

# SUMMARY OF DATA FOR CHEMICAL SELECTION

## Isoamyl Acetate

CAS No. 123-92-2

Prepared for NTP by Technical Resources International, Inc

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### Table of Contents

- I. Chemical Identification
  - II. Exposure Information
    - Table 1. Levels of isoamyl acetate reported in foods
  - III. Evidence for Possible Carcinogenic Activity
    - Appendix A: Structural Analogs of Isoamyl Acetate
  - IV. References
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### SUMMARY OF DATA FOR CHEMICAL SELECTION

#### CHEMICAL IDENTIFICATION

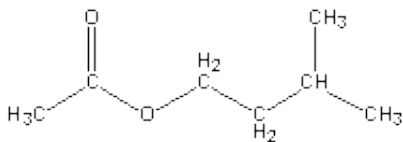
CAS Registry No.: 123-92-2

Chem. Abstr. Name: 1-Butanol, 3-methyl-, acetate

Synonyms:

- Acetic acid 3-methylbutyl ester;
- acetic acid,
- isopentyl ester;
- AI3-00576;
- banana oil;
- isoamyl ethanoate;
- isopentyl acetate;
- isopentyl alcohol, acetate;
- pear oil;
- 3-methyl-1-butanol acetate;
- 3-methyl-1-butyl acetate;
- 3-methylbutyl acetate;
- 3-methylbutyl ethanoate;
- i-amyl acetate

Structure: Molecular Formula and Molecular Weight:



C<sub>7</sub>H<sub>14</sub>O<sub>2</sub> Mol. Wt.: 130.18

### Chemical and Physical Properties:

Description:	Colorless, flammable liquid with a banana-like odor (ACGIH, 1993).
Boiling Point:	142°C (Lide, 1993)
Melting Point:	-78.5°C (Mark, et al, 1984; Lide, 1993)
Solubility:	Soluble in water (2000 mg/L at 25°C) (Howard, 1990); soluble in ethanol, diethyl ether, and acetone (Lide, 1993).
Vapor Pressure:	4.5 mm Hg at 20°C (Howard, 1990)
Refractive Index:	1.4003 (Lide, 1993)
Flash Point:	closed cup, 33°C; open cup, 38°C (Budavari, 1989)
Density:	0.876 (Lewis, 1993)
Reactivity:	Thermal decomposition of isoamyl acetate may produce acrid fumes. Contact with strong oxidizing agents, strong acids, and alkaline materials should be avoided (Haarmann & Reimer Corp., 1994). Hazardous decomposition products of isoamyl acetate include CO and CO <sub>2</sub> (AESAR/Alfa, 1994)
Log P(octanol/water partition coefficient):	2.13 (Howard, 1990)
Technical Products and Impurities:	Isoamyl acetate is commercially available as both a natural and synthetic product with a purity range of 95-99+%. (Allured Publishing Corp., 1993; Aldrich Chemical Co., Inc., 1994; Pfaltz & Bauer, 1994)

## EXPOSURE INFORMATION

### Commercial Availability

Production and Producers: Isoamyl acetate is derived by rectification of commercial amyl acetate (Lewis, 1993). It can also be prepared by esterification of commercial isoamyl alcohol with acetic acid (Opdyke, 1975). Two additional methods of preparation include esterification of pentyl alcohol with sodium acetate in the presence of sulfuric acid and by synthesis from pentane (Parmeggiani, 1983).

Isoamyl acetate is produced and supplied domestically in both bulk and research quantities by many manufacturers and distributors. There was little specific information on annual production volumes found in the available literature, but USITC reported a production volume of 112,000 pounds in 1984 (U.S. International Trade Commission, 1985). It was used in fragrances in the USA at about 10,000 lb/yr in the early 1970s (Opdyke, 1975).

It is manufactured and/or supplied/distributed by the following companies (Van, 1993; Hunter, 1994; Kuney, 1993; Dialog Information Services, 1994; Allured Publishing Corp., 1993):

<b>Manufacturers</b>	<b>Distributors</b>
Aldrich Chemical Co., Inc.	Aceto Corp.

