METHYL VINYL KETONE

CAS Number: 78-94-4

NTP Nomination History and Review

NCI Summary of Data for Chemical Selection

NTP NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute

2. Recommendation: -Carcinogenicity
-Mechanistic studies

3. Rationale/Remarks: -Commercially important synthetic intermediate
-Interest in toxicity of α,β-unsaturated ketones chemical class
-Parent compound of α,β-unsaturated ketones chemical class;
-Ubiquitous low level environmental pollutant
-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:

SUMMARY OF DATA FOR CHEMICAL SELECTION

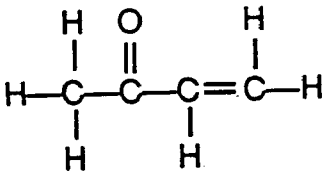
CHEMICAL IDENTIFICATION:

CAS Registry Number: 78-94-4

Chemical Abstracts Name: 3-Buten-2-one

Synonyms: Acetyl ethylene; 1-buten-3-one; 2-butenone; methylene acetone; methyl vinyl ketone; MVK; 3-oxobutene; 3-oxo-1-butene; r-oxo-α-butylene; vinyl methyl ketone

Structure, Molecular Formula, and Molecular Weight:



C_4H_6O Mol. wt.: 70.1

Chemical and Physical Properties:

Description: Colorless, flammable, liquid with pungent odor (Sax & Lewis, 1987; Budavari, 1989)

Boiling Point: 81.4°C (Budavari, 1989)

Melting Point: -7°C (Sax & Lewis, 1987)

Specific gravity: 0.84 at 20°C (Sax & Lewis, 1987)

Solubility: Readily soluble in water (10%), alcohols, ether, acetone, glacial acetic acid; slightly soluble in hydrocarbons (Budavari, 1989; forms a binary azeotrope with water with a boiling point of 75°C at 1 atm (HSDB, 1991)

Flash point: -66°C closed up (Sax & Lewis, 1987)

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

Octanol-Water Partition Coefficient (Log P):	-0.01 (Roberts, 1986)
Stability:	Uninhibited monomer may polymerize gradually on exposure to heat or sunlight; stabilized with hydroquinone (MTM Research Chemicals, Inc., 1991)
Reactivity:	Dangerous exothermic polymerization may be triggered by the action of air or alkalis; also reacts with oxidizing or reducing agents, ammonia, amines (MTM Research Chemicals, Inc., 1991)

Technical Products and Impurities: Methyl vinyl ketone (MVK) is commercially available in analytical grade at purities ranging from approx. 95% to 99% (FCD, 1991). MVK is stabilized with approx. 0.5% acetonitrile, 0.5% acetic acid, 0.5% hydroquinone and 3% water, 0.1% acetic acid and 0.05% hydroquinone, or with 1% hydroquinone (Aldrich Chemical Co., 1990; Janssen Chimica, 1990; Pfaltz & Bauer, 1990; MTM Research Chemicals, Inc., 1991).

BASIS OF NOMINATION TO THE CSWG

Conjugated carbonyl compounds represent a major class of chemicals, many of which have been shown to be biologically active. A class study was undertaken to focus on aliphatic α,β-unsaturated ketones (α,β-UKs) as a source of chemicals for which health effects testing may have been inadequate or lacking and for which there could be a structurally based potential for carcinogenicity. MVK emerged not only as the prototype of this subclass, the compound of lowest molecular weight and first in the series, but also as a compound with positive mutagenicity data and an absence of long term studies. Not only is it a chemical used commercially as a reactant and chemical intermediate but it is a ubiquitous low-level pollutant found in several environmental media. Several research groups (Chung *et al.*, 1988; Neudecker *et al.*, 1989; Eder *et al.*, 1990) have called attention to MVK's interaction with DNA or recommended that this chemical be tested for carcinogenicity.

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

SELECTION STATUS

ACTION BY CSWG: 12/13/91

Studies Requested: As a pair with ethyl vinyl ketone, nominated for carcinogenicity bioassay and also for mechanistic studies.

Priority: High

Comments: Crotonaldehyde, an analog of MVK, gave a positive result in an NTP *Salmonella* assay, giving good circumstantial evidence for investigating MVK.

