SUMMARY OF DATA FOR CHEMICAL SELECTION

Allyl Acetate

CAS # 591-87-7

and

Allyl Alcohol

CAS # 107-18-6

NTP NOMINATION HISTORY AND REVIEW

Nomination History

- Nomination Source: National Cancer Institute

Recommendations:

- Metabolism
- Carcinogenicity

Rationale/Remarks:

- Allyl acetate and allyl alcohol were nominated as a pair of chemicals

- High production

- Potential for high occupational and consumer exposure based on its extensive use in organic synthesis, agriculture and flavoring agents

- Mutagenic in Salmonella and mouse lymphoma assays

- Available carcinogenicity studies in rats and hamsters were negative but these studies were inadequate (insufficient number of doses, and animals in rat and hamster studies; only one sex used in hamster study)

- Higher priority for carcinogenicity testing should be assigned to allyl acetate; if allyl acetate proves to be carcinogenic, priority for carcinogenicity testing of allyl alcohol should be increased

Priority: High

- Date of Nomination: 4/1993

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CHEMICAL IDENTIFICATION
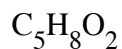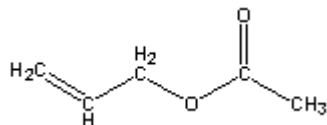
Allyl Acetate

CAS Registry Number:	591-87-7
Chem. Abstracts Name:	Acetic acid, 2-propenyl ester (9CI);
	Acetic acid, allyl ester (8CI)
Synonyms and Trade Names:	Allyl alcohol, acetate;
	3-acetoxy-1-propene;
	3-acetoxy- propene

Allyl Alcohol

CAS Registry Name:	107-18-6
Chemical Abstracts Name:	2-Propen-1-o1 (9CI)
Synonyms and Trade Names:	Allylic alcohol;
	3-hydroxypropene;
	1-propenol-3;
	2-propenol;
	2-propenyl alcohol;
	Shell unkrautted A;
	Weed Drench;
	vinyl carbinol

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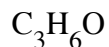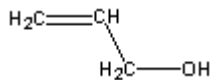
Allyl Acetate

$C_5H_8O_2$ Mol. wt.: 100.12

Allyl Alcohol

C_3H_6O Mol. wt.: 58.08

Chemical and Physical Properties

Allyl Acetate

Description: Colorless liquid with an acrid odor at high levels (HSDB, 1991)

Boiling Point: 103.5°C at 760 mm Hg (Weast, 1989)

Melting Point: 22°C (HSDB, 1991)

Solubility: Slightly soluble in water; soluble in acetone; very soluble with alcohol and ether (Weast, 1989; Sandmeyer & Kirwin, 1981)

Stability: Acrid smoke and irritating fumes are emitted when heated to decomposition (Sax & Lewis, 1987). Can be ignited under ambient conditions (HSDB, 1991)

Reactivity: Reacts with oxidizing materials (Sax & Lewis, 1989)

Density: 0.9276 g/ml (Weast, 1989)

Vapor Density: 3.45 (Sax & Lewis, 1989)

Refractive Index: 1.4049 (Sandmeyer & Kirwin, 1981)

Flash Point: 21°C (Sandmeyer & Kirwin, 1981)

Allyl Alcohol

From Budavari (1989) unless otherwise noted.

Description: Colorless liquid with a pungent mustard-like odor

Boiling Point: 96-97°C

Melting Point: -129°C (Weast, 1989)

Solubility: Miscible with water, alcohol, chloroform, ether, and petroleum ether

Density: 0.8540 (at 20°C/4°C)

Vapor Pressure: 20 mm @ 20°C; 32 mm @ 30°C (Verschueren, 1983)

Flash Point: 70°F (open cup), 75°F (closed cup)

Stability: Stable at ordinary temperatures and pressures (Weiss, 1986); Polymerizes and forms a thick syrup upon storage for several years

Technical Products and Impurities:

Allyl Acetate. Allyl acetate is available from Aldrich Chemical Co., Inc. (1990) at 99% purity and from Pfaltz & Bauer, Inc. (1991) at 98% purity.

Allyl Alcohol. Allyl alcohol is available from Aldrich Chemical Co., Inc. (1990) at 99% purity.

BASIS OF NOMINATION TO THE CSWG

Allyl acetate is used in several industries. Applications include the production of plastics and resins, as a builder in detergent compositions, in hair conditioning formulations, in the manufacture of ester-containing siloxanes for brake fluids, and, perhaps most important, as a synthetic flavoring agent in foods and beverages. These varied uses cause concern for occupational as well as consumer exposure to allyl acetate.

Evidence on which to evaluate the potential for human carcinogenicity is limited. No case reports or epidemiological studies associating allyl acetate with a cancer risk in humans has been reported. Allyl acetate is known to be highly irritating and toxic by ingestion, inhalation, and eye and dermal contact. Allyl acetate is an eye, skin, and respiratory tract irritant. Experimental animal data is limited. A study in rat liver homogenates indicates that enzymatic hydrolysis is a necessary step in the activation of allyl acetate to a hepatotoxin. In vivo studies in rats indicate that allyl alcohol is a metabolic intermediate. Urinary metabolites in rats injected subcutaneously with allyl acetate include 3-hydroxypropylmercapturic acid and N-acetyl-S-(3-hydroxypropyl)-L-cysteine.

Allyl acetate is a direct mutagen in Salmonella typhimurium strains TA1535 and TA100 when tested without metabolic activation; when tested with activation, mutagenicity was not observed, presumably due to hydrolysis to allyl alcohol. In addition, allyl acetate was negative with or without metabolic activation in strains TA1537, TA1538, and TA98 and was negative for mitotic gene conversion in Saccharomyces cerevisiae and for structural chromosome damage in a cultured rat-liver epithelial-like cell line.

The CSPG suggested that allyl alcohol be reviewed along with allyl acetate because of metabolism considerations. In addition, allyl alcohol was nominated to the CSWG based on its extensive use in organic synthesis beginning in 1947, and the attendant potential for exposure to workers in the chemical industry. Its applications in agriculture and flavoring agents extend this exposure potential to the general population. The mutagenicity of allyl alcohol has been demonstrated in both the Salmonella and mouse lymphoma assays. Although a negative long-term carcinogenicity study in rats and hamster was identified, there were several short-comings to the assay including the use of a single dose, a limited number of animals employed, and only one sex studied in hamsters.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

The following information on allyl acetate and allyl alcohol was received from the ITC:

Allyl acetate is a member of an ITC computerized substructure-based group; it has been detected in feral and food animals and is listed in NOES.

Allyl alcohol was recommended for testing in the ITC's 28th Report. It is a chemical for which EPA has insufficient data to set a confident risk level and was recommended to have those data developed. Non-public production and exposure information as well as lists of health and safety studies will be made available to the CSWG, after the TSCA section 8(a) and 8(d) submissions have been received by the ITC.

