DECOS and SCG Basis for an Occupational Standard

n-, iso-, sec-, and tert-Butyl acetate

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Arbete och Hälsa

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Summaries in Swedish and English as well as the complete original text are available at www.niwl.se/ as from 1997.

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 for Occupational Standards (SCG) of the Swedish National Institute for Working Life. The purpose of the agreement is to write joint scientific criteria documents for occupational exposure limits. The numerical limits will be developed separately by The Netherlands and Sweden according to their different national policies.

The evaluation of health effects of Butyl acetates is a product of this agreement. The draft document was written by H Stouten and W Bogaerts, from the Department of Occupational Toxicology of the TNO, Nutrition and Food Research Institute, Zeist, the Netherlands. The document has been reviewed by the Dutch Expert Committee as well as by the Swedish Criteria Group.

Gerard Mulder   Johan Högberg
Chairman   Chairman
DECOS   SCG

Contents

1. Introduction

As starting point in searching literature on the health effects of exposure to butyl acetates a number of review articles were used (25, 86, 87, 108, 110, 119). In addition, literature was retrieved from the on-line data bases CA SEARCH, MEDLINE and TOXLINE starting from respectively 1967, 1966, and 1965. The final search has been carried out in January 1997, and included Chem Abs 1997 vol 126/5 (970128/ED), Medline 970128/UP, and Toxline 970128/ED. An additional literature search in Medline (January 1995-November 2000) and Toxline (January 1995-September 2000) were performed and where relevant, these additional data are incorporated in the text. Scientific publications between 1997 and 2000 were no reason for adjustment of the conclusions.

2. Identity, properties, and monitoring

2.1 Identity

2.1.1 Structures

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2-CH_2-CH_2-CH_3$$

n-butyl acetate

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{CH}}$$

isobutyl acetat

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle CH_3}{|}}{CH}-CH_2-CH_3$$

sec-butyl acetate

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-CH_3$$
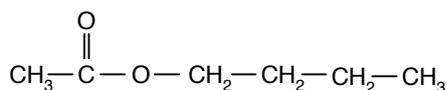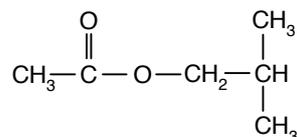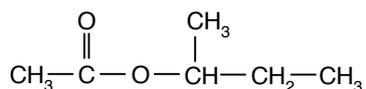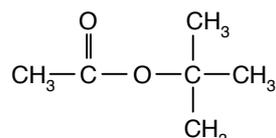
tert-butyl acetate

2.1.2 Chemical identity (106, 119)

n-butyl acetate:

synonyms	butyl acetate, butyl ethanoate, acetic acid, butyl ester
CAS registry no	123-86-4
EINECS no	204-658-1
EEC no	607-025-00-1
EEC labelling	R: 10
	S: (2)
EEC classification	R 10
RTECS no	AF7350000

isobutyl acetate:

synonyms	acetic acid isobutyl ester, 2-methyl-1-propyl acetate, b-methyl propyl ethanoate
CAS registry no	110-19-0
EINECS no	203-745-1
EEC no	607-026-00-7
EEC labelling	R: 11
	S: (2-)16-23-29-33
EEC classification	F; R 11
RTECS no	AI4025000

sec-butyl acetate:

synonyms	acetic acid sec-butyl ester, acetic acid 1-methylpropyl ester, 2-butanol acetate
CAS registry no	105-46-4
EINECS no	203-300-1
EEC no	607-026-00-7
EEC labelling	R: 11
	S: (2-)16-23-29-33
EEC classification	F; R 11
RTECS no	AF7380000

tert-butyl acetate:

synonyms	acetic acid tert-butyl ester, acetic acid 1,1-dimethyl ethyl ester
CAS registry no	540-88-5
EINECS no	208-760-7
EEC no	607-026-00-7
EEC labelling	R: 11
	S: (2-)16-23-29-33
EEC classification	F; R 11
RTECS no	AF7400000

2.2 Physical and chemical properties (83, 106, 119)

general:

isomers	n-butyl acetate, isobutyl acetate, sec-butyl acetate, tert-butyl acetate
molecular formula	$C_6H_{12}O_2$
molecular weight	116.16 g/mol
conversion factors[a]	1 ppm = 4.83 mg/m³
(20°C, 101.3 kPa)	1 mg/m³ = 0.207 ppm

_____

[a] These conversion factors are used in this document. However, in some cases they might deviate, since other figures were presented in the publications discussed.

The butyl acetates are colourless, flammable liquids with a fruity odour. Odour threshold values of 0.031 (determined according to NVN 2820) (70), 0.92 (40), and 1.88 mg/m³ (8) (0.006, 0.19 and 0.39 ppm, resp.) have been reported. Their vapours can form explosive mixtures with air. In water or under influence of light, the acetates slowly decompose into acetic acid and their respective alcohols. They violently react with oxidising agents. sec-Butyl acetate vapour is heavier than air, travels along surfaces, and can be ignited from distance.

n-butyl acetate:

boiling point (101.3 kPa)	127 °C
melting point (101.3 kPa)	-77 °C
specific gravity (20°C/4°C)	0.9
vapour pressure (20°C)	1.07 kPa
vapour density (air=1)	4.0
relative density of saturated vapour/air mixture (air=1; 20°C)	1.03
flash point	closed cup: 24 °C; open cup: 37 °C
explosive limits, vol% in air	1.2-7.5
solubility in water (20°C)	7 g/L
solubility in organic solvents	miscible with alcohols, ether, ketones, esters, most hydrocarbons and other organic solvents
odour threshold	10 ppm
partition coefficient log K_{ow}	1.82

isobutyl acetate:

boiling point (101.3 kPa)	117 °C
melting point (101.3 kPa)	-99 °C
specific gravity (20°C/4°C)	0.9
vapour pressure (20°C)	2.0 kPa
vapour density (air=1)	4.0

relative density of saturated vapour/air mixture (air=1; 20ºC)	1.05
flash point	closed cup: 17 °C; open cup: 35 °C
explosive limits, vol% in air	2.4-10.5
solubility in water (20ºC)	7 g/L
solubility in organic solvents	freely soluble in alcohol, acetone, ether
partition coefficient log K_{ow}	1.60

sec-butyl acetate (exists in D- and L isomeric forms):

boiling point (101.3 kPa)	D-form: 112 °C; L-form: 116-117 °C; DL-racemic: 112.2 °C
melting point (101.3 kPa)	-74 °C
specific gravity (20ºC/4ºC)	0.9
vapour pressure (20ºC):	2.5 kPa
vapour density (air=1)	4.0
relative density of saturated vapour/air mixture (air=1; 20ºC)	1.1
flash point	closed cup: 17 °C; open cup: 31 °C
explosive limits, vol% in air	1.7-9.8
solubility in water (20ºC)	30 g/L
solubility in organic solvents	soluble in alcohol, ether, acetone

tert-butyl acetate

boiling point (101.3 kPa)	97-98 °C
melting point (101.3 kPa)	no data available
specific gravity (20°C/4°C)	0.9
vapour pressure	no data available
vapour density	no data available
flash point	closed cup: 17-22 °C
solubility in water	practically insoluble
solubility in organic solvents	soluble in ethanol, ether
partition coefficient log Kow	1.38

2.3 EU Classification and labelling (11)

According to the 25th Amendment of Annex 1 of Directive 67/548/EEC, n-butyl acetate is classified as "flammable", "repeated exposure may cause skin dryness or cracking", and "vapours may cause drowsiness and dizziness", and is labelled as follows:

Symbols	-
Risk phrases	R10: flammable
	R66: repeated exposure may cause skin dryness or cracking
	R67: vapours may cause drowsiness and dizziness
Safety phrases	S25: avoid contact with eyes

Iso-, sec- and tert-butyl acetate are classified as "highly flammable" and "repeated exposure may cause skin dryness or cracking", and are labelled as follows:

Symbols	F: highly flammable
Risk phrases	R11: highly flammable
	R66: repeated exposure may cause skin dryness or cracking
Safety phrases	S16: keep away from source of ignition - No smoking
	S23: do not breathe gas/fumes/vapours/spray (appropriate wording to be specified by the manufacturer)
	S25: avoid contact with eyes
	S29: do not empty into drains
	S33: take precautionary measures against static discharges

2.4 Validated analytical methods

2.4.1 Environmental monitoring

NIOSH methods are available for measuring the respective butyl acetates (46). Ten litre of air is sampled on a solid sorbent tube (coconut shell charcoal) and desorbed with carbon disulphide. Aliquots are analysed by gas chromatography equipped with a FID. For 10 L air samples, the method is applicable at concentration ranges of 352-1,475 mg/m^3, 306-1,280 mg/m^3, 478-2,005 mg/m^3, and 424-1,780 mg/m^3 for n-butyl acetate, isobutyl acetate, sec-butyl acetate, and tert-butyl acetate, respectively.

The use of diffusive samples in monitoring butyl acetate vapours in indoor/ workplace air has been reported (33, 51, 68, 96).

Butyl acetates can be determined by infrared and UV spectroscopy, gas chromatography, gas chromatography/mass spectrometry, and headspace gas chromatography (110, 115).

Finally, concentrations of organic solvents including acetic acids, such as n-butyl acetate were quantitatively and quasi-continuously analysed in the waste air of a pharmaceutical production facility by means of infrared spectrometry (44).

2.4.2 Biological monitoring

Several chromatographic methods to determine butyl acetate(s) and butyl alcohol(s), to which the acetate is rapidly hydrolysed in the blood, have been published including one proposed by USEPA (49, 105, 107, 112).

