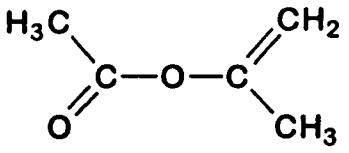
ISOPROPENYL ACETATE
CAS NO. 108-22-5

Structure, Molecular Formula and Molecular Weight:



$C_5H_8O_2$ Mol. wt : 100.11

BASIS OF NOMINATION TO THE CSWG

The nomination of isopropenyl acetate (IPA) is based on potential for widespread human exposure. IPA is an industrial petrochemical recently described in the chemical press as derived for industrial use through a methane gas conversion route. It has been reported to be used as a fragrance intermediate, a monomer for polymer manufacture and a chemical intermediate. It occurs naturally in Parmesan cheese.

In the NCI Division of Cancer Etiology (DCE) Short-Term Test Program (STTP), IPA was mutagenic in the mouse lymphoma assay without metabolic activation, and equivocal with activation. IPA was nonmutagenic in the Ames/*Salmonella* assay with and without metabolic activation. IPA is an analog of vinyl acetate which was mutagenic in both the mouse lymphoma and *Salmonella* assays and for which tumorigenicity data are reported. However, whereas vinyl acetate is known to metabolize to acetaldehyde, which is carcinogenic in rodents, IPA is expected to metabolize to acetone, which has a low (if any) suspicion of carcinogenicity. The possible metabolism of IPA to acetone is supported by nonmammalian data in the literature. Therefore, at this time, IPA is recommended for nomination to the NTP for only metabolism studies.

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SELECTION STATUS

ACTION BY CSWG: 12/16/94

Studies Requested: Metabolism studies and *in vitro* cytogenetics (chromosomal aberrations and sister chromatid exchanges)

Priority: Moderate

Rationale/Remarks:

- Potential for human exposure
- Used as chemical intermediate
- Potential use in detergent formulations
- Perform metabolism studies to determine whether IPA is metabolized to acetone or to another compound with a suspicion of carcinogenicity
- Perform *in vitro* cytogenicity studies to better characterize mutagenic activity of IPA
- Perform metabolism and *in vitro* cytogenetics studies prior to consideration of IPA for carcinogenicity studies.

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SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry Name: 108-22-5

Chemical Abstracts Name: 1-Propen-2-ol, acetate (9CI)

Synonyms and Trade Names: Propen-2-yl acetate; acetic acid isopropenyl ester; 1-acetoxy-1-methylethylene; 2-acetoxypropene; 1-methylvinyl acetate; *iso*-propenyl acetate; isopropenyl acetate; IPA

Chemical and Physical Properties

Description: Water white liquid with pleasant odor (Anon., 1994b; Sax, 1993)

Melting Point: -92.9°C (Lewis, 1993)

Boiling Point: 96-97°C (Anon., 1994b)

Solubility: 3.25% by wt. at 20°C, soluble in ether, alcohols, and esters (Anon., 1994b)

Specific Gravity: 0.926 at 20°C/20°C (Anon., 1994b)

Vapor Density: 3.45 (Anon., 1994b)

Stability: Stable (Anon., 1994b)

Reactivity: Flammable liquid, dangerous fire risk (Sax, 1993); incompatible with acids, alkalies, oxidizers, and reducing agents (Anon., 1994b)

Flash point: 66°F (18°C) (Anon., 1994a)

Technical Products and Impurities: IPA is available from several suppliers at a purity level of ≥ 99% Eastern Chemical and Janssen Chimica both offer their product at 99% pure, while Aldrich Chemical Co. offers both 99% and 99+% pure grades. According to Eastern Chemical, acetic acid may be present as an impurity at < 0.25%.

