1997:11

DECOS and SCG Basis for an Occupational Standard

Isopropyl acetate

Hans Stouten

ARBETE OCH HÄLSA VETENSKAPLIG SKRIFTSERIE
ISBN 91–7045–416–7 ISSN 0346–7821

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ISBN 91–7045–416–7
ISSN 0346-7821
Tryckt hos CM Gruppen

Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Dutch Health Council and the Swedish Criteria Group (SCG) at the Swedish National Institute for Working Life. The purpose of the agreement is to write joint scientific criteria documents for occupational exposure limits. These limits will be developed separately by the two countries according to their different national policies.

This document on health effects of Isopropyl acetate was written by Dr Hans Stouten from the department of Occupational Toxicology, TNO, Zeist, The Netherlands. The document has been reviewed by the Dutch Expert Committee as well as by the Swedish Criteria Group.

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Chairman
DECOS

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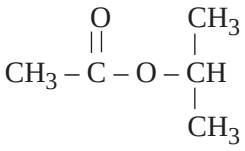
1. Introduction

Starting point in searching literature on the health effects of exposure to isopropyl acetate is the review by Zaleski (44). Unless otherwise indicated, data were derived from this document. Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the on-line databases CA SEARCH, TOXLINE, and MEDLINE starting from 1977, 1965, and 1980, respectively. The final search has been carried out in February, 1996, and included Chem Abs 1996 vol 124/6 (960131/ED) and Medline 960125/UP. HSDB and RTECS, databases available from CD-ROM were consulted as well (30, 32).

2. Identity, properties, and monitoring

2.1 Identity

Structure



Chemical names and synonyms/registry numbers

name	:isopropyl acetate
CAS registry number	: 108-21-4
CA index name	: acetic acid, 1-methylethyl ester; acetic acid, isopropyl ester
synonyms	: 2-propyl acetate; *sec*-propyl acetate; 1-methyl ethyl acetate; 2-acetoxypropane; isopropyl ethanoate; paracetat
EINECS No	: 203-561-1
EEC No	: 607-024-00-6
EEC Labelling	: R: 11 S: (2-)16-23-29-33
EEC Classification	: F; R 11
RTECS No	: AI4930000

2.2 Physical and chemical properties (data from refs 8, 25, 35, 42, 44)

Molecular formula	: $C_5H_{10}O_2$
Molecular weight	: 102.13
Boiling point (101 kPa)	: 89°C
Melting point (101 kPa)	: -73.4°C
Relative density (20°/4°C)	: 0.87
Vapour density (air=1; 101 kPa)	: 3.5
Relative density of saturated vapour/air mixture (air=1; 20° C)	: 1.2
Vapour pressure (101 kPa)	: 6.1 kPa (20°C); 9.73 kPa (25°C)
Percentage in saturated vapour/air mixture (101 kPa)	: 6.0
Flashpoint, closed cup	: 2°C
open cup	: 4°C
Explosive limits, vol% in air	: 1.8-8 %
Solubility in water, g/100 mL (20°C):	3.1
Solubility in organic solvents	: soluble in acetone; miscible with alcohol, ether
Physical form	: colourless liquid
Odour	: fruity
Odour detection threshold	: 1.9-140 mg/m^3
Odour recognition threshold	: 1.9-170 mg/m^3
Log $P_{octanol/water}$ (calculated)	: 1.3
Conversion factors	: 1 ppm = 4.22 mg/m^3
(20°C, 101 kPa)	: 1 mg/m^3 = 0.24 ppm

The isopropyl acetate vapour is heavier than air, travels along surfaces, and can be ignited from distance. Upon contact with water or moist air, isopropyl acetate decomposes into acetic acid and isopropanol[1]. It can react vigorously with oxidising agents (39).

Imbriani et al (23) have determined some Ostwald partition coefficients for isopropyl acetate: the (human) blood/air coefficient was 36, the urine/air coefficient 40.

Isopropyl acetate is available in grades of 85-88%, 95%, or 95-99+% (30).