BASF Corp	Alfa/AESAR (Johnson Matthey Co.)
Berje Chemical Products, Inc.	ChemService, Inc.
Bush Boake Allen	Crescent Chemical Co.
CA Aromatics Co.	EM Science
Elan Chemical Co.	Fluka Chemical Co.
F & C International, Inc.	ICN Biomedicals
Fleurchem, Inc.	Janssen Chimica
Givaudan-Roure Corp.	J.T. Baker
Haarmann & Reimer	Lancaster Synthesis, Inc.
Igene Biotechnology, Inc.	Mallinkrodt, Inc.
Northwestern Flavors, INC.	SAF Bulk Chemicals
Penta Manufacturing Co.	Sigma Chemical Co.
Pfaltz & Bauer, Inc.	Spectrum Chemical Mfg.
Rhone Poulenc, Inc.	TCI America
Robertet, Inc.	
Sanofi Bio Industries	

Use Pattern: Isoamyl acetate is used as a solvent for tannins, nitrocellulose, lacquers, celluloid, and camphor. It is also used as a flavoring agent in soft drinks, chewing gum, and candies. Isoamyl acetate is used during the manufacturing process of artificial silk, leather, pearls, photographic films, celluloid cements, waterproof varnish, bronzing liquids, metallic paints, dyeing, and finishing textiles (Howard, 1990).

The Merck Index lists the following uses for isoamyl acetate: in alcohol solution as a pear flavor in mineral waters and syrups; as a solvent for old oil colors; swelling bath sponges; covering unpleasant odors, and perfuming shoe polish (Budavari, 1989).

Isoamyl acetate is used in the following products at the following typical concentrations (%): soap, 0.05; detergent, 0.005; creams, lotions, 0.003; perfume, 0.05 (Opdyke, 1975).

Isoamyl acetate has reportedly been used in the following products at the following levels: non-alcoholic beverages, 28 ppm; ice cream, ices, etc, 56 ppm; candy, 190 ppm; baked goods, 120 ppm; gelatins and puddings, 100 ppm; and chewing gum, 2700 ppm (Furia & Bellanca, 1975).

Human Exposure: Workers are potentially exposed to isoamyl acetate during its use as a solvent. The general population is potentially exposed to it in foods in which it occurs naturally or to which it has been added as a flavoring agent and possibly in consumer products which contain isoamyl acetate as a solvent (Howard, 1990).

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 estimated that 97,668 employees, including 32,512 female workers, in 24 industries were potentially exposed to isoamyl acetate. The estimate of numbers of workers is based on a survey of U.S. companies and did not involve measurements of actual exposures (NIOSH, 1994).

The Priority-based Assessment of Food Additives (PAFA) database lists the exposure level of isoamyl acetate at 195,000 pounds/year (U.S. Food and Drug Administration, 1994a)

FEMA (1994) reports possible average daily intake of isoamyl acetate from foods at 24.49 mg.

Occurrence: Isoamyl acetate is a plant volatile. It is released during the fermentation process in making beer and whiskey. It is a sting pheromone of the honey bee (*Apis mellifera*), and a pheromone for *Lobesia botrana* and *Manduca sexta*. Isoamyl acetate is used as an agent in respirator fit tests and may be released to the environment during this procedure (Howard, 1990). It has been identified in whiskey, beer, and cognac. The concentration of esters, including isoamyl acetate, in US lager beer is 25-50 ppm and is responsible for giving beer a fruity flavor (Howard, 1990). It has been found in the following food products: fried bacon, Beaufort cheese (Howard, 1990). Levels of isoamyl acetate reported in foods are presented in [Table 1](#) (FEMA, 1994).

**Regulatory Status:** An occupational exposure limit and guideline for isoamyl acetate has been established by the American Conference of Governmental Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA). The 8-hour time-weighted average (TWA) threshold limit value (TLV) for isoamyl acetate is 100 ppm (525 mg/m<sup>3</sup>) (ACGIH, 1993; NIOSH, 1992; OSHA, 1993).

Isoamyl acetate is listed in the EPA TSCA Inventory (Sax & Lewis, 1989).