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EXPOSURE INFORMATION

Commercial Availability

Production and Producers: IPA can be prepared by reacting ketene with acetone (Budavari, 1989). No annual production volumes were found for IPA in the available literature. However, Wood and Young (1992) described this chemical as a feedstock petrochemical derived from methane and syngas by a methanol conversion route. Principal producers listed in recent chemical industry directories are Davos Chemical Corp., Eastern Chemical Div. of United Guardian, Inc., SAF Bulk Chemicals, and Wacker Chemicals (USA) Inc. According to Wood and Young (1992) there is growing interest in the petrochemical industry in developing methanol conversion routes to feedstock chemicals, including IPA. Several commodity petrochemical producers, including Eastman Chemical of Kingsport, TN, have been working on alternatives to thermal cracking of longer chain molecules from crude oil fractions or liquefied petroleum gases (LPG) as sources of petrochemicals, such as acetic anhydride and isopropenyl acetate. In addition, the following catalog producers/suppliers were listed in the DIALOG Fine Chemicals Database: Aldrich Chemical Co., American Tokyo Kasei, Chem Service, Inc., Crescent Chemical Co., Inc., Eastman Fine Chemicals, Fluka Chemical Corp., Janssen Chimica (Spectrum Chemical Mfg. Corp.), Lancaster Synthesis Ltd. and Pfaltz & Bauer, Inc.

IPA is listed in the EPA TSCA inventory (STN, 1994). According to the TSCA Plant and Production (TSCAPP) database, annual production/importation data reported for 1977 included the following: Union Carbide Corp. of Kanawha, WV, manufactured an undisclosed amount of IPA for site limited use, and International Flavors and Fragrances of Monmouth, NJ, imported 1,000 - 10,000 pounds of IPA (CIS, 1994).

Use Pattern: IPA is principally used as an acylation reagent (Lewis, 1993). It is a widely used and versatile chemical intermediate in organic and bioorganic syntheses in both industrial plants and academic laboratories.

- Papa & Sherman (1981) described the thermal and catalyzed isomerization of IPA as a major route for the commercial production of the chelating agent and polymer additive, 2,4-pentanedione.
- IPA is used as a chemical intermediate for perfumes and some agricultural products.
- IPA is also used as a chemical intermediate in polymerizations, for example, as a comonomer in polyvinyl acetate polymers.

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- IPA is under investigation for use in cleaning products, according to two recent patents (STN, 1994):

  - as a bleach activator in liquid peroxide detergent formulations
  - as a component of detergent formulations for cleaning wool fabrics.

Human Exposure: There is potential for occupational exposure to this chemical in industrial and academic laboratory settings by the inhalation, oral or dermal routes. However, inhalation is expected to be the primary route of entry (Anon., 1994b). Widespread exposures to very low levels of IPA may occur by ingestion of some food products.

Environmental Occurrence: IPA has been reported to occur in the volatile fraction of Parmesan cheese (Barbieri *et al.*, 1994).

Regulatory Status: No standards or guidelines have been set for the occupational exposure to or workplace maximum allowable levels of IPA in the United States. The American Conference of Governmental Industrial Hygienists (ACGIH) has not adopted a TLV or BEI for this compound. However, Russia has recommended a short-term exposure limit (STEL) of 20 mg/m^3 (NLM, 1994). In addition, EPA has issued a TSCA section 8(a) reporting requirement for production and exposure-related data useful for ranking substances for investigation and for preliminary risk assessments (STN International, 1994). Under the state of New Jersey Right-to-Know Program, IPA is listed as a special health hazard and as a third degree flammable substance (Shafer, 1995).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposures to IPA and cancer risk in humans were identified in the published literature. IPA may be harmful by inhalation, ingestion or skin absorption and is a skin and eye irritant. Prolonged exposure to IPA may cause nausea, dizziness and headache. IPA has a narcotic effect at high concentrations (Anon., 1994a; Budavari, 1989). According to the Eastern Chemical Material Safety Data Sheet (MSDS) there is no carcinogen list status for IPA; this chemical has not been listed by OSHA, EPA, NTP or IARC (Anon., 1992b).

Animal Data: No 2-year carcinogenicity studies of IPA in animals were identified in the published literature. The Registry of Toxic Effects of Chemical Substances (RTECS) record for IPA contains only general toxicity and skin and eye irritation data. An oral rat LD_{50} of 3 gm/kg was reported for IPA (NLM, 1994). IPA was lethal to 3 of 6 rats exposed to 4,000 ppm for 4 hours by inhalation (NLM, 1994)

Short Term Tests: In studies conducted in the National Cancer Institute's Division of Cancer Etiology Short-Term Test Program, IPA was mutagenic in the mouse lymphoma assay without metabolic activation and equivocal with activation, and non-mutagenic in the *Salmonella* assay both with and without S9 activation (NCI, 1994).