SELECTION STATUS

ACTION BY CSWG: 9/26/91

Priority: High

Studies Requested: Metabolism studies; carcinogenicity bioassay (allyl acetate)

Comments:	Nominated for testing as a pair. It was suggested that initially primary interest should be on allyl acetate because it is an approved food additive. Should allyl acetate prove to be carcinogenic, then the alcohol analog's priority should be increased. The selection of the compounds was based on potential for high human exposure, high production volume (both compounds taken together), and lack of information. By putting allyl acetate in metabolism studies, affected target tissues, other than the liver, may be found.

EXPOSURE INFORMATION

Commercial Availability:

Production and Producers:

Allyl Acetate. Allyl acetate is synthesized via decarboxylation by heating allylmalonic acid or from the corresponding ethyl ester prepared by boiling ethyl 4-chloro-n-valerate in quinoline (HSDB, 1991). When used in the production of 1,4-butanediol, allyl acetate is obtained by passing a mixture of propene, acetic acid, and oxygen over a palladium catalyst deposited on alumina and used in subsequent steps (Beacham, 1978). Allyl acetate can also be obtained by the vapor-phase reaction of propylene and acetic acid (Schoenberg *et al*., 1982).

Although one plant is listed in TSCAPP as a manufacturer of allyl acetate, no production volume was reported for 1977 (TSCAPP, 1991).

According to a representative of Penta Manufacturing Co. (1991), allyl acetate was previously manufactured by Union Carbide Corp. at a plant in Sisterville, WV.

Penta Manufacturing Co. (1991) currently produces 3,000 to 4,000 pounds per year of a specialized grade of allyl acetate used for flavoring, cosmetics, and pharmaceuticals.

Allyl acetate is also available from Fluka Chemical Corp. and several chemical suppliers including Pfaltz & Bauer, Inc., Monomer-Polymer and Dajac Labs., Inc., Kodak Laboratory Chemicals, K & K Laboratories, Fisher Scientific Company, Chem Service, Inc., Crescent Chemical Co., Inc., Atomergic Chemetals Corp., American Tokyo Kasei, Inc., and Aldrich Chemical Co., Inc. (CSChem/CSCorp., 1991; *OPD Chemical Buyers Directory*, 1991).

Allyl Alcohol. In the U.S., allyl alcohol is prepared commercially by three processes. The first commercial process came on stream in 1947 and employs the alkaline hydrolysis of allyl chloride. Reaction conditions involve steam injection and temperatures of about 150°C that assure nearly quantitative conversion of the chloride. A more recent commercial process employs oxidation of propylene to acrolein, which in turn reacts with a secondary alcohol to yield allyl alcohol and a ketone. This allyl alcohol is not isolated but its aqueous solution is converted directly to glycerol via reaction with hydrogen peroxide. In the most recent commercial process allyl alcohol is prepared by isomerization of propylene oxide over a lithium phosphate catalyst (Beacham, 1978).

Over the past 25 years, major U.S. manufacturers of allyl alcohol have included FMC, Shell Chemical Co., Arco Chemical Co. and Dow Chemical Co. (Anon., 1991a; USITC, 1961-1989). Of these companies, only Arco continues to produce allyl alcohol. In 1990, Arco opened a new allyl alcohol plant, a key component in its 75-million pound-per-year butanediol and derivatives complex at Channel View, TX. The allyl alcohol produced is used for external sale as well as internal feed stock for the butanediol facility (Anon., 1990).

Current domestic production volumes for allyl alcohol were not found in the literature [see Research Resource List]. However, Beacham (1978) reported that the bulk of allyl alcohol is consumed in the manufacture of glycerol and that total U.S. plant capacity for this conversion is approximately 50 kilotons while other uses of allyl alcohol total about 10 kilotons. The U.S. demand for allyl alcohol together with its 1,4-butanediol derivative has been predicted to increase from 40 million pounds in

1990 to 120 and 265 million pounds for 1995 and 2000 respectively (Anon., 1991b; The Freedonia Group, 1991).

According to the public portion of the TSCA inventory, in 1977 from 21 to 110 million pounds of allyl alcohol were produced (TSCAPP, 1991).

Importation volumes for allyl alcohol in 1984 and 1986 were 959,010 and 2,160,000 pounds respectively (HSDB, 1991).

Use Pattern:

Allyl Acetate. Allyl acetate is a reactive compound which is employed in several industries. The food and beverage industry uses allyl acetate as a synthetic flavoring agent. It has a sour, caramellic flavor with a sweet aftertaste. Allyl acetate is typically used in non-alcoholic beverages at 1.0 ppm; in ice cream, ices, etc. at 2.0 ppm; in candy at 5.0 ppm; in baked goods at 5.0 ppm; and in margarine at 2.0 ppm. It is also used in cheese, butter, and fruit (HSDB, 1991).

Allyl acetate is used in the synthesis of several chemicals. It has been used in the preparation of copolymers with maleic anhydride, acrylonitrile, vinyl chloride-vinyl laurate, vinylidene chloride, ethylene, methyl cyanoacrylate, and other monomers; and in the production of fire resistant rigid polyurethane foams (Fluka Chemical Corp., 1991). It is an important intermediate in the synthesis of 1,4-butanediol, which in turn is used principally in the synthesis of linear polyester resins (Beacham, 1978). Recently, a new approach has been described that uses allyl acetate in the presence of a palladium(II) catalyst to prepare the key intermediate, a (E)-5-acetoxy-3,4-dehydronorvaline derivative, in the synthesis of racemic (E)-2-amino-5-phosphono-3-pentenoic acid (Kirihata *et al.*, 1990). It has been suggested that allyl acetate can be used in the allylation reaction of (diethoxyphosphinyl)difluoromethyl zinc bromide with copper bromide as the catalyst to synthesize 1,1-difluoro-3-alkenephosphonates (Burton & Sprague, 1989). In addition, allyl acetate with palladium(O) catalysts is a specific N-alkylating agent in the synthesis of 1-alkyl-2(1H)pyrimidones (Keilen *et al.*, 1987). Butanediol and tetrahydrofuran have been prepared from propylene via allyl acetate (Smith, 1977, 1978). In addition, triacetin is prepared by reaction of oxygen with a liquid phase mixture of allyl acetate and acetic acid using a bromide as the catalyst (Budavari, 1989).

Allyl acetate is also used as an intermediate in General Electric's route to the 1,4-butanediol component of polybutylene terephthalate (Anon., 1976).

Other applications of allyl acetate include use as a builder for detergent compositions (replacing sodium tripolyphosphate); in hair conditioning formulations; and in the manufacture of ester-containing siloxanes for brake fluids (Fluka Chemical Corp., 1991).