Isoamyl acetate was Granted Generally Recognized as Safe (GRAS) status by FEMA in 1965 (Opdyke, 1975).

When isoamyl acetate, a hazardous material, is to be transported, Title 49 CFR, Transportation, Parts 100180, published by the US Dept of Transportation, contain the regulatory requirements and must be consulted (U.S. Department of Transportation, 1993).

Isoamyl acetate is a synthetic flavoring substance permitted for direct addition to food for human consumption, as long as (a) it is used in the minimum quantity required to produce its intended effect, and otherwise in accordance with all the principles of good manufacturing practice. (b) It consists of one or more of the following, used alone or in combination with flavoring substances and adjuvants generally recognizable as safe in food, priorsanctioned for such use, or regulated by an appropriate section in this part (U.S. Food and Drug Administration, 1994b).

The US Environmental Protection Agency has established regulations for the use of isoamyl acetate in or on raw agricultural commodities including exemption from the requirements of a tolerance (40 CFR 180.1001).

Isoamyl acetate is considered a Comprehensive Emergency Response, Compensation, and Liability Act (CERCLA) hazardous substance and has a Reportable Quantity (RQ) of 5,000 lbs (Business & Legal Reports, Inc., 1994).

The National Fire Protection Association (NFPA) ratings for isoamyl acetate are: Health, 1 (Material that on exposure would cause irritation but only minor residual injury even if no treatment was given); Flammability, 3 (Liquids and solids that can be ignited under almost all ambient temperature conditions); and Reactivity, 0 (Materials that in themselves are normally stable, even when exposed to fire, and that do not react with water) (Business & Legal Reports, Inc., 1994).

**Table 1. Levels of isoamyl acetate reported in foods<sup>a</sup>**

Food	Levels (ppm)
Apple ( <i>Malus species</i> )	0.01 - 4
Banana ( <i>Musa sapientum</i> )	0.2 - 25
Guava ( <i>Psidium guajava</i> )	0.0002 - 0.14
Muscat grape	0.6 - 1.1
Melon	0.1
Peach ( <i>Prunus persica L.</i> )	0.54
Strawberry ( <i>Fragaria spec</i> )	0.01 - 0.4
Butter	<1
Beer	0.1 - 7
Cognac	0.8 - 6
Armagnac	0.8

Weinbrand	<0.8
Rum Category I (total vol)	11
Rum Category II (total vol)	TRACE
Rum Category III (total vol)	TRACE
Bourbon whisky	1.1 - 5.1
Irish whisky	0.8 - 5
Malt whisky	0.8 - 30
Scotch blended whisky	1.6 - 8
Canadian whisky	0.3 - 0.8
Japanese whisky	1.1
Cider	13
Sherry	TRACE
White wine	0
Red wine	0
Cocoa	0.2
Black tea	1.3
Mango ( <i>Mangifera indica</i> )	0
Mountain papaya ( <i>Carica p</i> )	0.3 - 0.8

<sup>a</sup> From FEMA (1994)

## EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

**Human Data:** There is limited information in the published literature on the effects of isoamyl acetate in humans. No epidemiological studies or case reports concerning the carcinogenicity of this chemical were identified in the published literature.

Isoamyl acetate is an irritant and central nervous system depressant. In man, exposure to concentrations of 950 ppm for 30 minutes caused irritation of the nose and eyes, headaches, and weakness. Other symptoms, reported in cases of occupational exposure, include vertigo, palpitations, gastrointestinal disorders, anemia, cutaneous lesions and dermatitis. Exposure to the vapor has produced edema of the glottis. When tested at an 8% concentration in petrolatum, isoamyl acetate produced no irritation in a 8-hour closed patch test in 25 human subjects and it produced no sensitization reactions in humans when tested at a concentration of 8% in a maximization test (Opdyke, 1975; Parmeggiani, 1983; Gosselin *et al.*, 1984).

**Animal Data:** No 2-year bioassay studies concerning the carcinogenicity of isoamyl acetate were identified in the published literature. Toxicity information identified was limited to the following acute studies.