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

3. Sources

3.1 Natural occurrence

The n-butyl, isobutyl, and tert-butyl acetates occur naturally among other esters in bananas and related fruits (25). n-Butyl acetate is also formed during fermentation in yeast. It has also been found in a wide variety of food products: milk, cheese, beer, rum, brandy, wine, whisky, cocoa, black tea, coffee, roasted nuts, vinegar and honey (74). Isobutyl acetate occurs in natural products such as raspberries, pears, pineapples and natural cocoa aroma (86), black currants, guava, grapes, melons, peaches, strawberries, tomatoes, soy beans, plums, passion fruit, star fruit and dill herb (74).

3.2 Man-made sources

3.2.1 Production
All four isomers of butyl acetate are produced by a nucleophilic addition reaction during slow distillation of acetic acid and the corresponding butyl alcohol in the presence of sulphuric acid as a catalyst (119).

Isobutyl acetate is also prepared from methyl isobutyl ketone, the sec-butyl acetate from sec-butyl alcohol and acetic acid anhydride. The synthesis of the D- and L-forms has been reported (119).

tert-Butyl acetate is only slowly and incompletely formed from its alcohol and acetic acid; it is mainly produced from acetic acid and isobutylene (119).

Technical grades of butyl acetates contain butyl alcohol as an impurity; small amounts of water may also be present (108). Commercial grades that are currently used are more defined and purified than those used in the early 1930s, when studies on toxicity of these esters began (119).

In cosmetic grade butyl acetate, lesser amounts of n-butyl alcohol, isobutyl alcohol and traces of n-propyl acetate and isobutyl acetate are present (110).

3.2.2 Uses
Butyl acetates, especially n-butyl acetate and isobutyl acetate, are used as a solvent in many trades. The Dutch paint industry was reported to have used 1,750 tons of n-butyl acetate and 1,275 tonnes of isobutyl acetate in 1979 (43).

n-butyl acetate is a good solvent for nitrocellulose. It is mainly used as a solvent and a thinner in the production of nitrocellulose lacquers in the protective coatings industry. It is also used in the manufacturing of high-polish lacquers and varnishes, in a protective low viscosity vehicle coating used in the motor industry and in liquid floor wax (119). n-Butyl acetate is further used in:
- the cosmetics industry as a solvent in nail polish, base coats, nail polish removers and other preparations for manicuring (110);
- the food industry as a component in synthetic flavours, as a component used in articles used for food packaging, and also as a diluent for dyes in inks for marking vegetables and fruits (119);

- the production of artificial leather, shoe and leather glues, photographic films, plastics, and safety glass (119);
- the pharmaceutical industry as an extractant (119).

Both n-butyl and isobutyl acetate are used in perfumery. Isobutyl acetate is a component of hydraulic fluids and is used as a solvent in manufacturing lacquers and paint removers. sec-Butyl acetate serves also as a solvent for nitrocellulose, nail enamel, and in the production of paper coatings.

tert-Butyl acetate is used as a solvent for lacquers and also as an antiknock additive in motor fuels (119).

4. Exposure

4.1 General population

4.1.1 Ambient air
In the Netherlands, industrial emissions of butyl acetate into air amounted to approximately 1,170 and 1,280 tonnes in 1990 and 1988, respectively. Corresponding figures of isobutyl acetate were 4.2 and 5.6 tonnes (20).

In a German field study, in selected representative households, low levels of n-butyl acetate were found (n.d.-23 $\mu g/m^3$). In winter, the total concentration of volatile organic compounds was 2-3 times higher than during summer (100).

In a Swiss study of new and recently renovated buildings, a concentration of 549 $\mu g/m^3$ was measured. Butyl acetate was found to be offgassed from a sealing wax on a cork floor (94).

Concentrations of 0.1 and 4.8 $\mu g/m^3$ emanating from US industrial and chemical waste disposal sites have been reported (90).

4.1.2 Water
In the Netherlands, industrial emissions of butyl acetate into surface water were 0.5 and 2.9 tonnes in 1990 and 1988, respectively (20). No other data on the presence of the butyl acetate isomers in water were found.

4.1.3 Food
n-Butyl acetate was found in apples at a concentration of up to 29.5 mg/kg, and in grapes, mangoes, melons, and strawberries at an amount of up to 0.1 mg/kg. In vinegar, concentrations were up to 166 mg/kg. As to drinks, n-butyl acetate was found in apple juice at levels of up to 2.2 mg/kg, in cider up to 1.3 mg/kg, in beer up to 0.2 mg/kg, and in weinbrand up to 0.4 mg/kg (74).

sec-Butyl acetate was found in vinegar at concentrations of 43-67 mg/kg (74).

4.2 Working population

A summary of air levels in workplaces is presented in Table 1.

The occurrence of n-butyl acetate particulates in paint spray aerosols has been investigated in six US commercial furniture facilities where sealers and lacquers containing 13-42% (w/w) n-butyl acetate were used. Theoretically, n-butyl acetate in paint particles will vaporise very quickly (e.g., 0.5-1 s for a 20 micron particle). In practice, breathing zone eight-hour time-weighted average measurements (24 data sets) showed a mean total (i.e. vapour plus particles) exposure level of 19 mg/m^3 (range: 5.2-48.3 mg/m^3) of which the particle exposure (mean: 3.8 mg/m^3; range: n.d.-11.0 mg/m^3) contributed about 20% (117).

Table 1. Occupational air levels (personal air sampling).

work	isomer	mean concentration in mg/m^3 (ppm)	concentration range in mg/m^3	ref.
paint industry	n-butyl acetate	-	13, 17[a]	92
paint industry	n-butyl acetate	9.7 (2.0)	0-200	114
paint industry	n-butyl acetate	9 (1.9)[b]	1-1680	73
paint industry	n-butyl acetate		up to 330	18
	isobutyl acetate		up to 110	
glue manufacture	n-butyl acetate		up to 17	113
painter's workplace	isobutyl acetate	-	4-58	43
lacquering furniture	n-butyl acetate	-	0.3-120	43
	isobutyl acetate		0.2-486	
lacquering brushes (dipping)	n-butyl acetate	-	4-50	43
indoor painting (brushing, rolling)	butyl acetate	-	2-6	99
indoor painting (rolling water-based paint)	butyl acetate	0.006 (0.001)	up to 0.030	85
spray painting	butyl acetate	-	54, 65[c]	99
spray painting	butyl acetate	-	22.3-76.5	111
spray painting	butyl acetate	33 (6.8)	up to 629	71
spray painting	butyl acetate	9 (1.9)	-	7
spray painting	n-butyl acetate	19 (3.9)	5.2-48.3	117
spray painting	n-butyl acetate	-	16.5-180	39
	isobutyl acetate	-	37.6-134.0	
spray painting	butyl acetate	11.7 (2.4)	2-23	118
fingernail sculptors	butyl acetate	1.9±2.4 (0.4±0.5)	< 0.5-11.2	57
screen printers:	butyl acetate			97
- printing press		55.9±3.9 (11.6±0.8)	-	
- automatic dryer conveyor belt		12.1±6.3 (2.5±1.3)	-	
- manual drying		21.9±7.3 (4.5±1.5)	-	
- paint mixing		16.5±5.3 (3.4±1.1)	-	
- screen wash		413±82.6 (85±17)	-	

[a]n-Butyl acetate was found in two out of 22 air samples.

[b]Median concentration.

[c]Data from two subjects.

5. Kinetics

5.1 Absorption

The most common routes of entry into the body are via the lungs and through the skin. Although no quantitative data on the absorption of the butyl acetate isomers into the body were found, it can be expected that the butyl acetate isomers would readily be absorbed by the respiratory tract, the skin, and the gastro-intestinal tract.

5.2 Distribution

Human blood/air and rat blood/air partition coefficients for n-butyl acetate were experimentally determined to be 677 and 1,160, respectively; those for isobutyl acetate were found to be 578 and 880, respectively (64). Some rat tissue/blood partition coefficients for these acetates are presented in Table 2.

When a single dose of ^{14}C-labelled n-butyl acetate (in 0.9% NaCl), $\approx$30 mg/kg bw (16-18 μCi/animal), was injected iv in the tail vein of male Sprague-Dawley rats (n=32), n-butyl acetate was very rapidly eliminated from the blood ($t_{1/2}$ 0.4 min). [^{14}C]-n-Butyl acetate was detected in brain tissues only within the first 2.5 minutes following dosing, reaching a maximum concentration of 3.8 μg equivalents/g tissue after approximately two minutes. Of the metabolites, maximum [^{14}C]-n-butanol levels of 52 and 79 μg equivalents/g tissue were found in whole blood and brain, respectively, approximately 2.5 minutes postdosing. The metabolite was rapidly eliminated from both blood and brain ($t_{1/2} \approx$1 min) and twenty minutes after postdosing concentrations were below detection limit. Concerning other metabolites, n-butyric acid (max. 5.7 μg equivalents/g whole blood at t=7.4 min, followed by a slow decrease) and polar metabolites (i.e. citric acid cycle intermediates, glucuronide and sulphate conjugates: max. 12.2 μg equivalents/g tissue at t=4.2 min) were detected in the whole blood as well, but hardly in the brain (38).

Nembutal-anaesthetised rats were exposed for one hour to 33,880 mg/m^3 of n-butyl acetate via a tracheal cannula. Within one minute, a nearly constant blood level of 140 μmol/L (16.3 mg/L) was reached. Within one minute after ending exposure, n-butyl acetate had been disappeared. Blood levels of n-butanol increased within 40 minutes to 480 μmol/L (35.6 mg/L). After ending exposure, n-butanol was eliminated from the blood with a half-life of 5 min (47).