1 this is conflicting with other information which indicates that hydrolyses is likely to occur under basic conditions (pH>9) only

2.3 Validated analytical methods

2.3.1 Environmental monitoring

NVN method 2948/2970 (31). By this active personal sampling method of the Netherlands Normalisation Institute, the compound is adsorbed to Chromosorb 106, thermally desorbed, and analysed gas chromatographically using FID. The limit of detection is 20 ng per sample. The maximum sample size is 75 L for a sampling period of eight hours and 3 L for a period of fifteen minutes. The method is suitable in the concentration range 0.001-400 mg/m^3 for an eight-hour period and in the range 0.022-9999 mg/m^3 for a fifteen-minute period.

NIOSH method S50 (31). This active personal air sampling method uses charcoal as adsorbens and carbon disulphide to desorb the compound. Analysis is by gas chromatography using FID. The limit of detection is 0.01 mg per sample. Maximum sample sizes are 9 or 3 L for an eight-hour and fifteen-minute sampling period, respectively. The method is suitable in the concentration ranges 3.7-9999 mg/m^3 for an eight-hour period and in the range 11-9999 mg/m^3 for a fifteen-minute period.

HSE has published a method in the MSDH series (Methods for the Determination of Hazardous Substances), viz, MDSH 70 - general methods for gases and vapours (22).

The use of diffusive samplers in monitoring isopropyl acetate vapours in indoor/workplace air has been reported (18, 21).

Finally, concentrations of organic solvents including acetic acid esters such as isopropyl acetate were quantitatively and quasi-continuously analysed in the waste air of a pharmaceutical production facility by means of IR spectrometry (15).

Biological monitoring. Several methods to determine isopropanol and acetone, possible metabolites of isopropyl acetate, have been published (see e.g., ref 10).

No validated methods for biological monitoring of workers exposed to isopropyl acetate were found.

3. Sources

3.1 Natural occurrence

Isopropyl acetate is reported to occur in natural products such as apples, bananas, black currants, grapes, melons, nectarines, pineapples, strawberries, honey, beans, and soyabeans. In addition, it was found in food products such as honey, cheddar cheese, cocoa, beer, white and red wine, and plum brandy (26).

3.2 Man-made sources

Production. Isopropyl acetate is prepared from catalysed reactions of anhydrous acetic acid and propylene, or of acetic acid and isopropanol (30).

Uses. Isopropyl acetate is used as a solvent for coatings, printing inks, cellulose derivatives, plastics, oils, and fats, as a chemical intermediate, and in the manufacture of perfumes and flavouring agents (30).

4. Exposure

4.1 General population

Air. Although isopropyl acetate was qualitatively detected in ambient air of The Netherlands, and described as one of the principal compounds emitted (37), it was not included in a Dutch programme regarding industrial emissions into air (5).

Isopropyl acetate has been measured in 1976-1977 near a waste disposal site in New Jersey, USA (estimated concentration: 6.5 μg/m^3) and in a industrialised region in West Virginia, USA (concentration not specified) (30).

Water. If released to surface water, isopropyl acetate is expected to rapidly volatilise to the atmosphere; the half life for volatilisation from a model river was calculated to be approximately 6 h (30).

Hydrolysis rate constants indicate that hydrolysis of isopropyl acetate in aquatic systems is not likely to occur except under basic conditions of pH>9 (30).

In The Netherlands, isopropyl acetate was not listed among compounds that were monitored with respect to industrial emissions into surface waters (5).

Isopropyl acetate was reported to be qualitatively detected in US drinking water supplies (30).

Food. Isopropyl acetate was present at an amount of 0.05 ppm in black currants and of 0.035 ppm in grapes (26).

4.2 Working population

The use of isopropyl acetate in Dutch paint industry has been reported to amount to 200 tonnes in 1979 (14). In Sweden, 25-49 tonnes were used in 1994 (U. Rick, Chemicals Inspectorate, Sweden, 1996, personal communication).

In a survey carried out at 12 Dutch project locations with respect to exposure of maintenance and house painters to paint solvents, isopropyl acetate was detected in one of these (spray painting a two-component polyurethane lacquer for several minutes) at a level of 22-28 mg/m^3 (≈ 6 ppm) (8-h TWA; personal air sampling) (35). In a review on exposure levels of organic solvents at Dutch workplaces (measurements by the Directorate-General of Labour of the Ministery of Social Affairs and Employment), isopropyl acetate was mentioned once: when printing plastic foil, breathing zone air levels ranged between 2 and 125 mg/m^3 (0.5-30 ppm) (14).