EXPOSURE INFORMATION

Commercial Availability

Production and Producers: MVK and its analogs can be produced commercially by an Oppenhauer-type oxidation of the corresponding secondary alcohol. Numerous publications describe various catalysts which can be used to achieve the synthesis of MVK in reasonable yields (Nakano *et al.*, 1987). The precursor, 3-ketobutanol can be formed by condensation of acetone with formaldehyde (HSDB, 1991). Another route involves catalyzed oxidation from 1-butene, used as the starting material (Sinfelt & Barnett, 1976).

Two pharmaceutical manufacturers reported manufacture of this chemical to the EPA's TSCA plant and production database (TSCAPP, 1991). Pfizer, Inc., Groton, CT, reported annual production of 10,000 to 100,000 lbs, and Hoffmann-LaRoche, Inc., Nutley, NJ, declared no production volume (according to a company spokesman, they import MVK stocks from Switzerland). No companies specifically reported imports to the EPA for their TSCAPP data gathering effort. No other data on annual production volumes were found in the available literature. Recent press reports mention several additional companies currently using MVK in the manufacture of copolymers, including Ecolyte Atlantic, Inc. of Baltimore and EcoPlastics Ltd. of Ontario (Anon., 1988a; Anon. 1988b). MVK is also available in research quantities from CTC Organics, Monomer-Polymer & Dajac Labs (MTM Chemicals), and Pharmaglobe Laboratories, Ltd. Aldrich Chemical Co., Alfa Products, American Tokyo Kasei, Inc., Chem Service,Inc., Fluka Chemical Corp., GFS Chemical Co., Janssen Chimica, Lancaster Synthesis, Ltd., Pfaltz & Bauer, Inc., Riedel-De Haen AG, and Sigma Chemical Co. (FCD, 1991). Exxon Chemical Co. included MVK in a 1968 TSCA §8d submission to EPA on a series of ketones.

Aristech Chemical Corp., Eastman Kodak Co., Exxon Research & Engineering Co. and Mitsui Petrochemical Industries, Ltd. have been issued patents for syntheses of MVK and other unsaturated ketones and other pharmaceutical companies have had an interest in the use of this compound, including Hoffmann-LaRoche and Co. A.-G., Lilly Industries Ltd., Merck & Co., Squibb & Sons, Inc. and SmithKline Beckman Corp. (McMahon *et al.*, 1979;

Lukac & Soukup, 1988; Woltersdorf *et al.*, 1989; Badger *et al.*, 1989; Biller & Misra, 1989; Hotten *et al.*, 1990).

Use Pattern: MVK is an important monomer used in many polymer systems to produce plastics and resins. It is offered as a unique ketone monomer with good reactivity toward acrylates, methacrylates, vinyls and itaconates. It serves as a UV-sensitive comonomer which can be grafted to polyethylene, polypropylene, polyethylene terephthalate, polyvinyl chloride, nylon and polystyrene for improved degradability of such products as packaging materials. Styrene-MVK copolymers, for example, are useful as photodegradable polymers in packaging applications (Papa & Sherman, 1981). It has also been reported to be a component of a chain transfer agent used in the manufacture of low density polyethylene (LDPE). MVK dimerizes catalytically to form 3-methylene-2,6-heptadione which is also useful as a polymer precursor (Basavaiah *et al.*, 1987). Various homopolymers of MVK, which can be induced by imidazole in water-ethanol mixtures, are also useful in further polymerization reactions (Ozu *et al.*, 1989).

MVK is a versatile reactive chemical, alkylating agent, and important Michael acceptor used as a starting material in numerous commercial- and research-scale organic syntheses. This conjugated ketone is a starting material in a Skraup synthesis of 4-methylquinoline (Holter, 1982) and in a Michael reaction to yield the indole derivative, 1-(3'-indolyl)-butan-3-one (Bannister, 1981). It has been reportedly used in the pharmaceutical, agricultural chemical, cosmetic, coatings, and adhesives industries and in bioengineering. For example, Chapman *et al.* (1990) reported that the synthesis of potent hypolipidemic agents (anticholesteremics) started with the Michael addition of MVK to appropriately substituted phthalimides. MVK is used as a pharmaceutical intermediate in the synthesis of steroids and vitamin A and pyrazole derivatives as inhibitors of blood platelet aggregation (Ferroni, *et al.*, 1989; Matsuda, 1987; Nakayana *et al.*, 1985; Sax & Lewis, 1987; Tanaka, *et al.*, 1982). The U.S. Department of Agriculture was granted a patent in 1989 to use MVK as a chemical intermediate in the production of natural pesticides (Chuman *et al.*, 1989). Firmenich S.A.

was granted a patent in 1990 for the preparation of tricyclic spiroketone perfume ingredients using MVK as a starting material (Giersch & Schulte-Elte, 1990).