Table 2. Some rat tissue/blood partition coefficients for n-butyl and isobutyl acetate[a] (64).

isomer	liver	kidney	brain	muscle	fat
n-butyl acetate	3.14	2.72	1.85	1.76	17
isobutyl acetate	5.06	4.08	2.65	2.12	21.3

[a]calculated as (tissue/air)/(blood/air)

In a similar experiment, groups of five rats were exposed for five hours to a n-butyl acetate concentration of 4,840 mg/m^3. n-Butyl acetate and n-butanol concentrations in blood were measured during the first hour at ten-minute intervals and the next four hours at fifteen-minute intervals. After a steady increase followed by a slight decrease, the concentration of n-butyl acetate reached a nearly constant level of 24.6±3.8 μmol/L (2.9±0.4 mg/L) at about one hour. The concentration of n-butanol followed roughly a similar pattern reaching a nearly constant level of 52.4±10.3 μmol/L (3.9±0.8 mg/L). When given a single ip injection of 790 mg/kg bw ethanol after 30 minutes of exposure, the amount of n-butanol in the blood was doubled. Mean n-butyl acetate levels were slightly lower (53). Similar experiments were performed in rats with tert-butyl acetate. Inhalation of 22,264 mg/m^3 for two hours resulted in continuously increasing blood levels to approximately 400 μmol/L (46.5 mg/L). After ending exposure, tert-butyl acetate was eliminated in two phases with half-lives of 5 and 70 min. Blood levels of tert-butanol (the metabolite) increased continuously throughout the experimental period of 300 min (47). When rats inhaled about 2,100 mg/m^3, blood levels of both tert-butyl acetate and tert-butanol steadily increased during the five-hour experimental period. Tert-butyl acetate levels exceeded those of tert-butanol. At t=4 h these levels became approximately equal; tert-butyl acetate levels now reached a plateau value of about 285 μmol/L (33.1 mg/L), while tert-butanol continued to increase to approximately 340 μmol/L (25.2 mg/L) at the end of the experiment. During exposure to 4,356 mg/m^3 for 4.25 hours, peak concentrations of approximately 450 and 550 μmol/L (52.3 and 40.8 mg/L, resp.) were measured for tert-butyl acetate and tert-butanol, respectively. Thereafter, tert-butyl acetate levels rapidly declined to approximately 250 μmol/L (29.0 mg/L) within fifteen minutes (the end of the experiment), while the tert-butanol level remained constant (53).

5.3 Biotransformation

Butyl acetates may be readily hydrolysed to acetic acid and their respective alcohols in blood, the liver, the small intestine, and in the respiratory tract, as was shown in a number of *in vitro* experiments using homogenates from liver, small intestine mucosa, and ethmoturbinates (30, 72). In an *in vivo* experiment, in which male rats were iv injected with a single dose of ^{14}C-labelled n-butyl acetate of approximately 30 mg/kg bw, hydrolysis in blood and brain was reported to be almost complete within three minutes (38). *In vitro*, when added to blood samples from human men volunteers or female rats, hydrolysis half-lives of n-butyl acetate were 4 and 12 min, while those of tert-butyl acetate were 300 and 270 min (47).

The acetic acid is oxidised via the citric acid cycle to carbon dioxide and water. Isobutanol and n-butanol are rapidly metabolised by alcohol dehydrogenase and aldehyde dehydrogenase to the corresponding acids that are oxidised further to carbon dioxide. Small amounts of isobutanol may be excreted unchanged or conjugated as a glucuronide (116).

sec-Butanol is also metabolised by alcohol dehydrogenase and the metabolite methyl ethyl ketone is excreted in the breath or urine, or is further metabolised (116).

tert-Butanol, however, is a poor substrate for alcohol dehydrogenase and is only slowly metabolised in mammals. It is eliminated in urine as a glucuronide conjugate and as acetone, and via the breath as acetone and carbon dioxide (116).

When alcohol dehydrogenase is involved, metabolism may be inhibited or retarded by ethanol. When 790 mg ethanol per kg bw was given by ip injection 30 minutes after the start of n-butyl acetate inhalation, the n-butanol concentration doubled. This increase is explained by substrate competition between both alcohols and the alcohol dehydrogenase with ethanol in excess (53).

In vitro experiments have demonstrated that oxidative, cytochrome P450-mediated mechanisms may play a role in the cleavage of acetate esters.

Using microsomes isolated from phenobarbital-induced rat livers, butyl acetate (10% concentration, higher concentrations disrupt the microsomal suspension), bound to cytochrome P450 (type I), stimulated CO-inhibitable NADPH oxidation in a way typical for cytochrome P450 substrates. It did not alter cytochrome P450, cytochrome b5, and NADPH-cytochrome c reductase levels (63).

For the oxidation of n-butyl acetate by cytochrome P450 2E1, the major ethanol-inducible isoform purified from rabbit liver, a K_M of 1.5 mM and a V_{max} of 0.15 nmol aldehyde formed/min/nmol P450 were determined (91).

Using a reconstituted system containing cytochrome P450 2B4, the major phenobarbital-inducible isoform purified from rabbit liver, sec-butyl acetate was demonstrated to undergo hydroxylation to an unstable hemiketal (2-hydroxy-2-acetoxybutane) followed by a nonhydrolytic cleavage to 2-butanone (methyl ethyl ketone) (91).

5.4 Elimination

n-Butyl acetate is probably excreted partly unchanged via exhaled air and urine, and partly after transformation in the body. At an inhalatory concentration of 200 mg/m^3, 50% of the n-butyl acetate inhaled was reported to be excreted in exhaled air (9).

With respect to the other isomers, excretion data are available only for the butyl alcohol isomers.

5.5 Possibilities for biological monitoring

No studies on the relation between inhaled concentrations of butyl acetate and the excretion of parent compound or metabolites were found. From a communication in which it was reported that 50% of the amount inhaled was excreted in exhaled air (see Section 5.4), it may be concluded that measurements of butyl acetate in exhaled air may offer a method for biological monitoring.

5.6 Summary and evaluation

No quantitative data on the absorption of butyl acetate isomers are available.

Following a single iv injection of approximately 30 mg/kg bw n-butyl acetate to rats, n-butyl acetate was rapidly eliminated from the blood ($t_{1/2}$ 0.4 min) and the brain (only detectable within the first 2.5 min). Concentrations of n-butanol (its metabolite) in blood and brain reached a maximum after approximately 2.5 minutes and were below detection limits after twenty minutes ($t_{1/2}$ approx. 1 min).

When rats were exposed to n-butyl acetate via a tracheal cannula to approx. 34,000 mg/m^3 (7,000 ppm) for one hour or to approx. 4,800 mg/m^3 (1,000 ppm) for five hours, nearly constant blood levels of n-butyl acetate and n-butanol were rapidly reached. After ending the one-hour exposure, n-butyl acetate disappeared from the blood within 1 minute, while n-butanol was eliminated with a half-life of 5 min. Similar experiments in rats with tert-butyl acetate showed continuously increasing blood levels of both parent compound and metabolite (tert-butanol). After ending exposure, tert-butyl acetate was eliminated in two phases (half-life: 5 and 70 min), while tert-butanol levels continued to increase or remained constant depending on exposure conditions.

Biotransformation involves hydrolytic splitting of the ester in acetic acid and the respective alcohols. For n-butyl acetate this process occurs rapidly *in vivo* in rats and *in vitro* using rat or human blood ($t_{1/2}$: 3 and 4-12 min, respectively). Biotransformation of tert-butyl acetate *in vitro* is far more slowly ($t_{1/2}$: 270-300 min). Acetic acid is oxidised via the citric acid cycle to carbon dioxide and water. Generally, the butanols are readily metabolised by alcohol and aldehyde dehydrogenases to their respective aldehydes or ketones, their acids, and finally to carbon dioxide, except for tert-butanol which is a very poor substrate for the dehydrogenases and is metabolised only slowly. Ethanol inhibits or retards metabolism of butyl acetates.

Parent compounds and metabolites were identified in urine or exhaled breath. The committees could not retrieve any studies on methods for biological monitoring.

6. Effects

6.1 Observations in man

6.1.1 Irritation and sensitisation

n-Butyl acetate: In a volunteer study, the majority of the subjects (n=10) experienced exposure to approximately 970 mg/m^3 (200 ppm) for three to five minutes to be irritating to the throat and exposure to 1,450 mg/m^3 (300 ppm) to be irritating to the nose and the eyes (and severely to the throat) (81). The extent of irritation was scored subjectively based on three categories: not, slightly and very.

The results of a recent Swedish study on irritation effects on human volunteers without previous occupational solvent exposure were published by Iregren *et al.*

(61). Three experiments with different exposure levels were reported: 1) four 20-minute sessions with 24-hour intervals with 350, 700, 1,050 and 1,400 mg/m^3 (72, 145, 217 and 290 ppm) (n=24); 2) two 20-minute sessions, 7 days apart, with 70 and 1,400 mg/m^3 (14 and 290 ppm) (n=23); and 3) two 4-hour exposures with a 7-day interval and exposure concentrations of 70 and 700 mg/m^3 (14 and 145 ppm) (n=12). To evaluate the irritation produced by exposure to n-butyl acetate, ten-point rating scales (from 0 'not at all' to 9 'very much') for perceived irritation (eyes, throat, nose, skin, breathing difficulties, smell) and for CNS effects (headache, nausea, etc), various measures of eye irritation, and pulmonary function tests were used. The results show only a very low level of irritation from these exposures as revealed by categorical ratings (mean ratings were at the extreme lower part of the scale), magnitude estimation, and some of the clinical measures of eye irritation and pulmonary functions, such as eye redness, lipid layer thickness, and bronchial responsiveness. Thus, exposure to the highest concentrations tested (i.e. 1,400 mg/m^3 for 20 min and 700 mg/m^3 for 4 h) caused only minimal irritation to the eyes and respiratory tract (61).