Allyl acetate demonstrated fumigant activity against larvae of *Anastrepha suspensa* (the Caribbean fruit fly). Allyl acetate killed all the larvae exposed at the rate of 4.3 mg/l for 24 hours (Weber *et al.*, 1987).

Allyl Alcohol. Allyl alcohol is used in the organic synthesis of glycerol and acrolein as well as the production of various allyl esters including diallyl phthalate and diallylisophthalate which serve as monomers and prepolymers. Allyl alcohol also finds use in the production of plastic lenses, silicone surfactants, pharmaceuticals, and military poisons. Allyl alcohol is used as a flavoring agent as are many allyl esters. It also serves as a solvent, a corrosion inhibitor for metals, a polymerization inhibitor, and a catalyst for the polymerization of olefins. Allyl alcohol has been sold for seed bed sterilization and as a

contact pesticide for weed seeds and certain fungi (Anon., 1990; Beacham, 1978; Fishbein, 1979; Budavari, 1989; Verschueren, 1983; Rowe & McCollister, 1982; HSDB, 1991).

Human Exposure: In the chemical industry human exposure to allyl alcohol is generally associated with transfers and maintenance of equipment (Rowe & McCollister, 1982). Exposure may also result from the presence of allyl alcohol in the exhaust from internal combustion engines. Other exposure may result from the use of allyl alcohol as a contact pesticide for weed seeds and certain fungi; however, it should be noted that Dow Chemical Company has discontinued production of allyl alcohol, presumably for this pesticide purpose (HSDB, 1991).

Based on data collected during the period 1972 to 1974, the National Occupational Hazard Survey (NOHS) estimated that 780 workers were potentially exposed to allyl alcohol. The 1981 to 1983 National Occupational Exposure Survey (NOES) reported 3246 employees potentially exposed to allyl alcohol and 4280 workers to allyl acetate. Note that the NOES estimate represents actual observations (i.e., the surveyor observed the use of the specific compound) only, whereas the NOHS estimate is made up of actual observations, tradename observations (i.e., the surveyor observed the use of a tradename product known to contain the compound), and generic observations (i.e., the surveyor observed the use of a product in some type of general use which led NIOSH to suspect that the compound might be in that product).

Worker exposure to allyl alcohol was surveyed at a Union Carbide Corporation plant in South Charleston, WV employing approximately 1,700 workers, in May and June 1978. Atmospheric concentrations of allyl alcohol ranged from 0.4 to 4.7 ppm (Oser *et al.*, 1979).

Employee exposure to allyl alcohol was evaluated as part of a long-term mortality follow-up study of Union Carbide employees at three selected company locations in West Virginia. It was estimated that 18 employees among 200 production workers in the case-control study were exposed to allyl alcohol over the 1940 to 1978 study period. The case-control study consisted of 774 men (129 men with lymphatic or hematopoietic tissues malignancies except Hodgkin's disease and 645 controls). Three percent of these employees were potentially exposed for a minimum of 5 years (Ott *et al.*, 1989a).

Trace organic compounds were measured in the expired air of 8 male volunteers, 2 of whom were smokers. Allyl alcohol was identified in expired air from 1 smoker and 1 non-smoker (Conkle *et al.*, 1975).

Allyl acetate was identified at a mean level of 0.296 ng/liter in the expired air from an urban population of 54 normal, healthy, nonsmoking volunteers (Krotoszynski *et al.*, 1979).

It is recommended that workers who handle allyl alcohol or allyl compounds or who may be liable to exposure should wear protective equipment appropriate to the extent of exposure. Eye protection should be provided. The vapor should be prevented from escaping into the workroom by exhaust ventilation. When the process cannot be enclosed, exhaust hoods should be fitted to trap and extract the escaping vapor before it can diffuse into the workroom atmosphere. To prevent the liquid or vapor from coming into contact with workers, processes in which allyl alcohol is present should be conducted in closed systems (HSDB, 1991).

Environmental Occurrence:

Allyl Acetate. Allyl acetate was detected at a level of 31 μg/m^3 in the air at the Kin-Buc chemical waste

disposal site near Edison, NJ (Pellizari, 1982).

Allyl Alcohol. Environmental contamination of water by allyl alcohol may occur from aqueous waste stream releases from manufacturing, storage, handling, and process facilities and from agricultural runoff from soils treated with allyl alcohol. Fugitive gaseous emissions from production facilities may release allyl alcohol to the atmosphere and volatilization from soils treated with allyl alcohol may also be a source of exposure. Allyl alcohol is not expected to persist in the environment (USEPA, 1985).

Allyl alcohol has been detected but not quantified in exhaust gases from internal combustion engines (HSDB, 1991). It has also been identified in the organic volatiles emitted from heated plastics (USEPA, 1985).

No further monitoring data was found in the published literature [see Search Resource List].

Regulatory Status:

Allyl Acetate. No standards or guidelines have been set for occupational exposures to or environmental levels of allyl acetate.

Allyl Alcohol. The following occupational exposure values have been recommended for allyl alcohol (American Conference of Government Industrial Hygienists, 1990). No standards or guidelines have been set for environmental levels of allyl alcohol.

ACGIH TLVs:	TWA	2 ppm (4.8 mg/m^3)	(skin)
	STEL	4 ppm (9.5 mg/m^3)	
OSHA PELs:	TWA	2 ppm (5 mg/m^3)	(skin)
	STEL	4 ppm (10 mg/m^3)	
NIOSH RELs:	TWA	2 ppm (5 mg/m^3)	(skin)
	STEL	4 ppm (10 mg/m^3)	

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data:

Allyl Acetate. No epidemiological studies or case reports associating allyl acetate with a cancer risk in humans was found in the published literature [see Search Resource List]. Allyl acetate is highly irritant and toxic by ingestion, inhalation, and eye and dermal contact (Sandmeyer & Kirwin, 1981).

Allyl Alcohol. Nested case-control studies of non-Hodgkin's lymphoma (52 cases), multiple myeloma (20 cases), nonlymphocytic leukemia (39 cases), and lymphocytic leukemia (18 cases) were conducted within a cohort of employed men from two manufacturing facilities and a research and development center. Exposure odds ratios were examined in relation to 111 work areas, 21 specific chemicals, and 52 chemical activity groups. Allyl alcohol was included in the 21 specific chemicals selected as likely carcinogenic agents. The exposure odds ratios by ever/never classification of having worked with allyl alcohol for each disease subcategory among male employees at three Union Carbide Corporation facilities from 1940 to 1978 were as follows: non-Hodgkins lymphoma 2.6 (odds ratio), 2 cases; multiple myeloma 2.6 (odds ratio), 1 case; nonlymphocytic leukemia 2.5 (odds ratio), 1 case; lymphocytic leukemia, no cases. The significance of the findings for individual chemicals was confounded by the multiple-chemical exposure of employees (Ott *et al.*, 1989a,b; USEPA, 1989a,b).