Human Exposure: Human exposure to mutagenic α,β-unsaturated carbonyl compounds, including MVK, is said to be widespread by both exogenous and endogenous routes (Chung *et al.*, 1986). The odor threshold concentration for olfactory recognition of MVK is 0.5720 mg/m^3 (Ruth, 1986) or is approximately 200 ppb (Waritz, 1988).

Occupational exposure may occur by inhalation or contact as a result of use of MVK as an alkylating agent, chemical intermediate and monomer in polymer manufacture. MVK can be readily absorbed dermally and is considered extremely hazardous and toxic by all routes of exposure (HSDB, 1991).

Hercules, Inc., in a 1988 FYI submission to the EPA, reported the formation of small amounts of MVK in the combustion zone of a plant incinerator burning waste methyl ethyl ketone from a plant process (Waritz, 1988). They reported an approximately 25 ppm concentration of MVK exiting the incinerator combustion area which was reduced to approximately 2 ppm by a secondary catalytic combustion unit. A computer model downwash prediction, taking into consideration the locale of the plant, estimated an 8-hour average ground level concentration of 1 ppb MVK at the point of nearest human habitation.

MVK has been documented as one of the many combustion products found in cigarette/tobacco smoke (Curvall *et al.*, 1984; Florin *et al.*, 1980). Kusama *et al.* (1978) reported a semi-quantitative estimate of this low-boiling compound in cellulose cigarette smoke of 0.13 mg/cigarette.

Niemand *et al.* (1983) investigated the effects of γ-radiolysis on major sugars in subtropical fruits in connection with the safety of food irradiation. They identified MVK as one of the radiolytic products.

Sheiseido Laboratories has reported that MVK arises as one of several oxidation products resulting from the reaction of linalool, a common ingredient of perfumes, with cosmetic pigments in the presence of air (Sheiseido Laboratories, 1988).

Ase *et al.* (1985) reported MVK to be among a number of trace gaseous species identified in the combustion products obtained from firings of an M16 rifle.

Environmental Occurrence: MVK has been reported to be a naturally occurring compound. Shimizu (1982) identified MVK as a volatile component of grape musts of the Muscat of Alexandria variety. Isidorov *et al.* (1985) found this substance in the volatile organic compound (VOC) emissions characteristic of northern hemisphere forests. They identified two arboreous plant sources of MVK as aspen and European oak. MVK has also been identified in the underground environment of mines as a component of toxic fumes resulting from pyrolysis of virgin red oak and virgin and fire and rot retardant-treated Douglas fir (Christos & Hay, 1986).

Kallio (1989) described MVK as a component of natural birch syrup derived from birch sap by dehydrogenation. Jackson *et al.* (1990) identified MVK as a component of Dufour gland secretion in *Manica rubida* worker ants.

According to Herrington *et al.* (1987), MVK is a natural soil fungistatic agent. It is a volatile compound produced by the microorganism, *Streptomyces griseoruber*, and acts as a strong inhibitor of the spore germination of *Cladosporium cladosporioides*.

MVK has been reported to be one of several oxygen-containing impurities in crude isoprene used in the production of rubber, butadiene, 3-buten-2-ol and methyl ethyl ketone. Noguchi *et al.*, (1983) reported a 9.7% by-product yield of MVK in the synthesis of vinyl ether monomers. It has also been identified as a breakdown product in the autoxidation of isoprene and as a by-product of whiskey manufacture and biomass combustion.

MVK is an ubiquitous low-molecular weight oxygenated organic air pollutant. Jonsson and Berg (1983) identified MVK in city air and stressed the need to determine details of the occurrence and distribution of such oxygenates in ambient atmospheres, their possible role in photochemical smog formation, and their toxic and potentially carcinogenic properties. Jonsson *et al.* (1985) found this chemical in five sites of ambient air sampling in a one-year study of Stockholm air. These researchers documented higher concentration of MVK at two urban sites than at sites outside the city and reported a strong correlation of ambient air MVK concentrations at these two sites with vehicle exhaust concentrations. Westerholm *et al.* (1990) identified MVK in passenger car exhausts measured under different driving conditions; and Westerholm *et al.* (1991) determined that levels of MVK in exhaust emissions from a heavy duty diesel vehicle during transient driving conditions were in the range of 12 $\pm$5.9 mg/km.