In a study aiming at the development of test procedures for assessing individual sensitivity to smells and chemicals, by exploring reactions to low-level chemical challenge, two groups of male subjects with a different degree of solvent-induced toxic encephalopathy and one previously unexposed, age- and education-matched male reference group (n=12/group) were all exposed for two hours, starting after a clean-air exposure of 20 minutes, at 14 mg/m^3 which was gradually increased to 228 mg/m^3 (appr. 3-48 ppm). At each exposure level, smell intensity (on a 7-step category scale), mucous membrane irritation and annoyance reactions (on visual analogue scales), and fatigue were scored. Generally, the groups with toxic ence-phalopathy experienced significantly more irritation than the control group (88). However, since an unexposed control group was not included, the committees cannot draw conclusions from this study with respect to (no)-effect levels for irritation.

n-Butyl acetate (4% in petroleum), or as a nail enamel containing 25.5% n-butyl acetate, was reported to score negative in repeated insult patch tests, cumulative irritation tests, and a clinical use study. The North American Contact Dermatitis Group has listed butyl acetate as a dermatitis-causing ingredient identified by patch test (one cutaneous reaction in 149 patch-tested patients) (110).

In a penicillin factory, a worker developed allergic contact dermatitis (eczema of the hands, arms, and face). Patch testing revealed a positive reaction to butyl acetate (5% in olive oil) (93). The committee assumes that with butyl acetate is ment n-butyl acetate, because so far known in this kind of industry only n-butyl acetate is used.

Isobutyl acetate: Isobutyl acetate (2% in petroleum) scored negative in a 48-hour closed-patch test and in a maximisation test with volunteers (data from an unpublished report submitted to the Research Institute for Fragrance Materials, Inc, Englewood Cliffs NJ, USA, cited in (86)).

sec-Butyl acetate, tert-butyl acetat: The committees could not retrieve data on sec- and tert-butyl acetate.

6.1.2 Systemic toxicity

n-Butyl acetate: In a study to determine whether performance in neurobehavioural test deteriorates during subjectively annoying chemical challenge below known thresholds among persons with toxic encephalopathy with subjective hyper-sensitivity to chemicals, two groups of subjects with a different degree of solvent-induced toxic encephalopathy and one reference group (n=12/group) were exposed to n-butyl acetate according to the schedule presented by Ørbæk *et al.* (see (88), Section 6.1.1). Tests, measuring attention (digit symbol test) and motor speed (simple and complex reaction-time task), were given at three occasions throughout the exposure period, i.e. at the initial phase when exposure was to clean air, after 40 minutes when the concentration was 56 mg/m^3 (12 ppm; duration 20 min), and after 70 minutes when the concentration was 228 mg/m^3 (48 ppm; duration 20 min). This exposure scenario did not result in a detoriated performance in the applied tests in any of groups of subjects (89).

Isobutyl, sec- and tert-butyl acetate: No case-control or epidemiological studies were found in which systemic effects could be attributed to exposure to butyl acetate.

6.2 Animal experiments

The reports of studies on the toxicity of butyl acetate isomers were almost entirely limited to n-butyl acetate.

6.2.1 Irritation and sensitisation

n-Butyl acetate: Primary skin irritation of n-butyl acetate was tested using rabbits. Following application of 0.01 mL of the undiluted ester to the clipped skin of five albino rabbits, butyl acetate scored as a grade 1 irritant, i.e. giving rise to 'the least visible capillary injection'. This was the severest reaction of the skin within 24 hours following application (103). When a 0.5 mL dose was applied to the clipped intact dorsal skin of New Zealand White Rabbits (n=5) under gauze patches and loosely covered with impervious sheeting for four hours, no irritation was observed according to Draize readings for up to fourteen days (primary irritation index: 0.0/8.0). Severe irritation occurred following a 24-h occlusion period (observation time: up to 14 days) (27, 77).
   Guinea pigs showed signs of eye irritation at exposure to approximately 16,000 mg/m^3 (3,300 ppm) n-butyl acetate, for five minutes (98). Exposure to 2,420 mg/m^3 (500 ppm) for ten (guinea pigs) or twenty (rabbits) days, or to 4,840 mg/m^3 (1,000 ppm) for four days (guinea pigs, rabbits) did not result in corneal or conjunctival injury or in changes in corneal sensation (9). The degree

of corneal necrosis was reported after instillation of various volumes and concentrations of the liquid chemical into the eyes of rabbits. Following instillation of 5 μL of the undiluted compound, butyl acetate was scored as a grade 5 irritant (i.e. causing a 'severe burn'). It was not stated whether the eyes were rinsed with water after application of the test substance (103).

When tested according to OECD Guideline 405 (acute eye irritation/corrosion), instillation of 0.1 mL of n-butyl acetate (purity: 99%) into the conjunctival sac of 4 rabbits resulted in a maximum Draize score of 7.50 (observation time: 24 h; at 48 h: 2.0; at 72 h: 2.0; at 7 d: 0.5 (45)). In another study, a maximum mean Draize score of 14.7 was reported occurring at t=4 h (n=6; dose: 0.1 mL; observation period: 21 d). Iritis and minor to moderate conjuctivitis (all healed within 48 h), but no corneal injury were observed (27, 77). Kennah *et al.* reported Draize scores of 8, 11, 19, and 2 following instillation of 100, 30, 10, and 3%, respectively (observation time: 24 h) (66).

n-Butyl acetate was not a sensitiser when tested in the classical maximisation test using guinea pigs, and in an alternative test, i.e. the mouse ear swelling test (50).

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 Swiss OF1 mice (n=probably 10), the RD_{50} for n-butyl acetate was approximately 3,470 mg/m^3 (720 ppm; (75), see also (26)). In a separate study using male Balb/C mice (n=8-10), an RD_{50} of approximately 8,340 mg/m^3 (1,726 ppm) has been determined (67).

In a thirteen-week inhalation study using rats, olfactory epithelial necrosis of minimal to mild severity was found after exposure (6 h/day, 5 days/week) to 7,260 and 14,520 mg/m^3 (1,500, 3,000 ppm), but no such lesions were observed at exposure to 2,662 mg/m^3 (550 ppm) (see Section 6.2.3 (10, 102)).

Isobutyl acetate: Isobutyl acetate has been tested for skin and eye irritation, but not according to current standardised methods. The primary skin irritating properties of isobutyl acetate were tested in rabbits. The compound was found to be not irritating to the uncovered rabbit belly (scoring grade 1 on a scale of 1-10 within 24 hours following uncovered application of 0.01 mL of undiluted sample) (104). After full strength application to intact or abraded rabbit skin under occlusion for 24 hours, it was scored as moderately irritating (data from an unpublished report submitted to the Research Institute for Fragrance Materials, Inc, Englewood Cliffs NJ, USA, cited in (86)).

The ocular irritation of isobutyl acetate was evaluated in rabbits. Undiluted test substance (0.5 mL) was found to cause a moderate inflammation to the eye (grade 2 on a scale of 1-10) (104).

With respect to respiratory tract irritation, an RD_{50} of 3,890 mg/m^3 ($\approx$ 800 ppm) has been found in mice (see also n-butyl acetate (75), see also (26)).

sec-Butyl acetate, tert-butyl acetate: No data are available on irritation and sensitisation by sec-butyl acetate.

Concerning tert-butyl acetate, primary skin irritation of this isomer was tested by applying 0.5 mL of the test compound to the clipped intact dorsal skin of New Zealand White rabbits (n=3/sex) under gauze patches semi-occlusively wrapped with plastic, for four hours. Thereafter, wrappings were removed, residual test compound washed off with distilled water, and scored for dermal irritation according to Draize readings at 30-60 minutes and 24, 48, and 72 hours following patch removal. Very slight, barely perceptible erythema (score 1 on a scale of 0-4) was observed in 6/6, 4/6, 0/6 and 0/6 animals at 30-60 minutes, 24, 48 and 72 hours, respectively. Oedema was absent at all observation intervals. No ulceration, necrosis, or any other evidence of tissue destruction was seen at any of the observation intervals (4).

The primary eye irritation of tert-butyl acetate was tested by instilling 0.1 mL into the conjunctival sac of one eye of male New Zealand White rabbits (n=6). Treatment induced corneal opacity in 1/6 (cleared by day), iritis in 3/6 (cleared by day 2), and conjunctival irritation in 6/6 animals (cleared by day 3) and resulted in mean Draize scores of 14.5, 6.8, 2.0 and 0 at observation times of 1 hour and 24, 48, and 72 hours, and 7 days, respectively (35). In another study, instillation of 0.1 mL into the conjunctival sac of 5 New Zealand strain albino rabbits only caused minimal conjunctival irritation lasting for 96 hours. Mean Draize scores were 4.8, 3.6, 2.0, 2.0, 1.6, and 0 at observation times of 1 hour, 24, 48, 72, 96 hours and 7 days, respectively (65).

Tert-butyl acetate did not act as a skin sensitiser in a delayed contact dermal sensitisation test (Buehler method). Ten male Hartley Albino guinea pigs received a topical induction application of the test compound at a concentration of 100%, for three weeks (once/week). Skin reactions were recorded 24 and 48 hours following each application. Two weeks after the first application, animals were challenged with undiluted compound, and skin reactions were recorded at 24, 48 and 72 hours following the challenge dose. During the induction phase, no erythema was found apart from very faint reactions in one animal 24 and 48 hours after the first application, in two animals 24 hours after the second application, and in one animal 24 hours after the third application (all different animals). Upon challenge, no erythema was seen at any of the observations times except for a very faint reaction in one animal at 24 hours (58).

With respect to tert-butyl acetate, only one study on respiratory tract irritation has been found. The RD_{50} was $\approx$76,000 mg/m^3 ($\approx$15,750 ppm) (see also n-butyl acetate (75), see also (26)).

6.2.2 Toxicity due to acute exposure

n-Butyl acetate: Data on the lethal toxicity following acute inhalatory exposure to n-butyl acetate are summarised in Table 3.