No additional epidemiologic or case studies assessing human cancer risk in relation to allyl alcohol were identified in the published literature [see Search Resource List].

Allyl alcohol vapor and liquid are intensely irritating to the skin and mucous membranes. Skin irritation and burns occur from contact with the liquid but effects are usually delayed in onset and may be prolonged. Absorption through the skin leads to deep pain, probably due to muscle spasm. No evidence of liver damage or disturbed kidney function was noted among a group of employees working with allyl alcohol for 10 years (Rowe & McCollister, 1982; Sittig, 1985).

The probable oral lethal dose in humans is 50-500 mg/kg (Gosselin *et al.*, 1984).

Following the accidental ingestion of 150 ml of allyl alcohol, a male subject lost consciousness in 20 minutes and died 1.5 hours later. Strong irritation of the respiratory tract and acute defects of the gastric mucosa were noted. A strong mustard-like odor from the internal organs caused cough and lacrimation in the mortuary personnel (Kononenko, 1970).

Animal Data:

Allyl Acetate. No animal carcinogenicity tests for allyl acetate were found in the published literature [see Search Resource List]. Unsaturated aliphatic esters, which include allyl acetate, exhibit irritant and lacrimatory properties (Parmeggiani, 1983). Early short-term studies on allyl acetate reported the following. The oral LD50 in rats is 130 mg/kg. The dermal LD50 in rabbits is 1021 mg/kg. The LC50 in rats is 1000 ppm for a 1 hour exposure. Allyl acetate causes slight skin irritation (average reaction equivalent to a trace of capillary injection) in rabbits and moderate eye irritation (slight erythema) in rabbits (Smyth *et al.*, 1949). The oral LD50 in mice is 170 mg/kg (RTECS, 1991).

Allyl acetate and allyl alcohol are sensory and pulmonary irritants. In groups of four male CF1 mice

exposed for 30 minutes to allyl acetate (97% pure) or allyl alcohol (98% pure) followed by a 20-minute recovery period during which the respiratory pattern was monitored, the respiratory rate was depressed due to sensory irritation of the upper respiratory tract. The effects were rapid, reaching a plateau level within the first 10 minutes, and recovery was rapid even for high concentrations. The highest tested level for allyl acetate (455 ppm) did not show any delay in the response decrease. The RD_{50} was 2.9 ppm for allyl acetate and 3.9 ppm for allyl alcohol. TLV's predicted from the relation $TLV = 0.03 \times RD_{50}$ were 0.1 ppm for both allyl acetate and allyl alcohol. A mechanistic explanation could not be ascribed to metabolites (because of the rapid appearance and disappearance of the response) or lipophilicity. The authors suggested that the general chemical structure $CH_2=CH-CH-O$ may allow a molecule to act as a strong sensory irritant. They further suggested that for both allyl acetate and allyl alcohol the activation of the sensory irritant receptor most likely proceeded via a 1,2 addition of the nucleophilic group (-XH) in the receptor to the carbon-carbon double bond. In addition, a hydrogen bonding capacity of the sensory irritant receptor could enhance the reaction rate if the substances are taken out of the receptor phase and held in a close proximity to the nucleophilic group in the receptor (Nielsen *et al.*, 1984; Nielsen & Bakbo, 1985).

Studies on the effects of carboxylesterase inhibitors on the acute hepatotoxicity of allyl acetate, as well as two other esters of allyl alcohol (allyl cinnamate, allyl phenoxyacetate), have demonstrated that enzymatic hydrolysis is a necessary step in the activation to a hepatotoxin. Hydrolysis of allyl acetate by liver homogenates from rats treated with 125 mg/kg of triorthotolyl phosphate (TOTP) was almost completely inhibited (97.7%) compared to that of control livers. In rats gavaged with 60 to 150 mg/kg allyl acetate, pretreatment with 125 mg/kg TOTP significantly inhibited the rise in plasma alanine-α-ketoglutarate transaminase (AKT) activity and prevented liver necrosis. Pretreatment of rats with 0.5 to 10 mg/kg of the defoliant S,S,S-tributylphosphorotrithioate (DEF) also decreased liver esterase activity and protected against hepatotoxicity. Pretreatment with 0.5 mg/kg DEF inhibited liver esterase by 27.6%; a maximal effect was seen after treatment with 4 mg/kg DEF, which inhibited liver esterase by 85%. DEF pretreatment also decreased the hepatotoxicity produced by 60 mg/kg allyl acetate. Plasma AKT activity was reduced, and liver injury, as judged by gross appearance, was less severe. In addition, pretreatment of rats with 375 mg/kg pyrazole, an inhibitor of alcohol dehydrogenase, completely inhibited the elevation of plasma AKT activity after oral administration of 90 mg/kg allyl acetate (Silver & Murphy, 1978).

Hepatic ornithine decarboxylase (ODC) activity was not induced in CD rats administered a single oral dose (26 mg/kg bw) of allyl acetate. The hepatic ODC activity (nmol CO/g liver/h) 21 hours after administration was 2.47 versus 3.15 in vehicle controls. Induction of this marker enzyme has been considered necessary though not sufficient to cause carcinogenic promotion (Kitchin & Brown, 1987).

<u>Allyl Alcohol</u>. Allyl alcohol is neither currently on test nor scheduled for testing in a standard carcinogenicity bioassay [see Search Resource List]. The International Agency for Research on Cancer (1985) notes that allyl alcohol was considered for inclusion in the monograph on allyl compounds, aldehydes, epoxides, and peroxides but that consideration was postponed since no studies of carcinogenicity to experimental animals or to humans were available (an oral administration study in hamsters was in progress but results were not yet available).

Two years later Lijinsky and Reuber (1987) published the results of the carcinogenic effects of chronic exposure to allyl alcohol in rats and hamsters. Groups of 20 male and 20 female F344 rats were given 300 mg/l allyl alcohol in drinking water 5 days a week for 2 years. Male Syrian hamsters were administered 2 mg allyl alcohol in corn oil by gavage once a week for 60 weeks. There were no

statistically significant increased incidences of neoplasms in either rats or hamsters related to allyl alcohol administration. The authors note that the experiment cannot be considered a definitive bioassay due to the limited number of animals and use of only one sex in hamsters. Although only one dose level was used they felt that levels close to the maximally tolerated dose appeared to have been achieved.