Dumdel and Kenny (1988) identified MVK as a breakdown product resulting from the photooxidation of toluene in polluted urban atmospheres. They reported a determination of 6 ppb effluent concentration of the ring fragmentation product, MVK. In order to correlate ambient environmental pollutant levels with human body burden, Pellizzari *et al.* (1982) identified MVK in human milk in one of 12 samples from four urban areas studied. The atmospheric photochemical degradation of MVK by hydroxyl radicals was reported to be relatively rapid (half-life in air: ~20.8 hr.). MVK's fate in soil was reported to be less well documented, but leaching was considered likely based on an estimated K_{oc} value of 28.

MVK is a pollutant frequently found in industrial wastewaters (Levec, 1990). Several citations have identified MVK as a wastewater component resulting, for example, from the oxidative dehydrogenation of butenes (Chen *et al.*, 1983). Hall *et al.* (1986) studied the thermal decomposition characteristics of a 12-component mixture of organic solvents, including methyl ethyl ketone (MEK), devised to simulate an actual waste stream subjected to incineration in a liquid-injection incineration unit. MVK was among the stable thermal reaction products reported to occur at 650°C with a decomposition dependence observed relative to time-at-temperature and O_2 concentration in the decomposition atmosphere.

MVK was classified as a major product of incomplete combustion (PIC) in this system. The authors raised concern that products may be more toxic than input materials in full scale thermal destruction of VOC input materials and warrant attention as potential hazards. In fact, as reported above in the Human Exposure section, Hercules, Inc., identified MVK as a combustion zone PIC resulting from incineration of plant process MEK (Waritz, 1988).

Regulatory Status: MVK is listed as a hazardous chemical subject to transportation restrictions for labeling and handling (49 CFR 171-177). MTM Research Chemicals, Inc. (1991) recommends disposal by incineration and advises that MVK will not degrade microbiologically in wastewater treatment plants and should never be discarded by drain.

MVK is listed in the TSCA inventory and is subject to several rules under SARA. The following information is summarized based on a search of the CHEMLIST database (CHEMLIST, 1991).

TSCA/FYI: Toxicity/Exposure study and environmental fate monitoring information (Hercules study cited above), 12/30/88

SARA/Title III: Extremely hazardous substance under Section 302, proposed in FR 52 #77:13378, 4/22/87.

CERCLA: Hazardous substance under Section 102(a), proposed in FR 54 #13:3388, 1/23/89.

SARA/Title III: Final rule on reporting requirements under Section 313 (Toxics Release Inventory) revising reporting under Sections 311 & 312; proposed reduction from a reporting threshold (RT) of 10,000 lbs. to 500 lbs., 3/29/89.

EPA reported the following regulatory information in Anon. (1987):

Toxicity Value Used for Listing Under Section 302: LC_{50} inhalation (rat) = 0.007 mg/liter/4 hours

TPQ: 10 (lbs)

RQ: 1 (lb) (statutory, for notification under SARA Section 304(a)(2))

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports associating MVK with a cancer risk in humans were found in the published literature [see Search Resource List]. MVK is a lachrymator, highly irritating to skin, eyes and mucous membranes and is readily absorbed. Contact of eyes or skin with the liquid or inhalation of vapors is to be avoided (MTM Research Chemicals, Inc., 1991).

Animal Data: No chronic carcinogenicity studies of MVK in animals were found in PHS-149 or the published literature [see Search Resource List]. This chemical has not been studied in a 2-year bioassay by the NTP or evaluated by the IARC. Available information indicates that MVK is not currently on test or scheduled to be tested in a chronic/carcinogenicity mammalian bioassay.