In a survey on levels of organic solvents used in eleven Spanish auto paint shops, isopropyl acetate was detected in four of them at levels varying from approximately 8 to 107 mg/m^3 (≈ 2-26 ppm) (personal air sampling) (12).

In a sampling campaign carried out in 543 French workplaces between 1981 and 1985, isopropyl acetate was found to be present in 69 cases (total number of measurements: 2013). In 6% of them, levels exceeded the occupational exposure limit of 950 mg/m^3 (250 ppm) while in 85% levels were below 475 mg/m^3 (125 ppm) (approx half of these < 95 mg/m^3) (16).

In a Belgium survey carried out in the mid 1980s, isopropyl acetate was present in six out of 94 personal air samples from 24 printing facilities, but not in 168 samples from painting, car repair, and other facilities (43).

Data on occupational exposure levels in Sweden have not been found (U. Rick, Chemicals Inspectorate, Sweden, 1996, personal communication).

5. Kinetics

5.1 Absorption

The main route of entry into the body is via the lungs. Based on its physico-chemical properties, absorption of liquid isopropyl acetate through the skin can be expected.

However, no quantitative data on absorption were located.

5.2 Distribution

No data were located.

5.3 Biotransformation

No data were located.

However, as other acetates, isopropyl acetate will be hydrolysed by carboxylic esterases to acetic acid and its corresponding alcohol in the liver, the small intestine, and in the respiratory tract (11, 34). This may already occur in the blood although *in vitro* experiments in which a number of acetates were incubated with human blood in airtight sealed vials for up to eight hours did not demonstrate hydrolytic cleavage of isopropyl and *t*-butyl acetate (19). However, in a separate *in vitro* experiment, *t*-butyl acetate dissociated slowly (when compared to the *n*-butyl isomer) in human and rat blood ($t_{1/2} \approx 300$ min vs ≈ 10 min) (17). Based on the latter study, a relatively slow hydrolysis of isopropyl acetate in the blood may be expected.

The acetic acid is oxidised via the citric cycle to carbon dioxide and water. Isopropanol is metabolised mainly to acetone and carbon dioxide (10, 11).

Since the hydrolysis is catalysed by the rather aspecific carboxylic esterases, interference may occur by other compounds while the metabolism of isopropanol can be retarded by preceding or concomitant ethanol consumption (10, 34).

Both isopropanol and acetone can be formed endogenously (10).

5.4 Elimination

No data were located.

As was reported for ethyl acetate (34), isopropyl acetate may be excreted unchanged in exhaled air.

In rats and mice exposed to isopropanol by gavage, intravenous injection, or inhalation, exhalation of acetone and carbon dioxide was the major route of excretion (>80% of the absorbed dose). In workers occupationally exposed to isopropanol, 11-40% of the amount taken up was exhaled as acetone; acetone was found in the urine to a small extent only (10).

5.5 Biological monitoring

No studies were located in which the relation between inhaled concentrations of isopropyl acetate and the excretion of the parent compound or metabolites have been investigated.

Physiological levels of isopropanol, a possible metabolite, may amount up to 0.1 mg/L in serum and urine; for acetone, these levels are 7 and 3.5 mg/L respectively (10).

5.6 Summary

There are no data on the kinetics of isopropyl acetate.

Comparison with other acetates indicate that isopropyl acetate will be hydrolysed by carboxylic esterases to acetic acid and isopropanol in the liver, the small intestine, and the respiratory tract. In blood, it may dissociate relatively slowly. Excretion of isopropyl acetate and its metabolites may occur via the exhaled air and the urine.

6. Effects

6.1 Observations in man

6.1.1 Irritation and sensitisation

The majority (not specified) of twelve male and female volunteers complained of irritation of the eyes when exposed to ≈ 850 mg/m^3 (200 ppm) for fifteen minutes. No nose or throat irritation was reported (36).

Splashing may cause corneal burns which may heal promptly within 48 hours (27).

No reports on sensitisation were located.