The results from LC_{50} studies in rats show that exposure to nearly saturated atmospheres generated by evaporation did not result in mortality. The data from atmospheres/aerosols generated by atomisers are highly inconsistent ranging from

Table 3. Effects on experimental animals due to acute inhalatory exposure to n-butyl acetate.

species	concentration	duration	effect	remarks	ref.
rat	800 mg/m^3	4 h	6/10 dead	(n=5/sex/group) head-only; dynamic	32
	2,200 mg/m^3	4 h	10/10 dead	inhalation system; atomiser	
	5,200 mg/m^3	4 h	10/10 dead	LC$_{50}$ =740 mg/m^3	
rat	32,000 mg/m^3	4 h	0/10 dead	(n=5/sex/group) whole body; statically generated, nearly saturated vapour	78
	29,200 mg/m^3	4 h	0/10 dead	(n=5/sex) whole body; dynamic	
	13,890 mg/m^3	4 h	0/10 dead	inhalation system;	
	9,345 mg/m^3	4 h	0/10 dead	evaporation LC$_{50}$ >32,000 mg/m^3	
rat	1,305 mg/m^3	4 h	0/10 dead	(n=5/sex/group) whole body;	78
	2,490 mg/m^3	4 h	10/10 dead	dynamic inhalation system; atomiser LC$_{50}$ =1,800 mg/m^3	
rat	4,990 mg/m^3	4 h	0/10 dead	head only; dynamic inhalation system; atomiser	14
rat	21,395 mg/m^3	4 h	0/10 dead	head-nose only; dynamic inhal. system; atomiser	15
rat	2,005 mg/m^3	4 h	0/10 dead	head-nose only; dynamic inhal.	16
	21,395 mg/m^3	4 h	0/10 dead	system; atomiser	
rat	21,395 mg/m^3	4 h	0/10 dead	head-nose only; dynamic inhal. system; evaporation	17
rat	3,990 mg/m^3	4 h	3/10 dead	(n=5/sex/group) whole body;	79
	5,730 mg/m^3	4 h	5/10 dead	dynamic inhalation system; atomiser	
	5,790 mg/m^3	4 h	6/10 dead	LC$_{50}$ =5,055 mg/m^3	
	6,560 mg/m^3	4 h	9/10 dead		
rat	3,680 mg/m^3	4 h	0/10 dead	(n=5/sex/group) whole body;	80
	6,505 mg/m^3	4 h	0/10 dead	dynamic inhal. system; different	
	6,650 mg/m^3	4 h	0/10 dead	atomisers under varying conditions	
	6,995 mg/m^3	4 h	0/10 dead	(pressure, humidity) testing new and	
	7,260 mg/m^3	4 h	0/10 dead	old (latter two data) production	
	23,430 mg/m^3	4 h	0/10 dead	material	
	42,930 mg/m^3	4 h	0/10 dead	LC$_{50}$ >42,930 mg/m^3	
	6,980 mg/m^3	4 h	0/10 dead		
	7,140 mg/m^3	4 h	0/10 dead		
rat	9,700 mg/m^3	4 h		LC$_{50}$	82
mouse	6,000 mg/m^3	2 h		LC$_{50}$	82
guinea pig	16,000 mg/m^3	5 min	irritation		98
		13.5 h	no other effects		
	33,000 mg/m^3	6 h	incoordination		
		11.7 h	narcosis		
	67,000 mg/m^3	15-30 min	narcosis		
		4 h	dead		

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740 mg/m^3 (160 ppm) to above 42,930 mg/m^3 (9,312 ppm). After an LC$_{50}$ of 740 mg/m^3 (160 ppm) was reported for aerosolised n-butyl acetate in a study (32), six follow-up studies were conducted at three different laboratories in order to replicate the data, to differentiate between data from vapours and aerosols, and to investigate the role of small particles and of relative humidity (unpublished studies reviewed in (85)). The LC$_{50}$ values for aerosolised n-butyl acetate determined in these studies were all statistically significantly different and increased with time. These inconsistencies occurred not only between laboratories, but also within the same laboratory. Using identical inhalation equipment and aerosol generation procedures, one laboratory observed no mortality at concentrations up to approximately 21,395 mg/m^3 (4,429 ppm). In the second laboratory, experiments resulted in LC$_{50}$s of approximately 1,800 mg/m^3 (390 ppm) and 5,055 mg/m^3 (1,096 ppm), while no mortality occurred in the third experiment at exposure up to 42,930 mg/m^3 (9,312 ppm). In the third laboratory, findings not observed in any of the other two laboratories included low chamber relative humidity, brief times to death (all deaths within 24 hours post-exposure, 7/10 animals of the highest concentration group died in the last 2 h of exposure *vs* mortality 1 to 4 days post-exposure in the other studies), and the histological finding of vesicular emphysema, suggesting that there might have been methodological problems in this study. Overall, Norris *et al.* (85) could not find explanations for inconsistent results from exposure to aerosolised n-butyl acetate.

Clinical signs observed in rats during these experiments ranged from eye irritation (periocular wetness, blepharospasms) to nervous system effects (hypoactivity, ataxia, forced/shallowed breathing, narcosis). At gross necropsy in the deceased animals, discoloration of the lungs and fluid in the thoracic cavity and trachea were observed. Microscopical examination performed on some of the lungs showed congestion, alveolar haemorrhage, sloughing of bronchiolar mucosa, necrosis of alveolar epithelial cells, and oedema (78, 79). Discoloration of the lungs was also observed in rats surviving exposure to approximately 23,000 and 43,000 mg/m^3. In this study, no clinical signs were observed during the 14-day after exposure period, and only the highest exposure level produced clinical signs (narcosis, incoordination, perioral wetness), that were still present on the same day shortly following exposure. Exposure concentrations of 3,680 to 7,260 mg/m^3 caused blepharospasms (80).

A study, investigating the effects on the nervous system following acute exposure, has been conducted with n-butyl acetate vapours generated by evaporation. Measurements indicated that the test compound was not present in aerosol form. Based on the results of a range finding study, four groups of twenty rats (n=10/sex) were exposed to 0 and 7,260, 14,520, and 29,040 mg/m^3 (0, 1,500, 3,000, 6,000 ppm) for six hours. Deaths and clinical signs were not noted. During exposure, reduced activity and reduced response to stimuli (tapping on the chamber) were observed in all dose groups ranging from minimal in the low dose group to minor to moderate in the high dose group. These observations were subjective and incomplete, since they include only those animals that were visible through the inhalation chamber windows. Motor activity measured in ten-minute

intervals during a 60-minute period (30 min after ending exposure, and on postexposure days 1, 7, 14) was transiently (i.e. not on the postexposure days) reduced in the mid and high dose groups. The functional observational battery examinations (1.5 h after ending exposure, and on postexposure days 7, 14) showed no effects on motor activity in the open field. Effects were observed directly after exposure only and included slightly unkempt hair coat in the high dose group and increased forelimb grip strength for the female animals of the mid dose group. Differences in mean body weights (decreases) between treated and control animals did not exceed 10%, but were statistically significant for the male animals of the low (on postexposure day 7) and high dose (on postexposure days 7 and 14) groups (21).

In a separate study, the effects of exposure to vaporised n-butyl acetate on the behaviour of Wistar rats have been tested using the rotarod performance and the hot plate test (10 rats/group; exposure time: 4 h; testing immediately after ending exposure). All animals survived, which might imply that they may have sustained four-hour exposures of up to approx. 49,000 mg/m^3 or 10,000 ppm. The ED_{50} for the rotarod performance (i.e. the concentration at which 50% of the animals did not succeed in remaining on the rotating rod for 2 min) was calculated to be approximately 35,900 mg/m^3, while the ED_{50} for the hot plate test (i.e. the concentration at which the latency of the paw-lick response was increased by 50% when compared with the response under control conditions) was approximately 28,000 mg/m^3 (67).

Data, on mainly lethality, following single exposure to n-butyl acetate by other routes are summarised in Table 4. They indicate that n-butyl acetate is not very toxic via oral, ip, or dermal administration.

Table 4. Effects on experimental animals after single exposure to n-butyl acetate.

species	dose	route	effect	ref.
rat, male	14.5 mL/kg bw	oral	LD_{50}	27, 77
rat, female	12.2 mL/kg bw	oral	LD_{50}	27, 77
rat	14.1 g/kg bw	oral	increase in serum ornithine	103
mouse	7.1 g/kg bw	oral	LD_{50}	82
mouse	1.2 g/kg bw	ip	LD_{50}	82
rabbit	2.2 g/kg bw	oral	ND_{50}[a]	76
rabbit	7.7 g/kg bw	oral	LD_{50}	76
rabbit, male and female	16.0 mL/kg bw	dermal	no deaths	27, 77
guinea pig	1 mL/3.1 cm^2	dermal	no pathological changes in the skin. No alterations in morphology of liver and kidneys.	69
guinea pig	1.5 g/kg bw	ip	LD_{50}	42
guinea pig	750 mg/kg bw	ip	carbamyl transferase activity	42

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

Table 5. Effects on experimental animals after acute or single exposure to isobutyl acetate

species	conc./dose	duration	route	effect	reference
rat	38.9 g/m^3	4 h	inhalation	4/6 animals died	104
rat	14.0 g/m^3	6 h	inhalation	No toxicity symptoms	25
	100.0 g/m^3	2.5 h	inhalation	LD$_{100}$	25
rat	13.4 g/kg bw	-	oral	LD$_{50}$	104
rat	15.0 g/kg bw	-	oral	LD$_{50}$	104
rabbit	4.3 g/kg bw	-	oral	ND$_{50}$[a]	76
rabbit	4.8 g/kg bw	-	oral	LD$_{50}$	82
rabbit	>20.0 g/kg bw	-	dermal	LD$_{50}$	82

[a]ND$_{50}$: the quantity that produced stupor and loss of voluntary movements on half of the animals.