A maximum tolerated dose (MTD) in mice by intraperitoneal injection was established as 15.7 mg/kg (Anon., 1949). A postmortem examination on a male albino rat administered 0.2 ml of MVK by mouth (which resulted in cardiac arrest within 24 hours) revealed petechial pulmonary hemorrhages, "spectacle eye" (erythrodacryorrhea), and marked distention of the gastrointestinal tract (Anon., 1982). Additional acute toxicity data reported in RTECS (1991) include the following:

oral rat LD_{50}: 30 mg/kg
inhalation rat LC_{50}: 7 mg/m^3/4h
oral mouse LD_{50}: 33 mg/kg
inhalation mouse LC_{50}: 8 mg/m^3/2h
intraperitoneal mouse LD_{50}: 76 mg/kg

MVK has been described as a model alkylating agent and Michael acceptor which binds to cellular protein sulfhydryl groups and glutathione (GSH). Zollner (1973) examined the effect of MVK on respiration of isolated rat liver mitochondria and documented its high affinity for sulfhydryl groups. Lash and Woods (1991) studied MVK's cytotoxicity to

freshly isolated rat kidney nephron cells. They described their findings of irreversible cellular injury with distal tubular cells showing greater susceptibility to injury from MVK than proximal tubular cells. Incubation of cells with MVK led to altered cellular GSH status and pronounced inhibition of mitochondria. MVK 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: MVK was reported to be positive by the NTP in an Ames/*Salmonella* assay (NTP, 1991); no other testing of this chemical was reported. Various other *in vitro* tests of this chemical have produced mixed genetic toxicity indications and are summarized as follows.

McMahon *et al.* (1979) screened 855 chemicals in a large industrial laboratory setting using a modification of the Ames bioassay. Ten tester strains including 8 histidine auxotrophs and 2 tryptophan auxotrophs were used. MVK was reported as negative, but specific details regarding results in each of the tester strains were not reported.

Florin *et al.* (1980) tested 239 chemicals identified as tobacco smoke constituents, including MVK, for mutagenicity in *S. typhimurium* strains, TA98, TA100, TA1535, and TA1537, both with and without S-9 activation. The spot tests were carried out using 3 μmol/plate. MVK was listed as non-mutagenic with no further details reported.

Curvall *et al.* (1984) described α,β-UKs occurring in the neutral fraction (28% of the semi-volatile fraction) of cigarette smoke concentrates, including MVK, as highly reactive electrophiles that can combine with biochemical nucleophiles and constitute a highly cytotoxic group of compounds. They tested this fraction in 6 short term systems and found MVK to be a highly potent inducer of SCE. In a general cytotoxicity screening of tobacco smoke constituents in Ascites sarcoma BP8 cells, the unsaturated ketones as a group were

found to be among the most active constituents and MVK was reported to cause only 5% inhibition at a 1 mM concentration (Pilotti *et al.*, 1975).

Lutz *et al.* (1982) studied the mutagenicity of α,β-unsaturated carbonyl compounds and their corresponding allylic alcohols in an Ames/*Salmonella* test using strain TA100. They reported MVK to be mutagenic with and without S-9 activation as follows: 450 revertants/μmole without S-9; 250 revertants/μmole with S-9.

Niemand *et al.* (1983) investigated gamma-radiolysis products formed during irradiation of sugar solutions, including MVK, for mutagenicity in an Ames/*Salmonella* test using strains TA98, TA100, TA1535, TA1537 and TA1538. They reported that MVK (and analog, crotonaldehyde) were highly cytotoxic but that no mutagenic activity was obtained under the conditions of the test. They reported that, due to the volatility of these 2 compounds, they could not be tested quantitatively.

Marnett *et al.* (1985) tested MVK and 27 other carbonyl compounds in *S. typhimurium* strain TA104. They reported this compound to be negative for mutagenicity with a maximum non-toxic dose of 0.7 μmoles.

Williams *et al.* (1989) tested 300 chemicals, including MVK, for genotoxicity in a rat hepatocyte/DNA-repair system using hepatocytes isolated from adult male F344 rats. They reported negative results with MVK.

Chung *et al.* (1988), citing above referenced evidence of the mutagenicity of MVK (Lutz *et al.*, 1982) as strongly suggestive that this chemical might be capable of reacting with cellular DNA, demonstrated the formation under mild experimental conditions (24.3 mmoles added to 75 ml of phosphate buffer at pH 7.0 containing 1.1 mmoles of deoxyguanosine) of 2 major deoxyguanosine-MVK adducts. Two guanine adducts produced under basic conditions were also identified. The authors speculated that these adducts formed *in vitro* could play a role in the mutagenicity and/or potential tumorigenicity of this chemical.