6.1.2 Toxicity due to experimental or occupational exposure

No studies were located from which conclusions can be drawn concerning adverse effects in man due to experimental or occupational exposure.

6.2 Animal experiments

6.2.1 Irritation and sensitisation

Following application of 0.01 mL of the undiluted ester to the clipped skin of five albino rabbits, isopropyl acetate scored an injury grade of 1 (i.e., giving rise to 'the least visible capillary injection') on a scale from 1 to 10 (38).

No studies on skin sensitisation in experimental animals were found.

When tested for irritation on the eyes of rabbits, it scored an injury grade of 2 on a scale from 1 to 10. It was not stated whether the eyes were rinsed with water after application of the test substance (38).

With respect to the respiratory tract, the sensory irritation in the upper part was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). Using (probably ten male Swiss OF1) mice, the RD_{50} for isopropyl acetate was 17,783 mg/m^3 (4268 ppm) (28; see also ref 7).

6.2.2 Toxicity due to acute exposure

Data on the toxicity following single exposure to isopropyl acetate are summarised in Table 1.

In an abstract from a paper from one of the former Soviet Republics, it was mentioned that acute inhalation and single oral (gavage) administration of isopropyl acetate to rats and mice resulted in rapid intoxication. Irritation, increased motor activity, interrupted respiration, narcosis, and death were observed within one to three days (20).

Table 1. Effects on experimental animals after single exposure to isopropyl acetate

Species	Concentration/ dose	Duration	Route	Effect	Reference
rat	50.6 g/m^3	8 h	inhalation	LC_{50}	33
rat	27.9 g/m^3	?	inhalation	LC_{50}	20
rat	135.0 g/m^3	4 h	inhalation	5/6 animals	38
rat	≈250 g/m^3 [1]	30 min	inhalation	died	38
rat	6750 mg/kg	-	oral	no deaths	38
rat	10,900 mg/kg	-	oral (gavage)	LD_{50}	20
rat	14,960 mg/kg	-	oral	LD_{50}	33
mouse	37.0 g/m^3	?	inhalation	LD_{50}	20
mouse	6650 mg/kg	-	oral (gavage)	LC_{50}	20
rabbit	6945 mg/kg	-	oral	LD_{50}	29
rabbit	3064 mg/kg	-	oral	LD_{50}	29
rabbit	> 20 mL/kg	-	dermal	ND_{50} [2]	38
				LD_{50}	

[1] Vapours were stated to be concentrated, probably saturated; in this case, listed concentration can be calculated; rats could tolerate this level without death for a maximum of 30 min.

[2] ND_{50}: the quantity that produced stupor and loss of voluntary movements on half of the number of the animals.

Note: In reviews (1, 6, 44), another rat oral LD_{50} was mentioned referring to ref 24. However, in this latter paper, no rat oral LD_{50} for isopropyl acetate was reported.

Possible neurobehavioural effects following acute inhalation exposure were examined in mice (male Swiss OF1; n=10/group) using the "behavioural despair" swimming test. This bioassay is based on the finding that rodents that are forced to swim in a restricted space exhibit vigorous escape-directed activity during the first minute, then a transient period of swimming activity and immobility, and, after three minutes, a state of complete immobility. Exposure to 5798, 6073, 6769, 7929, and 8440 mg/m^3 (1374, 1439, 1604, 1879, 2000 ppm), for four hours, showed a dose-related decrease (stat sign at 6073 mg/m^3 and higher) in the duration of immobility measured over a three-minute period. The ID_{50}, i.e., the concentration responsible for a 50% decrease in immobility (compared to control values), was calculated to be 6773 mg/m^3 (1605 ppm; 95% CI: 1455-1641 ppm). De Ceaurriz et al suggested that the decrease in duration of immobility is caused by prolongation of escape-directed activity, and that further investigations are required to explain the meaning of this increase in initial swimming activity (9).