Isobutyl acetate: Data, on mainly lethality, following acute and single exposure to isobutyl acetate are presented in Table 5. They indicate that isobutyl acetate is not very toxic via the inhalatory, oral, or dermal route.

sec-Butyl acetate and tert-butyl acetate: All rats survived exposure to approximately 17,000 mg/m^3 (3,500 ppm) of sec-butyl acetate, for six hours, while all rats died when exposed to 116,000 mg/m^3 for four hours. An oral LD$_{50}$ of 3,200-6,400 mg/kg bw was reported for rats (unpublished data; no more details available) (95).

For tert-butyl acetate, a four hour LC$_{50}$ of 13,300 mg/m^3 has been determined for rats by exposing the animals (Sprague-Dawley; n=5/sex/group) to aerosol concentrations of 5,000, 10,000, 15,000 or 30,000 mg/m^3 (particle size and distribution not given). Generally, the time course of clinical signs during the exposure period was similar at all concentrations, but the onset of the effects was much shorter at the higher concentrations. Symptoms observed included inactivity and sedation, hyperactivity, comparable to the excitation state of anaesthesia, coma, and death. Post-mortem examination showed some evidence of pulmonary congestion and haemorrhage only (observation time 14 days) (65). In another study, all rats (Harlan Sprague-Dawley; n=5/sex) survived nose-only exposure to a mean vapour concentration of 2,230 mg/m^3 (470 ppm), for four hours. Apart from slight weight loss between days 0 and 7 in one female and red penile discharge in one male animal, no abnormalities were observed upon body weight, in-life, and gross necropsy observations (observation time 14 days) (19).

No mortality or effects on body weight were found in New Zealand White rabbits (n=5/sex/group) following application of a single dose of 2,000 mg/kg bw to the clipped intact dorsal skin under gauze patches wrapped with plastic, for 24 hours. Apart from instances of diarrhoea in 3/10 animals during the first week of fourteen days, no dermal responses (erythema or oedema) were observed during and at the end of the observation period. Apart from kidney abnormalities in one female animal, no abnormalities were observed upon post-mortem macroscopic examination (36). Only erythema (not indicated at which single doses) disappearing within 48 hours was reported following 24-hour, covered application of

five single doses ranging from 2.0 to 23.0 mL/kg bw ($\pm$1,800-20,700 mg/kg bw) to the clipped skin of New Zealand strain albino rabbits (n=2/sex/group) (observation time 14 days) (65).

An oral LD_{50} of 3.8 mL/kg bw ($\pm$3,420 mg/kg bw) was estimated in rats (Sprague-Dawley; n=5/sex/group) by using eight dose groups and a dose range of 1.0 to 12.0 mL/kg bw. At 1.0 mL/kg bw, only a slight restlessness was observed. At doses of 2.0 mL/kg bw and higher, initial restlessness was followed by ataxia, coma and death. Severeness and incidence of effects increased and time of onset of effects decreased with increasing doses. No gross histological changes were observed in the tissue and organs of the dead animals at post-mortem examinations (observation time 14 days) (65). In a separate study, oral administration of 2,000, 5,000 or 7,000 mg/kg bw to Wistar rats (n=5/sex/group) resulted in a LD_{50} of 4,500 mg/kg bw (males: 4,100 mg/kg bw; females: 4,750 mg/kg bw). Clinical signs observed included ataxia, flaccid muscle tone, lethargy, dyspnea, loss of righting reflex, prostration, piloerection, tremors, and coma. Necropsy findings in the surviving animals were normal, while in the treatment-related deaths there were abnormalities in various organs as well as wetness and red and brown staining of the nose and mouth area (37).

6.2.3 Toxicity due to short-term exposure

n-Butyl acetate: Data on toxicity due to short-term exposure to n-butyl acetate are mostly from very old studies (before 1940). In guinea pigs, exposure to 4,840 mg/m^3 (1,000 ppm) n-butyl acetate, 4 h/day, for 28 days did not have effects on blood counts, urine examinations or necropsy data (9).

Cats exposed to approximately 20,000 mg/m^3 (4,140 ppm) of n-butyl acetate, 6 h/day, for 6 days showed weakness, weight loss, and minor changes in blood values. At approximately 15,000 mg/m^3, changes in blood cell morphology were observed and at 7,600 mg/m^3 increased salivation (9).

In a study conducted to select exposure concentrations for a subsequent thirteen-week studies (see below), male and female Sprague-Dawley rats were exposed to n-butyl acetate vapour of $\pm$ 0, 3,630, 7,260 and 14,520 mg/m^3 (0, 750, 1,500 and 3,000 ppm), 6 h/day, 5 days/week for two weeks. Each exposure group consisted of five male and five female *ad libitum*-fed animals and five feed-restricted male animals. Treatment induced concentration-related reductions in activity levels (hypoactivity; reduced responses to extrachamber stimulation). In the 3,630 mg/m^3 exposed group, reductions were of minimal to minor severity at the beginning and absent by the end of the week. In the 7,260 mg/m^3 exposed group, severity decreased from minor to minimal over the course of the week, while it remained minor in the 14,520 mg/m^3 exposed group. Other occasional signs noted were sialorrhea in 4/15 and 8/15 animals of the 7,260 and 14,520 mg/m^3 exposed group respectively, and red sialorrhea, porphyrin tears and nasal discharge, brown-discoloured facial hair, and unkempt haircoat in individual animals of the 14,520 mg/m^3 exposed group. There was no apparent difference in these clinical signs between *ad libitum*-fed and feed-restricted animals. Apart from two animals

of the feed-restricted 14,520 mg/m^3 exposed group, animals in all treated groups were normal after exposure. Further, treatment did not affect performance in an abbreviated functional observational battery (FOB) after the final exposure. Some effects on mean body weights were observed (decreases in the female animals of the 7,260 mg/m^3 exposed groups and in the male and female animals of the 14,520 mg/m^3 exposed group), but only in the male animals of the feed-restricted 14,520 mg/m^3 exposed group, a statistically significant decrease in mean terminal body weight and in mean body weight gain was observed. At necropsy, there were no effects on absolute or relative lung, kidney, or liver weights or histological changes (22).

In a thirteen-week inhalation study, conducted in parallel with a subchronic neurotoxicity study (see below), male and female Sprague-Dawley rats (n=15/sex/group) were exposed to target vapour concentrations of approximately 0, 2,662, 7,260, and 14,520 mg/m^3 (0, 550, 1500, 3000 ppm), 6 h/day, 5 days/week, for thirteen to fourteen weeks. During exposure, clinical observations, body weight recordings, and feed consumption determinations were made regularly. Furthermore, effects on mortality, ophthalmology, haematology, and clinical chemistry parameters, organ weights, and gross and microscopical histology were evaluated. On day 30, five animals/sex/group were killed for clinical pathology. There was no compound-related mortality in any of the groups. In the 14,520 mg/m^3 exposed group, all animals showed reduced activity (defined as less movement, decreased alertness, and slower response to tapping on the chamber wall in comparison with control animals) of minor severity. Occasionally, signs of sialorrhea and red discoloration on the chin hair were observed. Mean body weights and food intake were statistically significantly lower than those of the control animals almost throughout the study. Overall, weight gains for males and females were respectively 38 and 22% lower than those for controls. There were no treatment-related ophthalmological changes or biologically or toxicological relevant effects on haematological or clinical chemistry parameters. Organ weight changes included, amongst others, decreased absolute liver and kidney weights, decreased absolute and relative spleen weights (males), and increased relative adrenals and lung weights (males). Upon macro- and micro-scopical examination, lesions found were limited to the stomach (minimal haemorrhage in the glandular gastric mucosa in 2/10 females; minimal white discoloration in the non-glandular gastric mucosa in 1/10 females; minimal to mild inflammatory and degenerative lesions of stomach mucosa in 3/10 females) and the nasal passages (olfactory epithelial necrosis of mild to moderate severity in all males and females). There was no effect on epididymal or testicular sperm counts. In the 7,260 mg/m^3 exposed group, all animals exhibited reduced activity of minimal severity. Mean body weights were statistically significant lower at week 6 onwards for male and at week 2 onwards for female animals. Overall, weight gains were approximately 20-30% lower than those for controls. Food intake was generally lower throughout the study. There were no effects on ophthalmology, haematology, or clinical chemistry parameters. Organ weight changes observed were, amongst others, decreased absolute spleen, liver, and

kidney (females) and increased relative adrenal (females) weights. Upon macro- and rnicroscopical examination, only histological lesions in the nasal passages consisting of olfactory epithelial necrosis of minimal to mild severity in 4/10 male and 3/10 female animals were observed. There was no effect on epididymal or testicular sperm counts. In the 2,662 mg/m^3 exposed group, no treatment-related effects were observed (23).

A neurotoxicity study was conducted in compliance with an Enforceable Consent Agreement, as outlined in the Testing Consent Order (see Fed Reg 1995; 60: 4516-20; January 23), negotiated with USEPA in accordance with the Toxic Substances Control Act (TSCA) and conforming USEPA's most recent relevant guidelines. Male and female Sprague Dawley rats (n=30-40/group) were exposed to 0, 2,662, 7,260, and 14,520 mg/m^3 (0, 550, 1,500, 3,000 ppm), 6 h/day, 5 d/week, for 13-14 weeks. End-points were functional observational battery (FOB) and motor activity (during week 1-13 in 10-15 animals/sex/group), neuropathology (gross and microscopic examination of -sections from- the brain, spinal cord, dorsal and ventral spinal roots, dorsal root ganglia, sciatic nerve, and tibial nerve at study termination in 5 animals/sex/group), and scheduled-controlled operand behaviour (SCOB) (during exposure and two weeks post-exposure in 10 feed-restricted male animals/group). Body weights were recorded regularly. Clinical observations were made through the inhalation chamber windows during exposure, and further before and after exposure and during performing FOB. In the *ad libitum*-fed animals of the 14,520 mg/m^3 exposed groups, treatment caused lower mean body weights throughout the study resulting in an overall decrease of 15-19% and lower mean body weight gains for males throughout the study and for females during the first six weeks resulting in an overall decrease of 36-41%. Exposure to 14,520 mg/m^3 further induced signs of sialorrhea, gasping, and red discoloration of the chin, as well as reduced activity of minor severity. In the 7,260 mg/m^3 exposed group, no effects were observed on body weights of the male animals, while those of females were lowered from week 6 onwards (overall decrease 9%). Mean body weight gain was affected occasionally (male, week 9, 14; female, week 6, 11) with an overall decrease of 16-26%. In addition, reduced activity of minimal severity was observed. No such effects were observed in the group exposed to 2,662 mg/m^3. No treatment-related effects indicative of neurotoxicity were observed in the FOB, motor activity, SCOB, and gross and microscopic examinations in any of the exposure groups. No signs of toxicity were observed at *in situ* observation of abdominal and thoracic organs (24), see also (31).