Kozuka and Sassa (1976) studied the effects of allyl alcohol on the hepatocarcinogencity of 2,7-bis(acetamido)fluorene (2,7-AAF) in mice. Male SMA/Ms strain mice were given 5 ml of 1% allyl alcohol in aqueous solution by gavage once a week for 8 weeks administered concurrently with 0.025% 2, 7-AAF in the diet followed by carcinogen-free diet to the end of the study at 24 weeks. Female SMA/Ms mice received 8 gavage treatments of 5 ml of 1% allyl alcohol administered alternately with 2,7-AAF in the diet 1 week a month for 32 weeks. Allyl alcohol treatment caused no apparent acceleration in the induction of hepatic nodules in the mice fed 2,7-AAF.

A 90-day inhalation study and a 13-week oral study were identified in PHS-149 (1969). No tumors were found following inhalation exposure of male Long-Evans rats to 1, 2, 3, 20, 40, 60, or 100 ppm of allyl alcohol for 7 hours per day for 5 days a week; pulmonary and hepatic lesions were noted. In the second study, male and female rats received 1, 5, 50, 100, 250, 500 or 1,000 ppm in drinking water. No tumors were seen but hepatic necrosis with regeneration was noted.

The teratogencity and embryolethality of allyl alcohol was assessed in Sprague-Dawley rats by intraamniotic injections on day 13 of gestation. Allyl alcohol treatment caused a dose-dependent increase in the incidence of resorbed fetuses, with significance found at 100 μg/fetus and 1000 μg/fetus. Eleven percent of the fetuses injected with 1000 μg of allyl alcohol were malformed. This includes two fetuses with limb defects. Two contralateral controls in the 100 μg/fetus group were malformed. There was one maternal death at the high dose of allyl alcohol the day after surgery and treatment of the embryos was performed. The authors state that allyl alcohol was not teratogenic (Slott & Hales, 1985).

Litters sired by male rats chronically treated with allyl alcohol were evaluated for the incidence of fetal malformations and karyotype abnormalities. Allyl alcohol was given at 25 mg/kg for 7 days a week for up to 12 weeks then 5 days a week from week 13 to the end of the study. Each male rat was caged with 2 virgin female rats on weeks 1-11 after the first week of dosing. On day 20 of pregnancy the females were killed. Allyl alcohol treated males were post-mortemed after 15 weeks of dosing. There was no evidence that chronic allyl alcohol treatment affected any of the reproductive parameters in the exposed male rats. Sperm counts were normal and there was no suggestion of any increase in dominant lethality at any mating week. The incidence of runted fetuses in the allyl alcohol groups was greater than that of controls but the increase was not significant. Three grossly abnormal fetuses were identified in the offspring of the allyl alcohol treated rats, including cases of exencephaly, anasarca, and a craniofacial/skeletal abnormality. While no grossly abnormal fetuses were seen in concurrent controls, the three observed in the allyl alcohol group were well within the levels recorded in historical data (Jenkinson & Anderson, 1990).

The short-term toxicity of allyl alcohol was assessed in male and female Wistar rats. Allyl alcohol was given in drinking water to 15 male and 15 female rats at concentrations of 50, 100, 200, or 800 ppm for 15 weeks. Additional rats received 200 or 800 ppm for 2 to 60 weeks. Blood and serum parameters in treated rats were normal. There was a dose-related decrease in fluid intake for all rats. Food intake and growth were reduced in both sexes given 800 ppm and in males given 200 ppm. There were no histopathologic lesions attributable to treatment in any of the organs examined; however, the relative organ weights of the liver, kidney and spleen were significantly increased at all except the 50 ppm level. Mean intakes at or above 8 mg/kg/d in males and 9.9 mg/kg/d in females had adverse effects on kidney

tissues in the rat (Carpanini *et al*., 1978).

The acute toxicity, histopathology, and liver enzyme alterations caused by allyl alcohol were studied in adult and neonatal F344 rats. Immature rats received an intraperitoneal injection of 0.294 umol/kg 14 hours before sacrifice. Mature rats were given 0.53 umol/kg by intraperitoneal injection 24 hours before sacrifice. Allyl alcohol administration did not produce any histological alterations in the liver of immature rats. In adult rats, allyl alcohol produced a moderate to marked periportal necrosis with attendant inflammation and hemorrhage. There was considerable variability in extent of hepatotoxicity in the different lobes. In adult rats, allyl alcohol also decreased hepatic cytochrome P-450, benzphentamine N-demethylation, and ethoxyresorufin O-deethylation activities by about 30%. In immature rats, it lowered both cytochrome P-450 activity (30%) and ethoxyresorufin O-deethylation (75%). Benzphetamine N-demethylation was not significantly affected in immature rats (Klinger *et al*., 1986).

Intraperitoneal administration of 1.5 mmol/kg of allyl alcohol to starved Swiss albino mice caused the development of hemolysis in nearly 50% of the animals. Malonic dialdehyde appeared in plasma of the animals showing hemolysis and a marked decrease in arachidonic and docosahexaenoic acids was found in erythrocyte phospholipids (Ferrali *et al*., 1990).

A number of studies have examined the acute and sub-chronic toxicity of allyl alcohol. These studies show the propensity of allyl alcohol to produce liver damage, often localized to the periportal regions, after short-term administration by all routes of exposure. Other toxic effects include renal necrosis, pulmonary edema and CNS effects at higher dose levels (USEPA, 1985). In their review, Atzori *et al*. (1989) conclude that allyl alcohol toxicity is related to its biotransformation into acrolein, a primary toxic metabolite, through the cytosolic enzyme alcohol dehydrogenase (ADH).

Additional, studies on the mechanisms of allyl alcohol toxicity include the following: Patel *et al*., 1983; Rikans, 1984; Rikans, 1987; Balazs *et al*., 1961; Smith *et al*., 1987; Jaeschke *et al*., 1987.

Short-term Tests:

Allyl Acetate. In a study of 41 industrial chemicals for genotoxic activity, allyl acetate (96% pure) in dimethyl sulfoxide tested positive in *Salmonella typhimurium* strains TA1535 and TA100 without S9 activation. The authors commented that this direct mutagenic effect was unexpected because the ester carbonyl group is too far away to exert a strong polarizing effect on the alkene bond; it is likely however, that C-3 of the allyl group is activated for alkylation by loss of acetoxy from C-1. Allyl acetate tested negative at doses up to 2000 μg/plate in these strains without S9 and in strains TA1537, TA1538, and TA98 with or without S9. The authors speculated that the destruction of the mutagenic activity of allyl acetate by the S9 fraction is due to the action of microsomal carboxylesterase which would catalyse hydrolysis to allyl alcohol nullifying the activating effect of the acetoxy leaving group. In addition, allyl acetate tested negative for mitotic gene conversion in *Saccharomyces cerevisiae* strain JD1 and for structural chromosome damage in a cultured rat-liver epithelial-like cell line (Dean *et al*., 1985).