Metabolism: The enzymatic hydrolysis of IPA could be expected to produce acetate/acetic acid and acetone (via isopropenol, the enol form of acetone). No mammalian studies on the metabolism of IPA were found in the literature. However, Cherton, *et al.* (1988, 1990) reported on the enzymatic biotransformation (hydrolysis) of IPA in the hemolymphatic fluid of the insect, *Shistocerca gregaria*: the enzymatic hydrolysis of this enol ester at pH 7.4 yielded acetone and acetate detectable by NMR. Cherton *et al.* (1990) reported that their research on the study of xenobiotics in the hemolymph of insects was applicable to the development of proinsecticides.

Structure/Activity Relationships: Vinyl acetate (VA) is a close analog of IPA. VA was considered by the CSWG in 1978 for nomination to the NTP for carcinogenicity testing but dropped because of a negative chronic (1 year) study unpublished but reported in an editorial in *C & E News* by Maltoni in 1974. An early IARC review of VA concluded that there was a lack of human data (ND) and insufficient animal data (I) on which to base a determination of evidence for carcinogenicity and placed this chemical in Group 3 (agent not classifiable as to its carcinogenicity

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to humans) (IARC, 1986). In a later study, Lijinsky and Reuber (1983) reported tumors in a variety of sites in M & F Fischer 344 rats dosed with 10-100 g/kg bw in drinking water 5x/wk for 2 years. At a recent working group meeting (February, 1995), IARC concluded that there was inadequate evidence for carcinogenicity in humans and limited evidence in for carcinogenicity in animals and placed VA in Group 2B (possibly carcinogenic to humans) (correspondence from Dr. Olin dated 2/18/95). The results of genetic toxicity testing of vinyl acetate in the DCE/STTP have been reported as follows: Ames plate, +A; mouse lymphoma, ++A.

REFERENCES

Anon. (1994a) Material Safety Data Sheet: isopropenyl acetate, Aldrich Chemical Co., Milwaukee, WI

Anon. (1994b) Material Safety Data Sheet, Eastern Chemical Division of United Guardian, Inc., Hauppauge, NY

Barbieri, G., Bolzoni, L., Careri, M., Mangia, A., Parolari, G., Spagnoli, S. & Virgili, R. (1994) Study of the volatile fraction of Parmesan cheese, *J. Agric. Food Chem.*, 42(5): 1170-6

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Merck & Co., Rahway, NJ, p. 819

Cherton, J.C., Davoust, D., Escoubas, P., Oumeddour, R., Clement, J.L., Ronzani, N. & Basselier, J J. (1988) Direct enzyme activity monitoring in insect hemolymph by high field NMR, *Analusis*, 16(8):440-443

Cherton, J.C. *et al.* (1990) Direct study of xenobiotics in the hemolymph of insects by high field NMR. Application to the development of proinsecticides, *Analusis*, 18(1):137-144

CIS (1994) Chemical Information Systems, PSI International, Inc., databases searched (see search resource list)

IARC (1986) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 39, *Some Chemicals Used in Plastics and Elastomers*, Lyon, pp. 113-131

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

Lijinsky, W. & Reuber, M.D. (1983) Chronic toxicity studies of vinyl acetate in Fischer rates, *Toxicol. Appl. Pharmacol.*, 68:45-53

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

NLM (1994) National Library of Medicine, Toxicology Data Network (TOXNET) Information Services, databases searched (see search resource list)

Papa, A.J. & Sherman, P.D. (1981) Ketones. In: Grayson, M. & Eckroth, D., *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., John Wiley & Sons, New York, Vol. 13, p. 930

Shafer, D. (1995) *The Book of Chemical Lists*, Vol. II, Business & Legal Reports, Inc., Madison, CT, p. 15-8

STN (1994) The Scientific and Technical Information Network, STN International, databases searched (see search resource list)

