

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:

7/94

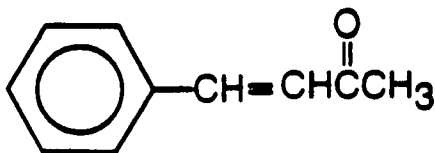
122-57-6
Methyl styryl ketoneSUMMARY OF DATA FOR CHEMICAL SELECTIONCHEMICAL IDENTIFICATION

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 WeightC₁₀H₁₀O

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

Prepared for NCI by Technical Resources, Inc. under Contract No. NO1-CP-56019 (5/94; rev. 7/94)

<u>Boiling-point:</u>	260-262° C
<u>Melting-point:</u>	39-42° C
<u>Solubility:</u>	Slightly soluble in water; soluble in acetone, benzene, chloroform, diethyl ether, and ethanol
<u>Vapor pressure:</u>	0.01 mm Hg at 25° C
<u>Log P:</u>	2.07 (Sangster, 1989)
<u>Flash-point:</u>	65° C
<u>Reactivity:</u>	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).

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.

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.

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).

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.

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 LD₅₀ has been reported at >5 g/kg (Opdyke, 1973). In a more recent study from US EPA (1991), the oral LD₅₀s for male and female rats have been reported as 2,031 and 3,536 mg/kg, respectively. In rabbits the acute dermal LD₅₀ is >3 g/kg and in mice the acute intraperitoneal and intravenous LD₅₀s 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

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 $\mu\text{g}/\text{plate}$. 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 $\mu\text{g}/\text{ml}$ without activation but was positive at 50-10 $\mu\text{g}/\text{ml}$ with activation (NCI, 1994).

When tested at 10-3000 $\mu\text{g}/\text{plate}$ 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 (Prester *et al.*, 1993).

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).

REFERENCES

ACGIH (1993) *1993-1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH

Aldrich Chemical Co. (1993) *Flavors and Fragrances Catalog - 1994*, Milwaukee, WI, p. 8

Aldrich Chemical Co. (1994) *Material Safety Data Sheet: Benzylideneacetone (Product No. W28810-1)*, Milwaukee, WI

Anon. (1993) *Flavor and Fragrance Materials - 1993*, Allured Publishing Corp., Carol Stream, IL, p. 41

Anon. (1994a) Ingredients added to tobacco in the manufacture of cigarettes by the six major American cigarette companies, a list provided by direct mail by the Consumer Affairs Department, Philip Morris Company (800-343-0975)

Anon. (1994b) Chemical prices, week ending January 21, 1994, *Chemical Marketing Reporter*, 245(4):31

Brorson, T., Bjorklund, I., Svenstam, G. & Lantz, R. (1994) Comparison of two strategies for assessing ecotoxicological aspects of complex wastewater from a chemical-pharmaceutical plant, *Environ. Toxicol. Chem.*, 13(4):543-552

Brulos, M.F., Guillot, J.P., Martini, M.C. & Cotte, J. (1977) The influence of perfumes on the sensitizing potential of cosmetic bases. 1. A technique for evaluating sensitizing potential, *J. Soc. Cosmet. Chem.*, 28:357-365

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Merck & Co., Inc., Rahway, NJ, p. 177

Canarus, V.M. (1993) Additive composition, acid zinc and zinc-alloy plating baths and methods for electrodepositing zinc and zinc alloys, US patent 5200057 A, 6 April 1993, McGean - Rohco, Inc. [STN abstract CA 119(16):169273c]

Chalk, A.J., Virgilio, J.A., Wertheimer, L. & Wertheimer, T.B. (1993) Palladium catalyzed process for making acrylic acids and their esters from arylamines and olefins, European patent application, EP 553668 A2, 4 August 1993, Givaudan-Roure (International) S.A., Switzerland [STN abstract, CA 119(19):203158]

Cheh, A.M. (1986) Mutagen production by chlorination of methylated α,β -unsaturated ketones, *Mutat. Res.*, 169:1-9

DIALOG (1994) The DIALOG Information Retrieval Service, PIERS Imports (File 574), *The Journal of Commerce/PIERS*, New York

Edenharder, R., von Petersdorff, I., & Rauscher, R. (1993) Antimutagenic effects of flavonoids, chalcones and structurally related compounds on the activity of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and other heterocyclic amine mutagens from cooked food, *Mutat. Res.*, 287:261-274