Allyl Alcohol. The mutagenicity of allyl alcohol has been tested through the DCE Short-term Test Program of the National Cancer Institute. Positive results were obtained in the mouse lymphoma assay when allyl alcohol was tested at 1.5 - 9.2 ul/ml without metabolic activation. Results in the Ames *Salmonella typhimurium* standard plate assay were negative (CCRIS, 1991; NCI, 1990). Allyl alcohol was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 using a variety of treatments (standard plate or preincubation) and solvents (water or DMSO). Positive results

were reported only in TA1535 at 10 - 500 μg/plate using the preincubation method with water as the solvent and hamster liver S9 activation (Lijinsky & Andrews, 1980). Lutz *et al.* (1982) reported positive results when allyl alcohol was tested in TA100 using the preincubation method and DMSO as the solvent. Revertants per μmol were 750 without activation and 145 with S9. Principe *et al.* (1981) tested the mutagenicity of allyl alcohol in *Salmonella* strains TA98, TA100, TA1535, TA1537, and TA1538 as well as in *Streptomyces coelicolor* and *Aspergillus nidulans*. Allyl alcohol was negative in all tests systems. At 1 and 2 μM, allyl alcohol was mutagenic in V-79 cells using 6-thioguanine resistance as the measure of mutagenicity (Smith *et al.*, 1990).

Metabolism: Figure 1 summarizes the current state of knowledge regarding the metabolism of allyl alcohol and of its esters with organic acids. It is presumed that the majority of allyl esters will be hydrolysed rapidly *in vivo* through the action of various esterases resulting in a quantitative liberation of allyl alcohol (Fig. 1 Step I). In addition, there is ample evidence to support the view that allyl alcohol is converted to acrolein (Fig. 1 Step II) *in vivo* through the action of ADH. The reactivity of acrolein in biological systems is well known leading to the conclusion that step II is of material importance in determining allyl alcohol toxicity. The urinary excretion of 3-hydroxypropylmercapturic acid following the administration of allyl alcohol and allyl esters as well as acrolein is consistent with the operation of steps III, IV, and V in Figure 1 as a common pathway for the elimination of allyl moieties and indicates that sequence VI is unlikely to be of significance (Carpanini *et al.*, 1978).

The major site of allyl alcohol metabolism is the liver. Three metabolic pathways have been linked to its hepatic metabolism. The main route of allyl alcohol metabolism is by cytosolic alcohol dehydrogenase (ADH) while catalase and microsomal cytochrome-P450 dependent mixed-function-oxidase (MFO) may be involved in the biotransformation (Atzori *et al.*, 1989).
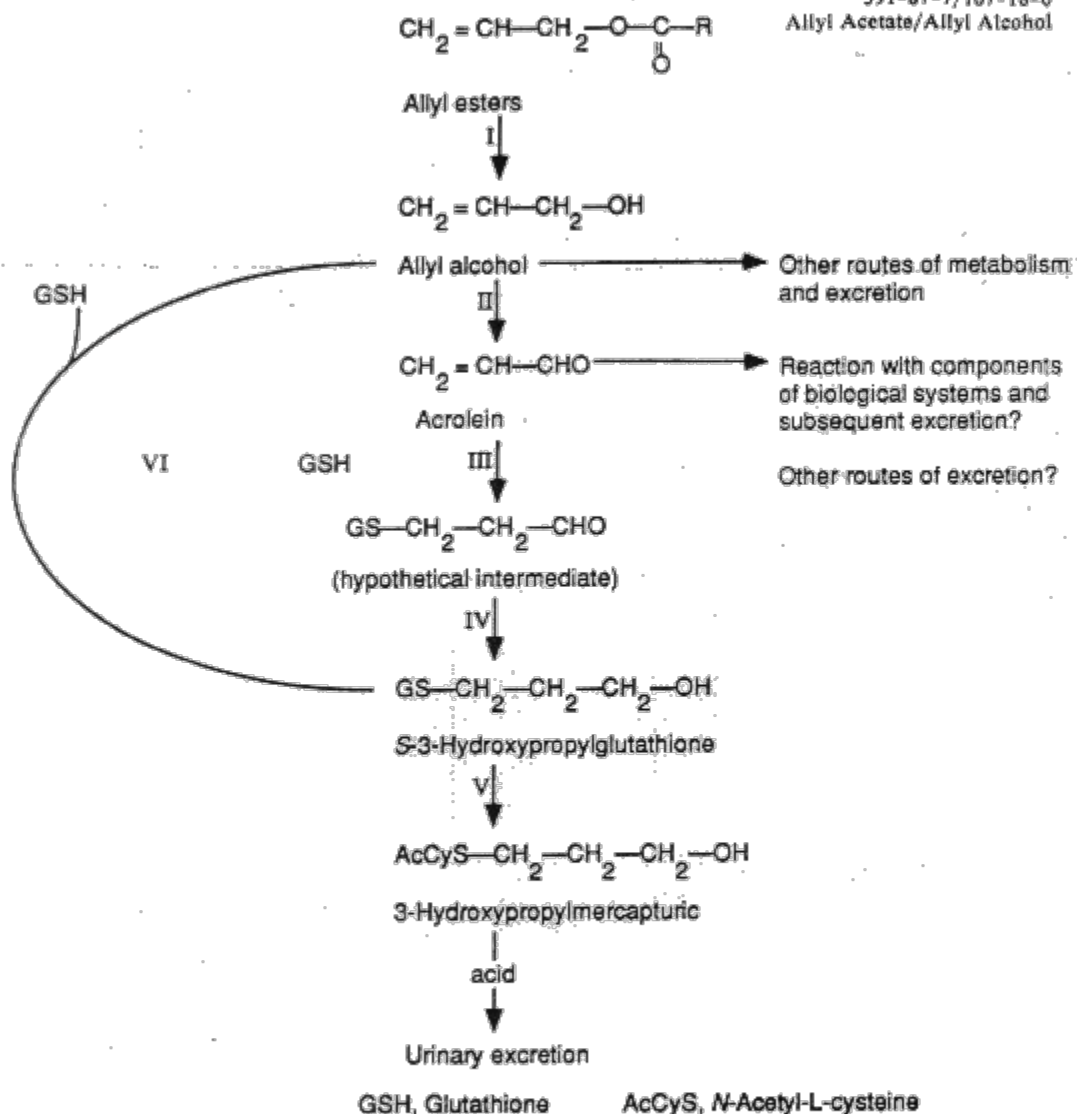
Figure 1. Summary of Available Information on the Metabolism of Allyl Alcohol and Its Esters.