Eder *et al.* (1990) confirmed the results of Chung *et al.* (1988) by demonstrating the formation of MVK-deoxyguanosine and MVK-guanine adducts. They further conducted mutagenicity/genotoxicity tests with this chemical, reporting the following results: positive in an Ames/*Salmonella* test using strain TA100 with a result of 472 revertants/7μmole; positive in an SOS Chromotest using *E. coli* strain PQ37 with an inducing potency of 7.3 x 10^{-3};and positive in an SOS Chromotest using strain *E. coli* PM21 with an I_{MAX}(maximal SOS induction factor) of 2.1 where genotoxicity is considered significant at an $I_{MAX}$of 1.5.

Neudecker *et al.* (1989) studied MVK in an Ames/*Salmonella* assay in strain TA100 for mechanism and characterization of the mutagenic effect. Concluding that this compound is an unequivocal mutagen under optimal conditions and that its genotoxic effect involved epoxidation of the carbon-carbon double bond, these researchers recommended MVK be tested for carcinogenicity and noted that a related compound, crotonaldehyde, has been shown to be carcinogenic to laboratory animals.

MVK was studied as one of a group of unsaturated compounds structurally related to acrolein for possible antimutagenic properties relative to UV-induced mutagenesis in *E. coli* strain B/r WP2. Aikaiva and Chikuni (1989) reported that MVK was antimutagenic based on the following results: doses of 15, 30, and 45 μg/plate yielded 234, 105 and 46 Trp^+ colonies per plate, respectively, with 121, 123, and 114 viable cells per plate, respectively.

Metabolism: Ketones are known to undergo metabolic transformations to the corresponding alcohols, diols, epoxides and various other metabolites. Conversion in mammals to the relatively less toxic alcohols is reported to proceed slowly (Pilotti *et al.*, 1975).

Ivanetich *et al.* (1978) studied the interaction of MVK with hepatic microsomal cytochrome P-450 and its effect on hepatic microsomal drug metabolizing enzymes. They reported that MVK bound to hepatic microsomal P-450 in a type I manner and that it enhanced CO-inhibitable NADPH oxidation *in vitro*. In rat liver mitochondria, MVK is an alkylating agent and inhibitor of cellular (mitochondrial) respiration, less potent than acrolein by one

order of magnitude. It is an inhibitor of glutamate transport, inorganic phosphate transport, and succinate dehydrogenase activity.

Compounds with ketone functionality are known to react reversibly with glutathione (GSH). α,β-UKs are considered classic substrates for a 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 aldehyde, 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. Crotonaldehyde, a close analog of MVK with the structure, $CH_3CH{=}CHCHO$, was found to be mutagenic in an Ames/*Salmonella* test using strain TA100 both with and without S-9 activation. Crotonaldehyde was also tested by the NTP and found positive in three test systems - *Salmonella*, *Drosophila*, and *in vitro* cytogenics (NTP, 1991). It has been reported by Neudecker *et al.* (1989) to be carcinogenic to laboratory animals.

Mesityl oxide (isobutenyl methyl ketone; MO), an analog of MVK and a widely used industrial chemical, has been reported by Clayton and Clayton (1981) to cause narcosis, liver, lung, spleen and kidney toxicity. EPA issued a final test rule under TSCA §4(a) in 1985 establishing health effects testing requirements for MO by manufacturers and processors (CIN, 1991).

Cheh (1986) reported that MO was non-mutagenic but chlorinated MO, formed in substantial amounts at pH's between 7.5 and 9.5 in chlorinated wastewater polluted with

MO, was mutagenic in an Ames/*Salmonella* assay using strain TA100. Brondeau *et al.* (1990) studied the effect of airborne MO administered in a laminar air flow chamber for a single 4-hour duration at irritant concentrations to intact and adrenalectomized male Sprague-Dawley rats. MO caused a significant leucocytosis in blood of exposed adrenalectomized rats in a dose dependent fashion.

According to information available in EPA's public files (Anon., 1991) the Chemical Manufacturers Association (CMA) Ketones Program Panel has committed itself to overseeing voluntary testing by industry of saturated ketone analogs, methyl ethyl ketone (MEK) and methyl isobutyl ketone (MIBK).

Eder *et al.* (1982) compared the alkylating activity of a group of 12 α,β-unsaturated compounds with otherwise varying structural features. They found a nearly quantitative overall correlation between alkylating and direct mutagenic activities for this set of compounds.

Portoghese *et al.* (1989), in a study of α,β-UK reactivity toward glutathione, compared MVK to N-ethylmaleimide which has been documented to have high selectivity and reactivity toward sulfhydryl groups. They reported that MVK reacted 30 times slower with GSH than N-ethylmaleimide.

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