In rats and rabbits, the acute oral LD<sub>50</sub>s were reported to be 16.6 g/kg and 7.4 g/kg, respectively. The acute dermal LD<sub>50</sub> value in rabbits exceeded 5 g/kg (RTECS, 1994; Opdyke, 1975).

Dogs exposed to 5,000 ppm isoamyl acetate for 1 hour exhibited drowsiness and nasal irritation. In cats exposed to 7,200 ppm for 24 hours, light narcosis and delayed death due to pneumonia were reported while 4,000 ppm for

20 minutes caused eye and nose irritation (Sandmeyer & Kirwin, 1981).

Amyl acetate, a mixture of the isomeric forms of pentyl acetate, which contained 5% isoamyl acetate was investigated for its potential to cause allergic contact dermatitis using a guinea pig maximization procedure. It was considered a possible marginal skin sensitizer for the guinea pig (Cosmetic Ingredients Review Expert Panel, 1988; Ballantyne *et al.*, 1986).

Short-term Tests: The genetic and developmental toxicity of isoamyl acetate has been assessed in a variety of short-term assays with the following negative results.

- In the Ames *Salmonella typhimurium* assay carried out under the National Toxicology Program's (NTP) testing program, isoamyl acetate was not mutagenic in strains TA100, TA1535, TA1537, TA97, and TA98. The tests were conducted at concentrations ranging from 10-10,000 µg/plate using the preincubation protocol in the absence of exogenous metabolic activation and in the presence of rat and hamster liver S-9 (Zeiger *et al.*, 1992). Isoamyl acetate was also negative in strains TA92 and TA94 when tested up to 5 mg/plate both with and without metabolic activation (Ishidate *et al.*, 1984).
- Under the auspices of the NTP, isoamyl acetate was tested and found negative for mutagenicity in the *Drosophila melanogaster* sex-linked recessive lethal (SLRL) assay. Doses in the feeding and injection studies were 4,800 ppm and 14,000 ppm, respectively (Foureman *et al.*, 1994).
- At doses up to 2 mg/ml, isoamyl acetate did not induce chromosomal aberrations in Chinese hamster lung cells (Ishidate *et al.*, 1984).
- Isoamyl acetate was not mutagenic in the mouse lymphoma forward mutation assay both in the absence and presence of metabolic activation (McCarroll *et al.*, 1985).
- In the *E. coli* and *B. subtilis* microsuspension assay for DNA repair, no evidence of preferential inhibition of repair-deficient strains was observed following exposure to isoamyl acetate (McCarroll *et al.*, 1985).
- Exposure to 0.15-0.24% isoamyl acetate failed to induce mitotic chromosomal malsegregation, mitotic recombination or point mutation in *Saccharomyces cerevisiae* strain D61.M (Zimmerman *et al.*, 1985).
- In the Hydra developmental toxicity assay, the adult (AMAC) and developmental (DMAC) minimal affective concentrations of isoamyl acetate were both established as 0.2 ml/l. Since it was equally toxic to adults and embryos, it was considered to have a low-priority for more elaborate developmental testing (Newman *et al.*, 1990).

Metabolism: No information was found in the published literature on the metabolism of isoamyl acetate in humans. However, the available data suggests that it may undergo enzymatic hydrolysis to form acetic acid and isoamyl alcohol. Five acetate esters including isoamyl acetate were administered orally to rabbits to study the mechanism of drunkenness. The ester administration decreased the blood pCO<sub>2</sub> and pO<sub>2</sub> and the acetate esters were hydrolyzed to acetic acid and the corresponding alcohols. The enzymic hydrolysis of isoamyl acetate was studied *in vitro* with preparations of pancreatin and whole homogenates of pig jejunum. Following incubation of pancreatin with 100 µl/l isoamyl acetate for 2 hours, the degree of hydrolysis was low at 20%. However, incubation of 500 µl/l isoamyl acetate and pig jejunum resulted in 100% hydrolysis. It was presumed that those esters hydrolyzed rapidly *in vitro* would also be degraded readily in the intact animal (Cosmetic Ingredients Review Expert Panel, 1988; Sandmeyer & Kirwin, 1981; Tambo, 1973; Grundschober, 1977).