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The formation of acrolein from allyl alcohol in rat liver was investigated using whole liver homogenates and subcellular fractions from male albino rats incubated with allyl alcohol in the presence or absence of nicotinamide dinucleotide (NAD^+). Acrolein was formed in the microsomal preparations and post microsomal supernatants only in the presence of NAD^+. In homogenates and mitochondria, acrolein was formed without NAD^+, but addition of NAD^+ significantly enhanced acrolein formation. The conversion rate to acrolein was 5% (Serafini-Cessi, 1972).

3-Hydroxypropylmercapturic acid (as its dicyclohexylammonium salt) was identified in the urine of rats after the subcutaneous injection of allyl alcohol; allylmercapturic acid was not detected in the urine. The failure to detect allylmercapturic acid suggests that allyl alcohol is not metabolized by alkylation of glutathione with the allylic bond remaining intact (Kaye, 1973).

In vivo animal studies on the metabolism of allyl acetate have focused on mercapturic acid formation. Preliminary studies found that the urine of rats injected subcutaneously with allyl acetate contained 3-hydroxypropylmercapturic acid and N-acetyl- S-(3-hydroxypropyl)- L-cysteine while there was no evidence for the presence of allylmercapturic acid. Similar results were found after the administration of allyl alcohol to rats (Clapp *et al*., 1969). A later study on the metabolism of allyl esters also detected 3-hydroxypropylmercapturic acid but failed to detect allylmercapturic acid in the urine of male albino CFE rats injected subcutaneously into the lumbar region with a 1% (v/v) solution of allyl acetate in arachis oil. Urine was collected for two successive 24-hour periods immediately after dosing. The possibility that metabolic conversion of allyl acetate into 3-hydroxypropylmercapturic acid involves allyl alcohol and S-(3-hydroxypropyl)-L-cysteine as intermediates was supported by other results in the study including: (1) the identification of S-(3-hydroxypropyl)-L-cysteine in the bile of a rat injected subcutaneously with 1 ml of a 2% (v/v) solution of allyl acetate in arachis oil and (2) and the presence of 3-hydroxypropylmercapturic acid as a urinary metabolite in rats dosed with allyl nitrate, sodium allyl sulphate, triallyl phosphate, diallyl phthalate, allyl nitrite, allyl formate, allyl benzoate, allyl propionate, and allyl stearate. 3-Hydroxypropylmercapturic acid formation was independent of the route of administration (subcutaneous, intraperitoneal injection, stomach tube). The authors concluded that the type of fission undergone *in vivo* may be deduced from the mercapturic acid derivative present in the urine. If allyl mercapturic acid is present, then alkyl-oxygen fission is likely to have occurred, whereas if 3-hydroxypropylmercapturic acid but not allyl mercapturic acid is present, then acyl-oxygen fission was likely. The authors suggest that allyl alcohol is an intermediate in the metabolism of the esters of weak acids whereas in the case of allyl esters of strong acids (pK_a value less than about 2.0), the allyl group becomes a carbonium ion which is then open to nucleophilic addition with glutathione or a hydroxyl group. Of the allyl esters studied, only those derived from strong acids underwent alkyl-oxygen fission. These esters were triallyl phosphate, sodium allyl sulphate, and allyl nitrate (Kaye, 1973).

Bioactivation of allyl acetate may also proceed according to the following scheme. Allyl esters are cleaved by nonspecific esterases to allyl alcohol, which is then oxidized by alcohol dehydrogenases to the reactive allyl aldehyde. This aldehyde reacts with macromolecules or may be detoxified by glutathione conjugation. The rapid reactions catalyzed by the esterase and alcohol dehydrogenase produce a concentration of the aldehyde that overwhelms the detoxication pathways and results in toxicity (Klaassen *et al*., 1986).

Allyl acetate is absorbed through the intact skin (Sandmeyer & Kirwin, 1981).

Structure/Activity Relationships: The International Agency for Research on Cancer (1985) has evaluated the carcinogenic risk of four allyl compounds--allyl chloride, allyl isothiocyanate, allyl isovalerate, and eugenol. For each allyl compound, it was decided that the agent is not classifiable as to its carcinogenicity to humans. Subsequent to the IARC evaluation, the National Toxicology Program conducted carcinogenesis bioassays of allyl isothiocyanate, allyl isovalerate, and eugenol. Summaries of IARC and NTP conclusions follow.

Allyl Chloride

<u>IARC</u>. There is inadequate evidence for the carcinogenicity of allyl chloride in experimental animals. Allyl chloride has been tested for carcinogenicity by intragastric intubation in mice and rats, by skin application in mice (both by repeated application and in a two-stage assay) and by intraperitoneal injection in mice. Following its oral administration to mice, a nonsignificant increase in the incidence of squamous-cell papillomas and carcinomas of the forestomach was observed; the experiment in rats was inadequate for evaluation. No skin tumors were observed in mice following repeated skin applications; however, a single application followed by treatment with 12-O-tetradecanoylphorbol-13-acetate gave some evidence that allyl chloride acts as an initiator. Following its intraperitoneal injection to strain A mice, a slight increase in the incidence of lung adenomas was observed.

Inhalation exposure to allyl chloride of high purity did not induce teratogenicity in rats or rabbits.

Allyl chloride caused DNA damage in bacteria, and was mutagenic to bacteria and fungi.

No case report or epidemiological study of the carcinogenicity of allyl chloride to humans was available.

<u>NTP</u>. Allyl chloride was negative for carcinogenicity in male and female Osborne-Mendel rats and equivocal for carcinogenicity in male and female B6C3F$_1$ mice administered the compound by gavage five days a week for 78 weeks. The observation period was up to 33 weeks for rats and 14 weeks for the mice. The time-weighted average doses, respectively, were 77 and 57 mg/kg/day for high and low dose male rats; 73 and 55 mg/kg/day for high and low dose female rats; 199 and 172 mg/kg/day for high and low dose male mice; and 258 and 129 mg/kg/day for high and low dose female mice (National Toxicology Program, 1978). In addition, allyl chloride tested positive in *Salmonella* (National Toxicology Program, 1991b).

Allyl Isothiocyanate

<u>IARC</u>. There is limited evidence for the carcinogenicity of allyl isothiocyanate to experimental animals. Allyl isothiocyanate was tested for carcinogenicity by gastric intubation in one strain each of mice and rats. In mice, no increase in the incidence of tumors was observed. An increased incidence of epithelial hyperplasia and transitional-cell papillomas of the urinary bladder was observed in male rats only, and some subcutaneous fibrosarcomas occurred in female rats administered the high dose.

Allyl isothiocyanate was not teratogenic to mice, rats, hamsters, or rabbits, but resorptions occurred in mice and rats.

Allyl isothiocyanate did not induce DNA damage in bacteria. It induced mutations in bacteria and insects and chromosomal aberrations in plants. It did not induce dominant lethal mutations in mice.