Iso-, sec- and tert-butyl acetate: No data found.

6.2.4 Toxicity due to long-term exposure and carcinogenicity

No data were found on long-term toxicity or carcinogenicity studies on butyl acetates.

Table 6. *In vitro* genotixicity tests with n-butyl acetate.

test system	endpoint	test concentrations	result[a]	ref.
S. typhimurium:				
TA100/-1535/-1537/-98/-97	gene mutation	33-10,000 μg/plate	-/-	92
TA100/-1535/-1537/-98/-1538	gene mutation	1- 5,000 μg/plate	-/-	101
TA100/-1535/-1537/-98/-94/-92	gene mutation	up to 10,000 μg/plate	-/-	62
E.coli WP2 uvrA	gene mutation	1- 5,000 μg/plate	-/-	101
S.cerevisiae D61.M	mitotic aneuploidy	0.25-0.4%	-/nt	92
Chinese hamster fibroblasts	chrom. abberations polyploidy	up to 2,000 μg/plate	-/nt	62

[a]Results of tests without/with a metabolic activation system respectively; - = negative result;
nt = not tested.

6.2.5 Genotoxicity

n-Butyl acetate was adequately tested at sufficiently high concentrations in bacteria (*S. typhimurium*, *E. coli*), yeast (*S. cerevisiae*), and in one mammalian cell system (Chinese hamster fibroblasts) (see Table 6). In all these systems, negative results were obtained. There were no data from *in vivo* tests.

No data are available on mutagenicity of the other butyl acetate isomers.

6.2.6 Reproduction toxicity

The reproduction toxicity of n-butyl acetate has been evaluated in rats and rabbits (55). Rats (n=37-42/group) were exposed to 0 or 7,260 mg/m^3 (1,500 ppm), 7 h/day, during GD7-16 (group 2), during GD1-16 (group 3), or pregestationally for three weeks (5 days/week) and subsequently during GD1-16 (group 4). The animals of all groups were mated with unexposed male rats. Mating and reproductive performance (pregnancy rates, numbers of corpora lutea, implantation sites, resorptions, live foetuses per litter) were not affected by treatment. During exposure, a statistically significant decrease in food intake was observed in all exposure groups. Maternal toxicity, including decreased body weight ($p<0.01$) and decreased absolute liver ($p=0.01$), and increased relative kidney and lung weights ($p=0.03$ and 0.01, respectively), was observed in all exposure groups. Signs of minor developmental toxicity were observed. In all exposure groups, foetal growth (body weight, crown-rump length) was statistically significantly reduced. Increased incidences of rib dysmorphology and reduced pelvic ossification were observed in group 2 ($p=0.05$ and 0.08, resp) and group 3 ($p=0.07$ and 0.002, resp). In addition, there was an increased incidence of hydroureter in group 4 ($p=0.05$).

Groups of rabbits (n=21-25/group) were exposed to 0 or 7,260 mg/m^3 (1,500 ppm) n-butyl acetate, 7 h/day, during GD7-19 (group 2) or 1-19 (group 3). No effect on maternal body weights was found, but in both exposure groups absolute organ weights (kidney, spleen, lung) were statistically significantly increased. Increased incidences in minor developmental effects including retinal

folds (p=0.04), misaligned sternebrae (p=0.04), and morphological variations in gallbladder (p=0.05) were noticed in group 3 (55).

The committees consider the results found in these reproduction tests inconclusive, because only one concentration was tested. At that concentration, both maternal and foetal effects were found. The committees cannot exclude that these foetal effects are caused by effects on the mother.

No data were available on sec- and tert-butyl acetate.

6.3 Summary

6.3.1 Human data
n-Butyl acetate is only minimally irritating to the eyes and respiratory tract of volunteers exposed to 700 mg/m^3 ($\approx$145 ppm) for four hours. It may occasionally cause allergic contact dermatitis. Isobutyl acetate probably has no sensitising properties.

No case-control or epidemiological studies were found in which systematic effects could be attributed to exposure to butyl acetate.

6.3.2 Animal data
Under not-occluded conditions n-butyl acetate has no skin irritant properties and it has not shown to be a sensitiser. The committees consider n-butyl acetate at most slightly irritating to the eyes of rabbits. Tert-butyl acetate is a very slight eye and skin irritating compound, and has probably no skin sensitising properties.

Data from acute inhalatory exposure (parameter mortality) of n-butyl acetate are conflicting, but n-butyl acetate as well as isobutyl acetate can be considered to be of low toxicity via the inhalatory, oral, and dermal route. Exposure to n-butyl acetate levels of $\approx$3,700-7,300 mg/m^3 ($\approx$800-1,575 ppm) for four to six hours result in transient effects on the eyes and behaviour of rats.

Subchronic exposure for 13 weeks (6 h/day, 5 days/week) to up to $\approx$ 14,520 mg/m^3 (3,000 ppm) n-butyl acetate did not induce persistent neurotoxic effects in rats. Exposure to $\approx$7,260 mg/m^3 (1,500 ppm) caused decreased body weight gain, reduced transient activity on the nervous system, and minimal to mild olfactory lesions. From these data, the committees derive a NOAEL of $\approx$2,662 mg/m^3 (550 ppm).

No valid data are available on systematic and carcinogenic effects following chronic exposures. Furthermore, n-butyl acetate did not induce mutations in bacteria and yeast nor did it induce clastogenic effects in Chinese hamster fibroblasts.

In a developmental study in which rats and rabbits were exposed to approximately 7,260 mg/m^3 (1,500 ppm) in a number of exposure schemes, minor developmental effects in the presence of maternal toxicity were observed in both species. Since this was the only level tested, and both maternal and developmental toxicity were found, the committees consider the results of this study to be inconclusive.

Data on short-term effects, carcinogenicity or genotoxicity and reproduction toxicity of isobutyl, sec- and tert-butyl acetate are lacking.

7. Existing guidelines, standards and evaluations

7.1 General population

The Commission of the European Communities did not classify, and consequently did not label, the butyl acetate isomers with respect to irritation and toxicity (29).

n-Butyl acetate as well as isobutyl acetate were given GRAS (generally recognised as safe) status in 1965 by Flavouring Extracts Manufacturers' Association, which were accepted by FDA for food use and were listed by the Council of Europe with an ADI of 1 mg/kg (86, 87). However, according to a recent publication by FAO/WHO, no ADI has been allocated and no toxicological monograph has been prepared (108). No guidelines or standards for the general population were found for n-butyl acetate, isobutyl acetate, sec-butyl acetate, and tert-butyl acetate.

7.2 Working population

The occupational exposure limits for n-butyl acetate, isobutyl acetate, sec-butyl and tert-butyl acetate in the Netherlands and some other countries are summarised in Table 7.

ACGIH (USA)
ACGIH stated that the marked toxicity of the atomised n-butyl acetate observed in animal bioassays (i.e. an LC_{50} of $\approx$750 mg/m^3 (156 ppm) found in an acute mortality study in rats) is not of practical concern in the workplace where exposures to n-butyl acetate occur almost universally to the vapour. ACGIH has recommended a TLV of $\approx$725 mg/m^3 (150 ppm) for n-butyl acetate to minimise the potential risk of eye and mucous membrane irritation reported in the studies by Nelson *et al*. (81) and Iregren *et al*. (61) in volunteers exposed at $\approx$ 965 to 1425 mg/m^3 for 3 to 20 minutes, and a STEL of $\approx$965 mg/m^3 (200 ppm) to control the excursions that produced mucous membrane irritation in the same studies. A skin designation has not been assigned, because of the high vapour pressure and the lack of systemic toxicity following topical application to rabbits and guinea pigs (4).

With respect to isobutyl acetate, ACGIH concluded that the animal data on acute toxicity indicate that isobutyl acetate is somewhat more toxic, but somewhat less irritating than n-butyl acetate. In view of these data, an identical TLV of $\approx$725 mg/m^3 (150 ppm) was recommended to minimise the potential for ocular and respiratory tract irritation (3).

Table 7. Occupational exposure limits in the Netherlands and some other countries.

country	isomer	level mg/m^3	ppm	time TWA	remark	ref.[a]
The Netherlands	n-	710	150	8 h	administrative	109
	iso-	700	150	8 h	force	
	sec-, tert-	950	200	8 h		
Germany						
- AGS	all	950	200	8 h		28
		950	200	15 min		
- DFG MAK-kom.	n-, iso-	480	100	8 h	e	41
		960	200	15 min[b]		
	sec-	c				
	tert-	96	20	8 h	e	
		480	100	30 min[d]		
Sweden	all	500	100	8 h		13
		700	150	15 min		
Denmark	all	710	150	8 h		12
UK						
- HSE	n-	724	150	8 h	OES	59
		966	200	10 min		
	iso-	724	150	8 h	OES	
		903	187	10 min		
	sec-, tert-	966	200	8 h	OES	
		1210	250	10 min		
European U.						60
-SCOEL		-	-			
USA						
- ACGIH	n-	-	150	8 h	TLV	6
		-	200	15 min	STEL	
	iso-	-	150	8 h	TLV	
	sec-, tert-	-	200	8 h	TLV	
- OSHA	n-	710	150	8 h	PEL	5
	iso-	700	150	8 h	PEL	
	sec-, tert-	950	200	8 h	PEL	
- NIOSH	n-	710	150	10 h	REL	5
		950	200	15 min	STEL	
	iso-	700	150	10 h	REL	
	sec-, tert-	950	200	10 h	REL	

[a]Reference to the most recent official publication of OEL.