Edwards, M.L., Ritter, H.W., Stemerick, D.M., & Stewart, K.T. (1983) Mannich bases of 4-phenyl-3-buten-2-one: a new class of antiherpes agent, *J. Med Chem.*, 26(3):431-436

FEMA (1993) *FEMA Monograph: 4-Phenyl-3-buten-2-one*, Flavor and Extract Manufacturers' Association of the United States, Washington, DC

FEMA (1994) *FEMA Monograph: 4-Phenyl-3-buten-2-one (FEMA 2881)*, Flavor and Extract Manufacturers' Association of the United States, Washington, DC

Fukuhara, K., Fujimori, T., Shigematsu, H. & Ohnishi, A. (1987) Essential oil of *Scutellaria baicalensis* G., *Agric. Biol. Chem.*, 51(5):1449-1451 [STN abstract, CA 107:046151]

Givaudan-Roure Corp. (1993) *Specification Sheet: Benzylideneacetone (Product Code 1-2205)*, Specialties Division, Clifton, NJ

Haarmann & Reimer Corp. (undated) *Specification Sheet: Benzalacetone (Product No. 613009)*, Aroma Chemicals Division, Springfield, NJ

Hale, R.C. (1988) Disposition of polycyclic aromatic compounds in blue crabs, *Callinectes sapidus*, from the southern Chesapeake Bay, *Estuaries*, 11(4):255-263

Hunter, D., ed. (1993) *Chemical Week 1994 Buyers' Guide*, Chemical Week Associates, New York, NY, p. 162

Krasavage, W.J., O'Donoghue, J.L. & Divincenzo, G.D. (1981) *Ketones*. In: Clayton, G.D. & Clayton, F.E., Eds., *Patty's Industrial Hygiene and Toxicology*, 3rd ed., Vol. 2C, John Wiley and Sons, New York, pp. 4710-4711

Kuney, J.H., Ed. (1993) *Chemyclopedia 94: The Manual of Commercially Available Chemicals*, American Chemical Society, Washington, DC, p. 259

Lewis, R.J., Sr. (1993) *Hawley's Condensed Chemical Dictionary*, 12th ed., Van Nostrand Reinhold Co., New York, p. 136

Lide, D.R., Ed. (1993) *CRC Handbook of Chemistry and Physics*, 74th ed., CRC Press, Inc., Boca Raton, FL, p. 3-144

Matsuda, H., Ose, Y, Sato, T., Nagase, H., Kito, H. & Sumida, K. (1992) Mutagenicity from ozonation of humic substances, *Sci. Total Environ.*, 117/118:521-529

Matthews, E.J. (1992) Investigation of the α,β -unsaturated ketones: response to a request for CFSAN database information on the α,β -unsaturated ketones, memorandum of information from the Food and Drug Administration's Center for Food Safety and Applied Nutrition, December 16, 1992.

Millington, D.S., Bertino, D.J., Kamei, T. & Christman, R.F. (1983) Analysis of organic compounds adsorbed on granular activated carbon filters used in treatment plants, *Water Chlorination: Environ. Impact Health Eff.*, Vol. 4, Book 1:445-454

Murahashi, S-I & Naota, T. (1993) Ruthenium-catalyzed oxidations for selective synthesis of ketones and acyl cyanides. Selective acylation of amino compounds with acyl cyanides, *Synthesis*, 4:433-440.

Nakayama, T., Hara, A. & Sawada, H. (1982) Purification and characterization of a novel pyrazole-sensitive carbonyl reductase in guinea pig lung, *Arch. Biochem. Biophys.*, 217(2):564-573

NCI (1994) *NCI Short-Term Test Results: National Cancer Institute, Division of Cancer Etiology Short-Term Test Program*, Bethesda, MD

NIOSH (1992) *NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements (DHHS/NIOSH) Publ. No. 92-100*, Division of Standards Development and Technology Transfer, Cincinnati, OH

Ohta, T., Watanabe, K., Moriya, M., Shirasu, Y., & Kada, T. (1983) Anti-mutagenic effects of coumarin and umbelliferone on mutagenesis induced by 4-nitroquinoline 1-oxide or UV irradiation in *E. coli.*, *Mutat. Res.*, 117:135-138