Wood, A. & Young, I. (1992) Special report: methanol leads petchem growth, *ChemicalWeek*, March 25, 1992

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Summary Sheet Checklist for Isopropenyl acetate (108-22-5)

NLM

- CANCERLIT
- CCRIS
- DART
- EMIC
- EMICBACK
- ETICBACK
- GENETOX
- HSDB
- IRIS
- RTECS
- TOXLINE
- TOXLIT

STN INTERNATIONAL

- BIOSIS-RN
- CHEMLIST
- LIFESCI
- REGISTRY

CIS

- TSCAPP

DIALOG

- Life Sciences Collection (76)
- Chemical Safety NewsBase (317)
- APIPAT (353)
- APILIT (354)
- Fine Chemicals Database (360)

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MANUAL SOURCES

Amdur, M.O., Doull, J. & Klassen, D.C., Eds. (1991) *Casarett and Doull's Toxicology The Basic Science of Poisons*, 4th ed., Macmillan Publishing Co., New York

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

Anon. (1984) *Fire Protection Guide on Hazardous Materials*, 8th ed., National Fire Protection Association, Quincy, MA

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Merck & Co., Inc., Rahway, NJ (available online as Merck Online, DIALOG file #304)

Chemical Company Guides and Directories

Aldrich Catalog/Handbook of Fine Chemicals
Chemcyclopedia
Chemical Week Buyers' Guide
Lancaster Organic Research Chemicals
OPD Chemical Buyers Directory
Pfaltz & Bauer Catalog
Sigma Chemical Company Catalog

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

Clayton, G.D. & Clayton, F.E., Eds (1994) *Patty's Industrial Hygiene and Toxicology*, 4th ed., John Wiley & Sons, Inc., New York

Considine, D.M., ed. (1974) *Chemical and Process Technology Encyclopedia*, McGraw-Hill Book Co., New York

Considine, D.M., ed. (1989) *Van Nostrand's Scientific Encyclopedia*, 7th ed., Vol. I & II, Van Nostrand Reinhold, New York

Gilman, A.G., Goodman, L.S., Rall, T.W. & Murad, F., eds. (1985) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed., Macmillan Publishing Co., New York

Grayson, M., ed. (1978-1984) *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., John Wiley & Sons, Inc., New York (available online as Kirk-Othmer Online, DIALOG file #302)

IARC (1972-1994) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vols. 1-60, International Agency for Research on Cancer, Lyon, France

IARC (1994) *Directory of Agents Being Tested for Carcinogenicity*, Number 16, International Agency for Research on Cancer, World Health Organization, Lyon, France

Kent, J.A., Ed (1992) *Riegel's Handbook of Industrial Chemistry*, 9th ed., Van Nostrand Reinhold, New York

Prepared for NCI by Technical Resources International, Inc. under Contract No. NO1-CP-56019 (5/94; rev. 6/95)

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

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

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

National Cancer Institute (1994) Division of Cancer Etiology Short Term Test Program Results tracking file

National Toxicology Program (1994) *Chemical Status Report*, 5 October 1994 Report

National Toxicology Program (1994) *NTP Results Report. Results and Status Information on All NTP Chemicals*, April 8, 1994 Report

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

Perry, R.H. & Green, D. (1984) *Perry's Chemical Engineer's Handbook*, 6th ed., McGraw-Hill Book Co., New York

PHS-149 (1951-1992) *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, National Cancer Institute, U.S. Department of Health and Human Services, Bethesda, MD

Sax, N.I. & Lewis, R.J., Sr. (1989) *Dangerous Properties of Industrial Materials*, 7th ed., Van Nostrand Reinhold Co., New York

Sittig, M. (1980) *Pesticide Manufacturing and Toxic Material Control Encyclopedia*, Noyes Data Corporation, Park Ridge, NJ

Sittig, M. (1985) *Handbook of Toxic and Hazardous Chemicals and Carcinogens*, 2nd ed., Noyes Publications, Park Ridge, NJ

USITC (1974-1993) *Synthetic Organic Chemicals*, US Production and Sales, US Government Printing Office, Washington, DC

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

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