[b]Maximum frequency per shift, 4 (with an interval of 1 hour).

[c]Listed among substances for which the toxicological data base was considered to be not sufficient to derive an OEL.

[d]Maximum frequency per shift, 2.

[e]Listed among compound for which there is no reason to fear a risk of damage to the developing embryo or foetus when the OEL is observed.

ACGIH stated that there were no data on the toxicity of sec- and tert-butyl acetate, and that there were no reports of harmful effects on workers either. It was concluded that sec- and tert-butyl acetate were less irritating than n-butyl acetate,

and that therefore a slightly higher TLV of ≈ 965 mg/m^3 (200 ppm) could be recommended for these isomers (1, 2).

Germany

In Germany, DFG concluded for n-butyl acetate that irritation of eyes, nose, and throat is the critical effect due to occupational exposure. Data on irritation in humans were concluded to be inconsistent, but urged the need for lowering the occupational exposure limit which was subsequently set at 480 mg/m^3 (100 ppm). Based on the subchronic neurotoxicity inhalation study and data on the systemic toxicity of its metabolite n-butanol, having a MAK-value of 100 ppm, it was stated that n-butyl acetate is not expected to induce systemic effects at this level. From data on the reproduction toxicity of n-butyl acetate and n-butanol, DFG concluded that there would be no reason to fear a risk of damage to the developing embryo or foetus when this occupational exposure limit is observed. The available data did not indicate the need for assigning notations of danger of cutaneous absorption or of sensitisation (52).

Concerning isobutyl acetate, DFG stated that irritation might be the critical effect, but that there were no data on the relationship between doses and irritative effects. However, it was assumed that there would be no significant difference in the irritation potency of n- and isobutyl acetate, and, therefore, the occupational exposure limit was set at 480 mg/m^3 (100 ppm). Based on the data on the systemic toxicity of the metabolite iso-butanol (MAK-value 480 mg/m^3 (100 ppm)), DFG did not expect such effects to occur or reason to fear a risk of damage to the developing embryo or foetus when this occupational exposure limit is observed. Because of lack of data no skin notation was assigned. The data available did not indicate the need for assigning a notation of sensitisation (52).

Because of lack of data on local and systemic effects of sec-butyl acetate as well as its metabolite sec-butanol, DFG withdrew the existing limit value and listed sec-butyl acetate among substances for which the toxicological data base is considered to be not sufficient to derive an occupational exposure limit (52).

For tert-butyl acetate, there were no relevant data on irritation or systemic effects. According to DFG, irritation might be the critical effect, but systemic effects due to the increasing presence of tert-butanol in the body following inhalation exposure to tert-butyl acetate cannot be excluded. Since, based on experimental animal systemic toxicity data, the limit value for tert-butanol is 96 mg/m^3 (20 ppm), DFG decided to set the occupational exposure limit for tert-butyl acetate at 96 mg/m^3 as well. Analogous to tert-butanol, tert-butyl acetate was listed among compounds for which pregnancy risk group classification was not possible, because although the data available may indicate a trend they are not sufficient for final evaluation. Because of lack of data, notations of danger of cutaneous absorption or of sensitisation were not assigned (52).

CIREP (USA)

The US Cosmetic Ingredient Review Expert Panel (CIREP) concluded that n-butyl acetate was mildly irritant to the skin of rabbits. It was mildly and

moderately to severely irritant to rinsed and unrinsed rabbit eyes, respectively. It had no sensitising properties when tested in guinea pigs and mice. n-Butyl acetate was not teratogenic when inhaled by rats and rabbits at a concentration of $\approx$7,245 mg/m^3 (1,500 ppm). It did neither induce mutations in *S typhimurium* nor mitotic aneuploidy in yeast nor chromosomal aberrations in Chinese hamster fibroblasts. When tested as an ingredient of cosmetic formulations, it was not a sensitiser in humans and was at most mildly irritating. From these data, the CIREP concluded that butyl acetate could be used safely as a cosmetic ingredient in the current practices of use and concentration (110).

8. Hazard assessment

8.1 Assessment of health risk

n-Butyl acetate: The committees could not find case-control or epidemiological studies in which systemic effects could be attributed to exposure to n-butyl acetate. Only very minimal irritation was observed in volunteers exposed to 700 mg/m^3 (145 ppm) for four hours, in a study designed to examine irritation from exposure to organic solvent vapours, including n-butyl acetate, in an objective way. Since butyl acetates are hydrolysed to their respective alcohols, data on systemic toxicity induced by these alcohols may be of interest. However, in a criteria document on n-, sec-, and tert-butanol, no relevant data on the systemic toxicity of these alcohols could be presented (56).

There are no relevant data available from chronic, carcinogenicity and reproduction toxicology animal studies, on which conclusions regarding carcinogenicity and reproduction toxicity can be based. The committees conclude that n-butyl acetate is not mutagenic in bacteria and yeast, nor clastogenic in a mammalian cell system *in vitro*. *In vivo* data on mutagenicity are not available.

The committees find the varying results of the acute inhalatory studies, particularly those in rats exposed to atmospheres generated by atomisers, difficult to interpret. Although ACGIH suggested that the difference in toxicity might be due to the difference in methods of generating atmospheres (i.e. evaporation *vs* atomisation, or vapours *vs* aerosols (9)), the results from several studies with atomised n-butyl acetate are already conflicting. In addition, it was demonstrated that the concentrations of n-butyl acetate particulates in these experiments were very low or virtually non-existing. Therefore, the mortality observed cannot be attributed to the presence of aerosols. From the results of a recent well designed and performed experiment, resulting in a LC$_{50}$ exceeding 43,000 mg/m^3 (9,312 ppm (80)), the committees conclude that the toxicity of n-butyl acetate following a single four-hour inhalation exposure is low. Furthermore, the committees state that n-butyl acetate has a very low acute toxicity following oral administration and dermal application.

In two other animal studies (21, 55), slight transient behavioural effects (exposure duration 6 h), and effects on body weight, absolute liver and relative

kidney and lung weights (exposure duration: 7 h/day, 10-31 days) were found in rats following exposure to $\approx$7,260 mg/m^3 (1,500 ppm).

Furthermore, two subchronic studies have been performed, in which rats were exposed to 0, 2,662, 7,260 or 14,520 mg/m^3 (0, 550, 1,500 or 3,000 ppm) n-butyl acetate for 13 to 14 weeks (23, 24). Animals exposed to 7,260 mg/m^3, showed decreased mean body weight (9%, males), decreased mean body weight gain (16-26%), decreased transient motor activity (nervous system) and minimal to mild necrosis on the olfactory epithelium. There was no persistent neurotoxicity following exposure up to 14,520 mg/m^3. From these study results, the committees conclude that both systemic and local effects do occur. From the subchronic study of Bernard and David (23), the committees derived a NOAEL of 2,662 mg/m^3 (550 ppm).

8.2 Groups at extra risk

No data are known that enables the identification of groups at extra risk.

9. Recommendations for research

The following studies are recommended for all four isomers:
- kinetic studies;
- 28-day inhalation toxicity studies (except for n-butyl acetate);
- reproduction toxicity studies;
- a respiratory and eye irritation test with human volunteers using exposure periods long enough to determine no-adverse-effect levels for irritation.

10. Summary

Stouten H, Bogaerts W. *DECOS and SCG Basis for an Occupational Standard. n-, iso-, sec-, and tert-Butyl acetate*. Arbete och Hälsa 2002;11:1-38.

The butyl acetates are colourless, flammable liquids with a fruity odour. They are slightly soluble or insoluble in water, and soluble in ethanol and ether. The butyl acetates occur in natural and food products, but are also produced chemically. The main use of butyl acetates is as solvents in paints and lacquers. There are no quantitative data on the absorption of butyl acetate isomers. Butyl acetates are quickly metabolised in the body to acetic acid and their respective butanols; tert-butyl acetate, however, slower than the tree other isomers. Based on human experimental data the critical effect of occupational exposure to *n-butyl acetate* is irritation of eyes, skin and mucous membranes. For isobutyl acetate, irritation is probably the critical effect, but the data are less convincing. For the other isomers, there are no data indicating a critical effect.

Keywords: Butyl acetates, Hazard assessment, Irritation, Occupational Exposure Limit, Toxicity.

11. Summary in Swedish

Stouten H, Bogaerts W. *DECOS and SCG Basis for an Occupational Standard. n-, iso-, sec-, and tert-Butyl acetate*. Arbete och Hälsa 2002;11:1-38.

Butylacetater är vid rumstemperatur färglösa lättantändliga vätskor med fruktig lukt. De är något lösliga eller olösliga i vatten och lösliga i etanol och eter. Butylacetater förekommer naturligt i livsmedel men produceras också kemiskt. Huvudanvändningen är som lösningsmedel i målarfärger och lacker. Det saknas kvantitativa data om absorptionen av butylacetater hos människa. Butylacetater hydrolyseras snabbt i kroppen till ättiksyra och respektive butanol, tert-butylacetat emellertid något långsammare än de andra tre isomererna. Baserat på experimentella humandata är den kritiska effekten vid yrkesmässig exponering för n-butylacetat irritation av ögon, hud och slemhinnor. För iso-butylacetat torde irritation vara den kritiska effekten men data är osäkrare. För övriga isomerer saknas det data för att ange någon kritisk effekt.

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

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