Opdyke, D.L.J. (1973) Monographs on fragrance raw materials: Benzylidene acetone. *Food Cosmet. Toxicol.*, 11:1021

OSHA (1993) Air Contaminants. *U.S. Code Fed. Regul., Title 29*, Part 1910.1000, pp. 6-19

Popkin, D.J. & Prival, M.J. (1985) Effects of pH on weak and positive control mutagens in the Ames *Salmonella* plate assay, *Mutat. Res.*, 142:109-113

Prester, T., Holtzclaw, W.D., Zhang, Y. & Talalay P. (1993) Chemical and molecular regulation of enzymes that detoxify carcinogens, *Proc. Natl. Acad. Sci.*, 90(7):2965-2969

Prival, M.J., Sheldon, A.T., Jr., & Popkin, D. (1982) Evaluation, using *Salmonella typhimurium*, of the mutagenicity of seven chemicals found in cosmetics, *Food Chem. Toxicol.*, 20:427-432

Roussel, R. & Gaboury, A. (1987) Decoating of used beverage containers: environmental analyses, *Light Met.*, 1987:639-643

RTECS (1994) *Registry of Toxic Effects of Chemical Substances: 4-Phenyl-3-buten-2-one*, National Library of Medicine, Bethesda, MD, March, 1994

Sandmeyer, E.E. (1981) *Aliphatic Hydrocarbons*. In: Clayton, G.D. & Clayton, F.E., Eds., *Patty's Industrial Hygiene and Toxicology*, 3rd ed., Vol. 2B, John Wiley and Sons, New York, pp. 3194-3198

Sharp, D.W. (1978) The sensitization potential of some perfume ingredients tested using a modified Draize procedure, *Toxicology*, 9:261-271

Spencer, S.R., Xue, L., Klenz, E.M. & Talahay, P. (1991) The potency of inducers of NAD(P)H: (quinone-acceptor) oxidoreductase parallels their efficiency as substrates for glutathione transferases, *Biochem. J.*, 273(3):711-717

Ueyama, Y., Hashimoto, S., Furukawa, K. & Nii, H. (1989) The essential oil from the flowers of *Campsis grandiflora* (Thumb.) K. Schum. from China, *Flavor. Frag. J.*, 4(3):103-107 [STN Abstract, CA 118:066566]

USEPA (1991) Letter from Eastman Kodak Company to US EPA: Initial submission concerning an acute oral toxicity test with 4-phenyl-3-buten-2-one with attachments. United States Environmental Protection Agency, Office of Toxic Substances (USEPA No. 8EHQ-0391-1194)

US Food and Drug Administration (1993) Food and Drugs. *US Code Fed. Regul.*, Title 21, Part 172.515, pp. 48-55

Utesch, D., Traiser, M., Gath, I., Dorresteijn, A.W.C., Maier, P. & Oesch, F. (1993) Effects of sodium butyrate on DNA content, glutathione S-transferase activities, cell morphology and growth characteristics of rat liver nonparenchymal epithelial cells *in vitro*, *Carcinogenesis*, 14(3):457-462

Van, H., Ed. (1993) *OPD 1994 Chemical Buyers Directory*, 81st ed., Schnell Publishing Co., New York, NY, p. 242

Walker, J.D. (1994) Direct communication by telephone call between Dr. John Walker, Executive Secretary of the Interagency Testing Committee (ITC) and Dorothy Cannon of Technical Resources, Inc., February 15, 1994

Welling, W. & De Vries, J.W. (1985) Synergism of organophosphorus insecticides by diethyl maleate and related compounds in houseflies, *Pestic. Biochem. Physiol.*, 23(3):358-369

Yaozu, C., Zhaolin, L., Dunyuan, X. & Limin, Q. (1987) Determination of volatile constituents of Chinese medicinal herbs by direct vaporization capillary gas chromatography/mass spectrometry, *Anal. Chem.*, 59(5):744-748

Yates, R.L. & Wenninger, J.A. (1988) Fluorometric determination of benzylideneacetone in fragrance products by liquid chromatography with post-column derivatization, *J. Assoc. Off. Anal. Chem.*, 71(5):965-967

