gave the following genetic toxicity test results: negative and weakly positive in Ames/*Salmonella* assays; positive in *Drosophila* (SLRL), negative in *Drosophila* (RT); negative for chromosomal aberrations (CAs) but positive for sister chromatid exchanges (SCEs) in *in vitro* cytogenetic assays (NTP, 1993). In the DCE short-term testing program, *trans*-cinnamaldehyde tested negative in an Ames assay but positive with and without activation in a mouse lymphoma assay (NCI, 1993). In the published literature, several other Ames assays were reported including mostly negative, but one weakly positive, results; positive mouse lymphoma assays, positives for CAs in Chinese hamster cells with polyploidy; negative for unscheduled DNA synthesis (UDS); positive in a DNA repair/rec assay; and negative for mutagenicity in *E. coli*.

Cinnamyl alcohol was also negative in an Ames assay but positive both with and without activation in a mouse lymphoma assay conducted for the DCE short-term testing program (NCI, 1993). This analog has also been tested in numerous assays reported in the published literature with mixed results,

including: negative in several Ames assays; negative in *E. coli*; positive in mouse lymphoma assays; negative for SCEs in CHO cells; and positive in a DNA repair/rec assay.

Both cinnamaldehyde and cinnamyl alcohol have been evaluated and reported to have demonstrated some anti-mutagenic properties when tested with various known mutagens. Edenharder *et al.* (1993) studied 64 flavonoids to determine their antimutagenic potencies. A carbonyl function at C-4 of the flavone nucleus seems to be essential for antimutagenicity. Of 11 flavonoid glycosides tested all compounds except apigenin- and luteolin-7-glucoside (ID_{50}: 74, 115 nmoles) were inactive or only weakly mutagenic. Rings C and A of the nucleus were not essential for antimutagenicity; however, chalcone and three derivatives were nearly as active as comparable flavones while antimutagenicity of benzylidenacetone was considerably reduced (ID_{50}: 95 nmoles).

In a comparative study of enzyme inducing potency, MSK was determined to be a moderately potent inducer of quinone reductase (QR) in Hepa 1c1c7 murine hepatoma cells with a CD (i.e., concentration capable of doubling the specific activity of QR) of 17 μM. MSK was a much more potent inducer than analogs, methyl cinnamate (CD=82 μM) or cinnamaldehyde (CD=133 μM) (Spencer *et al.*, 1991).

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