Other Biological Effects:

Structure/Activity Relationships: Seven isoamyl acetate analogs, as well as isoamyl alcohol, a product of isoamyl acetate hydrolysis, were researched to identify data relevant to an association of compounds structurally similar to isoamyl acetate with mutagenic or carcinogenic activity. Names, CAS registry numbers and structures of these compounds are shown in [Appendix A](#). Limited information was found on three of these chemicals as follows.

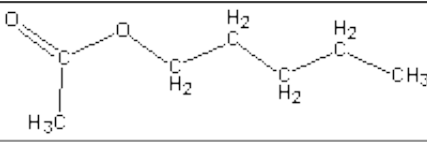
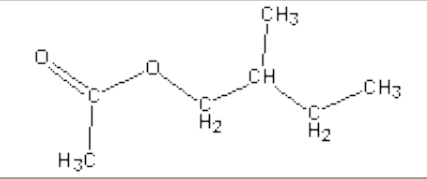
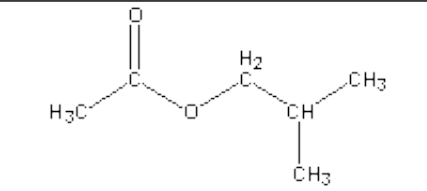
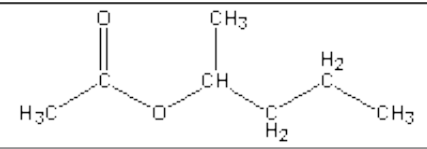
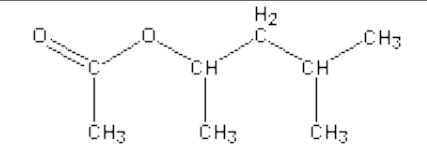
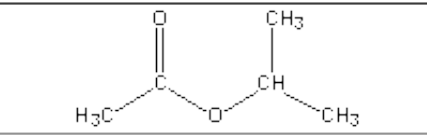
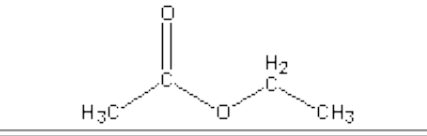
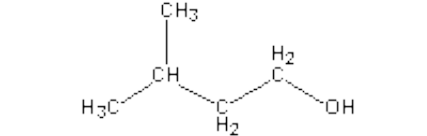
Isoamyl alcohol produced a positive carcinogenic response in male and female Wistar rats following oral or sc administration (total doses of 27 and 3.8 ml, respectively). Four of 15 rats in the oral trial had malignant tumors including: 2 with liver cell carcinomas, 1 forestomach carcinoma and 1 myelogenous leukemia. Ten of 24 rats in the sc group had malignant tumors including: 4 with liver sarcomas and 2 with liver carcinomas, 1 spleen carcinoma, 2 myelogenous leukemia and 1 glandular stomach carcinoma. There were no malignant tumors in control animals of either group (Gibel *et al.*, 1974; Gibel *et al.*, 1975; PHS-149, 1951-1994). No information was found on the mutagenic potential of isoamyl alcohol.

Ethyl acetate was not carcinogenic in rainbow trout (oral administration, 12 month study), CD-1 mice (dermal administration, 22 week study) or rats (oral administration, 300 day study) (PHS-149, 1951-1994). It was negative in the Ames *Salmonella* and chromosomal aberration assays. Positive results were reported for sister chromatid exchanges (NTP, 1994).

Isopropyl acetate was negative in the Ames *Salmonella* assay (NTP, 1994).

Neither short-term test data nor chronic bioassay data were found addressing the potential mutagenicity or carcinogenicity of the remaining analogs screened.

## Structural Analogs of Isoamyl Acetate

Chemical Name	CAS #	Chemical Structure
n-Pentyl acetate	628-63-7	
2-Methylbutyl acetate	624-41-9	
Isobutyl acetate	110-19-0	
1-Methylbutyl acetate	626-38-0	
4-Methyl-2-pentyl acetate	108-84-9	
Isopropyl acetate	108-21-4	
Ethyl acetate	141-78-6	
Isoamyl alcohol	123-51-3	

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