SEARCH RESOURCE LIST

DIALOG

BIOSIS (5)
NTIS (6)
PTS Prompt (16)
Chem. Ind. Notes (19)
Embase (72,172,173)
Fed. Reg. Abstr. (136)
PASCAL (144)
NIOSH/OSHA (161)
F-D-C Reports (187)
Merck Online (304)
Analytical Abstr. (305)
Chem. Bus. NewsBase (319)
Piers Imports (573,574)
PTS Newsletter (636)
Journal of Commerce (637)
Federal Register (669)

NLM

CANCERLINE
CCRIS
DART
EMICBACK
HSDB
MEDLINE 85,80
RTECS
TOXLINE
TOXLINE65
TOXLIT
TOXLIT65

CIS

CASR
SANSS

STN INTL

BEILSTEIN
CA/CAOLD
CAPREVIEWS
CHEMLIST
CSCHEM
HODOC
REGISTRY

MANUAL SOURCES

American Conference of Governmental Industrial Hygienists (1990) 1993-1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices, Cincinnati, OH, ACGIH

American Conference of Governmental Industrial Hygienists (1991) Documentation of Threshold Limit Values and Biological Exposure Indices, 6th Ed., Cincinnati, OH, ACGIH

American Conference of Governmental Industrial Hygienists (1990) Guide to Occupational Exposure Values - 1990, Cincinnati, OH, ACGIH

Budavari, S., ed. (1989) The Merck Index, 11th Ed., Rahway, NJ, Merck & Co., Inc. (available online as Merck Online)

Chemical Company Guides and Directories

Aldrich Catalog/Handbook of Fine Chemicals
Chemyclopedia
Chemical Week Buyers' Guide
OPD Chemical Buyers Directory

Chemical Information Services, Ltd. (1991) Directory of World Chemical Producers, 1992/93, Oceanside, NY

Clayton, G.D. & Clayton, F.E., eds. (1981) Patty's Industrial Hygiene and Toxicology, 3rd Rev. Ed., New York, John Wiley & Sons, Inc.

Considine, D.M., ed. (1989) Van Nostrand's Scientific Encyclopedia, 7th Ed., Vol. I, A-I, New York, Van Nostrand Reinhold

Considine, D.M., ed. (1989) Van Nostrand's Scientific Encyclopedia, 7th Ed., Vol. II, J-Z, New York, Van Nostrand Reinhold

Grayson, M., ed. (1978-1984) Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Ed., New York, John Wiley & Sons, Inc. (available online as Kirk-Othmer Online)

IARC (1972-1993) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vols. 1-49, Lyon, International Agency for Research on Cancer, Vols. 1-55

Lewis, R.J., Sr. (1993) Hawley's Condensed Chemical Dictionary, 12th Ed., New York, Van Nostrand Reinhold Co.

Lide, D.R. ed., (1993) CRC Handbook of Chemistry and Physics, 74th Ed., Boca Raton, FL, CRC Press, Inc.

Mannsville Chemical Products Corp. (1978-87) Mannsville Chemical Products Synopsis, Cortland, NY

Prepared for NCI by Technical Resources, Inc. under Contract No. NO1-CP-56019 (5/94; rev. 7/94)

National Toxicology Program (1994) Chemical Status Report, May 5, 1994 Report

National Toxicology Program (1994) NTP Results Report: Results and Status Information on All NTP Chemicals, April, 1994

Parmeggiani, L., ed. (1983) Encyclopedia of Occupational Health and Safety, 3rd. Ed., Vol. 1, A-K, Geneva, International Labour Office

Parmeggiani, L., ed. (1983) Encyclopedia of Occupational Health and Safety, 3rd. Ed., Vol. 1, L-Z, Geneva, International Labour Office

PHS-149 (1951-1988) Survey of Compounds Which Have Been Tested for Carcinogenic Activity, National Cancer Institute, U.S. Department of Health and Human Services

US International Trade Commission (1974-1991) Synthetic Organic Chemicals, US Production and Sales, US Government Printing Office

USP (1989) 1990 USAN and the USP Dictionary of Drug Names, Rockville, MD., United States Pharmacopeial Convention, Inc.

Verschueren, K. (1983) Handbook of Environmental Data on Organic Chemicals, 2nd Ed., New York, Van Nostrand Reinhold Co.

Weast, R.C. & Astle, M.J. (1985) Handbook of Data on Organic Compounds, Boca Raton, FL, CRC Press, Inc.