Isopropyl acetate was examined as a solvent control agent in an experiment to test whether methyl *t*-butyl ether, a contact dissolution agent for gallstones (via a percutaneous transhepatic catheter into the gallbladder), might cause serious tissue injury if accidently infused outside the gallbladder. A single injection of 0.2 mL/kg bw (≈ 1750 mg/kg) into the inferior vena cava or a peripheral (tail) vene, or into the intrahepatic parenchyma of ether-anaesthetised rats (male; Sprague-Dawley; n=6, 5, and 5, resp) resulted in lung injury and death of all treated animals. Intrahepatic injection induced liver injury in 3/5 animals. Injection of a similar amount ip caused lung injury in 1/5 rats only (3).

6.2.3 Toxicity due to short-term exposure

No short-term toxicity studies on isopropyl acetate were located.

6.2.4 Toxicity due to long-term exposure and carcinogenicity

No long-term toxicity or carcinogenicity studies on isopropyl acetate were located.

6.2.5 Genotoxicity

Isopropyl acetate (purity: > 99%) was negative when tested in *S. typhimurium* strains TA100, TA1535, TA1537, TA97, and TA98 at concentrations of 100-10,000 µg/plate with and without metabolic activation (i.e., 10 and/or 30% S9 fractions of induced livers from male rats and hamsters) (45).

Isopropyl acetate (concentration in the medium: 0.74-1.23%) was a weak inducer of aneuploidy in the yeast *S. cerevisiae* (diploid strain D61.M), but it did not cause mitotic recombination or point mutations. The induction of aneuploidy was not due to interactions with DNA, but due to interference with the spindle apparatus. The effect was most pronounced using a treatment protocol in which growing cells were exposed during a growth period of four hours at 28^{o}C followed by incubation in ice (46). Under similar conditions, isopropyl acetate potentiated the effects of low concentrations of propionitrile (47).

6.2.6 Reproduction toxicology

The Commission of the European Communities has reviewed the reproduction toxicity of a number of compounds of industrial interest including isopropyl acetate. As to isopropyl acetate, no relevant data could be found (40).

Table 2. Occupational exposure standards in various countries

country organisation	occupational exposure limit		time-weighted average	type of exposure limit	note*	lit ref**	year of adoption***
	ppm	mg/m^3					
The Netherlands							
- Ministry	250	950	8 h	admini-strative force		41	unknown
- DECOS							
Germany							
- AGS							
- DFG MAC-kom.	200 400	840 1680	8 h 5-min ceiling****	MAK		13	unknown
Great-Britain							
- HSE	200	840	15 min	OES		22	unknown
Sweden							
Denmark*****	200	840	8 h			4	unknown
USA							
- ACGIH	250 310	1040 1290	8 h 15 min	TLV		2	1976
- OSHA	250 310		8 h 15 min	PEL		1	unknown
- NIOSH	no limit					1	
European Union							
- SCOEL							

* S = skin notation; which mean that skin absorption may contribute considerably to body burden.
sens = substance can cause sensitisation.

** Reference to the most recent official publication of occupational exposure limits.

*** Year that this limit was officially adopted or established.

**** Limited to maximal eight times per shift.

***** Intended to be changed to 150 ppm.

6.3 Summary

The human data on effects of exposure to isopropyl acetate are limited to old data concerning irritation. They indicate that liquid and vaporous isopropyl acetate may cause corneal burns and eye irritation, respectively.

Isopropyl acetate was not irritating to the skin and eyes of rabbits, but was not tested according to EEC- or OECD-guidelines. In mice, an RD_{50} of approximately 18 g/m^3 (4300 ppm) has been reported. From lethality data following single exposure, it can be seen that isopropyl acetate is hardly toxic via the various exposure routes. When mice were exposed to levels of approximately 6000 mg/m^3 (≈ 1400 ppm) and higher, for four hours, changes in a behavioural parameter in a non-validated test were observed.

No experimental animal studies were located regarding effects (including those on reproduction) following repeated exposures.

Isopropyl acetate was negative when tested with and without metabolic activation in several *S. typhimurium* strains. It did not cause point mutations or mitotic recombinations in *S. cerevisiae*, but was a weak inducer of aneuploidy probably because of interference with the spindle apparatus functioning.

7. Existing guidelines, standards, and evaluations

7.1 General population

No data on guidelines concerning the general population were found.

7.2 Working population

Occupational exposure limits. Occupational exposure limits in the Netherlands and in some other countries are presented in Table 2.