No case report or epidemiological study of the carcinogenicity of allyl isothiocyanate was available.

<u>NTP</u>. Food grade allyl isothiocyanate (>93% pure) was tested in a 2-year bioassay by administering 12 or 25 mg/kg five times a week for 103 weeks by gavage to rats and mice. Allyl isothiocyanate was carcinogenic for male F344/N rats, causing transitional-cell papillomas in the urinary bladder. Evidence for associating allyl isothiocyanate with subcutaneous fibrosarcomas in female F344/N rats was equivocal. Allyl isothiocyanate was not carcinogenic for B6C3F$_1$ mice of either sex (National Toxicology Program, 1982).

Allyl Isovalerate

<u>IARC</u>. There is limited evidence for the carcinogenicity of allyl isovalerate in experimental animals. Allyl isovalerate was tested for carcinogenicity in mice of one strain and in rats of one strain. In mice, allyl isovalerate induced papillomas of the forestomach in males and increased the incidence of lymphomas in females. In rats, an increased incidence of mononuclear-cell leukemia was observed in animals of both sexes.

Allyl isovalerate was not mutagenic to bacteria.

No case report or epidemiological study of the carcinogenicity of allyl isovalerate was available.

<u>NTP</u>. Allyl isovalerate (96% pure) was carcinogenic for F344/N rats and B6C3F$_1$ mice gavaged with 31 or 62 mg/kg five times per week for 103 weeks, causing increased incidences of hematopoietic system neoplasms (mononuclear-cell leukemia in male rats and lymphoma in female mice) (National Toxicology Program, 1983b).

Eugenol

<u>IARC</u>. There is limited evidence for the carcinogenicity of eugenol in experimental animals. Eugenol was tested in mice of one strain and in rats of one strain by administration in the diet. In mice, there was a significant increase in the incidence of liver tumors in females; in males, the increase was significant only for those receiving the lower dose. No increased incidence of tumors was observed in rats. Other studies in mice by oral administration, skin application, and intraperitoneal injection were inadequate for evaluation of carcinogenicity, mainly due to the short duration of treatment.

Eugenol gave both positive and negative results in tests for DNA damage in bacteria. It was not mutagenic in several studies in bacteria. The compound was not active in a host-mediated assay in mice, nor was the urine of rats treated with eugenol mutagenic. Eugenol induced chromosomal aberrations and a small increase in sister chromatid exchanges in mammalian cells *in vitro*.

In one two-stage mouse-skin assay, 2',3'-epoxyeugenol, an *in vitro* metabolite of eugenol, showed initiating activity.

No case report or epidemiological study of the carcinogenicity of eugenol was available.

<u>NTP</u>. Carcinogenesis studies of eugenol (>99% pure) were conducted by feeding diets containing 6,000 or 12,500 ppm of eugenol to F344/N rats and by feeding diets containing 3,000 or 6,000 ppm to B6C3F$_1$ mice for 103 weeks. There was no evidence of carcinogenicity in rats. For mice, there was equivocal evidence of carcinogenicity since eugenol caused increased incidences of both carcinomas and adenomas of the liver in male mice at the 3,000 ppm dietary level and because eugenol was associated with an increase in the combined incidences of hepatocellular carcinomas or adenomas in female mice (National Toxicology Program, 1983a).

The International Agency for Research on Cancer (1985, 1987) also evaluated acrolein, a metabolite of allyl alcohol, and determined that it is not classifiable as to its carcinogenicity in humans. The IARC summary of data is provided below. The CSWG nominated acrolein to the National Toxicology Program in 1985 with high priority on the basis of widespread exposure and lack of carcinogenicity information.

The compound was reviewed by the Chemical Evaluation Committee in July, 1988; in January of 1989, the Executive Committee approved acrolein for testing in fiscal year 1989 with high priority (National Cancer Institute, 1989; National Toxicology Program, 1991a). Preliminary toxicity results have been completed by NTP. Genetic toxicology tests revealed acrolein to be weakly positive for mutagenicity in *Salmonella*, negative in *Drosophila*, and both negative and weakly positive for *in vitro* cytogenetic tests (National Toxicology Program, 1991b).

Acrolein. The evidence for carcinogenicity to experimental animals was considered inadequate. Acrolein was tested in mice by skin application and in hamsters by inhalation. The study in mice was inadequate for evaluation. No carcinogenic effect was detected in hamsters.

The evidence for carcinogenicity to humans was considered inadequate. Exposure to traces of acrolein was reported to have occurred in a chemical plant in the German Democratic Republic, where the main exposures were to acetaldol, acetaldehyde, butyraldehyde, and crotonaldehyde. Nine cases occurred in the plant; the relative frequencies of the tumors observed were reported to be higher than those expected in the German Democratic Republic. Acrolein was a relatively minor component of the exposure. Because of the mixed exposure pattern, the small number of cases and the poorly defined exposed population, the study was inconclusive.

No data were available on the genetic and related effects of acrolein in humans. It did not induce dominant lethal mutation in mice. It induced sister chromatid exchanges in Chinese hamster ovary cells *in vitro*. In yeast, it did not cause DNA cross-links or strand breaks and was not mutagenic. Acrolein was mutagenic to bacteria.

The CSWG previously considered another allyl compound -- allyl caproate. This compound was considered in 1976 because of reported allergic response in humans; a class study on flavors and fragrances, including allyl caproate, was deferred until a report from FDA on food additives was complete. Since that time no further action has been taken (National Cancer Institute, 1989).

The National Toxicology Program (1991b) has also tested several other allyl compounds. The evidence for carcinogenicity of allyl glycidyl ether following inhalation exposure was considered equivocal in male rats, negative in female rats, positive in male mice, and equivocal in female mice. In the Ames assay, allyl nonanoate is on test; allyl urea tested positive; and allyl acrylate, allylamine, allyl anthranilate, allyl propyl disulfide, and allyl thiourea tested negative.

It is also interesting to note that allyl alcohol is a metabolite of diallylnitrosamine. This nitrosamine proved to be a potent respiratory tract carcinogen in Syrian hamsters, but failed to induce tumors in BDIX rats. In addition, in hamsters, intragastric administration of diallylnitrosamine resulted in a considerably lower tumor incidence than subcutaneous administration. Metabolic studies in BDIX and Wistar rats demonstrated that a large portion of diallylnitrosamine is expired in the air and only a small fraction is metabolized in the liver, whereas in hamsters the opposite was the case. The activity of the microsomal fraction of the hamster liver for metabolizing diallylnitrosamine to allyl alcohol was about 10 times higher than that in rats. No significant species differences were found in the cytosolic fraction. In addition, in bacterial mutagenesis assays, hamster liver microsomes were twice as active as those in BDIX rats (Grandjean *et al*., 1985).

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