ACGIH has based its threshold limits on rather old acute toxicity data and on comparison with other alkyl acetates. It was stated that the irritative and narcotic potential of these esters increases as a function of molecular weight and volatility. Since isopropyl acetate was somewhat less toxic than n-propyl acetate, slightly higher levels were recommended. These levels should minimise potential ocular and upper respiratory tract irritation in humans resulting from exposure to isopropyl acetate (date of review: 1992) (1).

Biological limit values. No biological limit values have been established by ACGIH or DFG.

8. Hazard assessment

8.1 Assessment of health hazard

Apart from two old studies reporting effects on the eyes from contact with liquid or vapour, no toxicity data in humans due to exposure to isopropyl acetate were available.

Animal data were limited to those from single exposure. Isopropyl acetate was not irritating to the eyes and skin of rabbits, and showed little toxicity (parameter: lethality) via the inhalatory, oral, or dermal route. Exposure to approximately 6000 mg/m^3 (≈ 1400 ppm) for four hours caused some impairment in a non-validated behavioural test in mice.

Isopropyl acetate was negative when tested with and without metabolic activation in *S. typhimurium*, nor did it cause point mutations or mitotic recombinations in *S. cerevisiae*. It was a weak inducer of aneuploidy probably due to interference with the spindle apparatus functioning.

There were no data on toxicokinetics.

Since there were no data on kinetics, and since some information from *in vitro* experiments indicates that isopropyl acetate may relatively slowly dissociate into isopropanol and acetic acid, it is considered unjustifiable to use the toxicological data base of isopropanol to derive an occupational exposure limit for isopropyl acetate.

8.2 Groups at extra risk

No groups at extra risk could be identified.

9. Recommendations for research

In order to allow a proper evaluation of the toxicity of isopropyl acetate, studies on inhalatory kinetics, and on subchronic and reproduction toxicity are recommended. In addition, an *in vitro* gene mutation and a chromosome aberration test in mammalian cells should be conducted.

10. Summary

10.1 Summary in English

Stouten H. Isopropyl acetate. DECOS and SCG Basis for an Occupational Standard. *Arbete och Hälsa* 1997;11:1-15.

Isopropyl acetate is a colourless liquid with a fruity odour. It is soluble in water and acetone and miscible with alcohol and ether. Its vapour is heavier than air. Methods for personal air sampling are available. No data were available on the kinetics of isopropyl acetate. It can be expected that it will hydrolyse to acetic acid and isopropanol in the liver and the respiratory tract. Human data on effects are limited to old data concerning irritation. From lethality data following single exposure to animals, it can be seen that isopropyl acetate is hardly toxic via the various exposure routes. No experimental animal studies were allocated regarding effects following repeated exposure. Isopropyl acetate was negative in most genotoxic test systems, but was a weak inducer of aneuploidy. Based on the few existing data, the critical effect of occupational exposure to isopropyl acetate is irritation.

Key words: Hazard assessment, Irritation, Isopropyl acetate, Occupational exposure limit, Toxicity.

10.2 Summary in Swedish

Stouten H. Isopropyl acetate. DECOS and SCG Basis for an Occupational Standard. *Arbete och Hälsa* 1997;11:1-15.

Isopropylacetat är en färglös vätska med fruktig doft. Den är löslig i vatten och aceton och blandbar med alkohol och eter. Ångorna är tyngre än luft. Det finns metoder för personburen provtagning. Det finns inga data avseende isopropylacetats kinetik. Man kan förmoda att den hydrolyseras till ättiksyra och isopropanol i lever och andningsorgan. Data över effekter på människa är begränsade till äldre data avseende irritation. Från letalitetsdata efter engångsexponering av försöksdjur kan man se att isopropanol knappast är toxiskt oavsett exponeringsväg. Det finns inga data avseende långtidsexponering av djur. Isopropylcetat var negativ i de flesta genotoxiska testsystem men gav en svag induktion av aneuploidi. Baserat på de få existerande data är den kritiska effekten vid yrkesmässig exponering irritation.

Nyckelord: Hygieniskt gränsvärde, Irritation, Isopropylacetat, Riskbedömning, Toxicitet.

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Submitted for publication May 6, 1997.