



SCOEL/REC/184 ***n*-Butyl acetate, *sec*-Butyl acetate and Isobutyl acetate**

Recommendation from the
Scientific Committee on Occupational Exposure Limits



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Directorate-General for Employment, Social Affairs and Inclusion
Directorate B — Employment
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SCOEL/REC/184
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acetate
and Isobutyl acetate**

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Scientific Committee on Occupational Exposure Limits

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**RECOMMENDATION FROM THE
SCIENTIFIC COMMITTEE ON OCCUPATIONAL
EXPOSURE LIMITS
FOR
n-BUTYL ACETATE, *sec*-BUTYL ACETATE
AND ISOBUTYL ACETATE**

8-hour TWA:	50 ppm (241 mg/m ³)
STEL:	150 ppm (723 mg/m ³)
BLV:	none
Additional categorisation:	Not applicable
Notation:	none

The present Recommendation was adopted by SCOEL on 2016-09-12.

This evaluation is based on Greim (1999), HCN (2001), ACGIH (2001a, b), WHO 2005 and the references cited in these reviews. The data-bases TOXLINE and MEDLINE were reviewed by March 2013.

Recommendation Executive Summary

n-Butyl acetate, *sec*-butyl acetate and isobutyl acetate have structural similarities and a common metabolic pathway. The main critical effect is local irritation, which is common to all three acetates. These common toxicological properties justify a recommendation of an OEL for all three butyl acetate isomers.

The critical effect of *n*-butyl acetate inhalation is irritation of the eyes, nose and throat. *n*-Butyl acetate is readily metabolised to *n*-butanol and acetic acid, the latter of which might also contribute to its irritating potential.

For *sec*-butyl acetate, hardly any data on human exposure were available and also very few animal data, but it can be assumed that it is well absorbed after inhalation and oral exposure, and is hydrolysed by unspecific esterases to acetic acid and *sec*-butanol, which is further metabolised to ethyl methyl ketone.

Also for isobutyl acetate, the critical effect appears to be irritation, although data on human exposure as well as animal data are limited.

Local toxicity

The effect concentrations obtained in several human studies on acute irritation after inhalation exposure to *n*-butyl acetate were inconsistent, possibly due to the differences in study design, subjective reporting and limited documentation in older studies. Nelson et al (1943) observed throat irritation after inhalation of 200-300 ppm (966-1449 mg/m³) for 3–5 min, and at 300 ppm eye and nose irritation together with severe throat irritation. Flury and Wirth (1933) found "moderate" irritation effects after inhalation of 2100 ppm (10000 mg/ m³) for 5 min. Despite these discrepancies, from the overall evidence of these human studies, *n*-butyl acetate is expected to cause airway irritation at ≥ 200 ppm after short term (5–20 min) exposure.

In contrast, Iregren et al (1993) observed only minimal effects in the throat after exposure to up to 290 ppm (1400 mg/ m³), which were not significantly different from the control values after 20 min of exposure. However, after 4 hours of exposure, throat irritation and breathing difficulties occurred at 145 ppm (700 mg/ m³) and eye redness was found in 50% of the exposed and 17% of the control persons. Bronchial responsiveness was also significantly increased.

For orientation, it has been proposed to estimate non-irritating exposure limits, for substances for which the critical effect is sensory irritation, from the relation $OEL \sim 0.03 \times RD50$ in mice (Schaper 1993; Nielsen et al 2007). For *n*-butyl acetate (RD50: 733 ppm) this would correspond to an OEL of about 20 ppm. Similar calculations can be performed for the other acetates. The sensory irritation effect is probably dependent on the hydrolysis in the airway as generated acidic metabolites may strongly influence the sensory irritating response. Acetic acid is a strong sensory irritant (Enstgård et al 2006), and as rodents have higher esterase activity, RD50 studies in mice may overestimate irritation in humans (Larsen and Nielsen 2012). The potency of sensory irritation for isobutyl acetate is similar to that of *n*-butyl acetate, since both isomers have similar RD50 values (818 ppm and 733 ppm, Alarie et al 1998). A similar irritating behaviour of isobutyl acetate and *n*-butyl acetate is also shown by animal experiments on skin and eye corrosion.

Systemic toxicity

No neurotoxicity or other systemic effects were observed in an animal study by David et al (2001) at 500 ppm (NOAEC), with decreased physical activity due to slight narcotic effects and unspecific effects (haematological changes within normal range and reduced weight) at 1500 ppm (7 245 mg/m³).

The half-life of *n*-butyl acetate in human blood is only about 4 minutes. Supplemental information exists for *n*-butanol from absorption studies and pharmacokinetic modelling (Teegarden et al 2005) and from toxicity data of *n*-butanol (Greim 1999), it can be concluded that no systemic effects are expected at 100 ppm *n*-butyl acetate or 190 ppm *n*-butanol in humans.

Overall assessment

Regarding the critical effect of acute irritation in humans, the LOAEC of 150 ppm (700 mg/m³) in the study by Iregren et al (1993) is the starting point for recommending an OEL. Due to the exposure duration of 4 hours and the minimal effects, an uncertainty factor of 3 is proposed for deriving the recommended OEL. An OEL of 50 ppm (240 mg/m³) is proposed for all three butyl acetates to protect workers against both local toxic and systemic effects during an 8-hour exposure.

Two subchronic inhalation studies in rats (David et al. 1998 & 2001) showed NOAECs of each 500 ppm which are not in contradiction to the OEL derived above but rather support it.

A STEL is recommended to avoid possible irritating effects by the parent compounds *n*-butyl, *sec*- and isobutyl acetate and the metabolite acetic acid as well as irritating and central nervous effects caused by isobutanol, a metabolite of isobutyl acetate. Based on the sensory irritation potency (RD₅₀), the STEL should be equivalent for the three acetates. A STEL of 150 ppm (700 mg/m³) is proposed.

Other assignments

n-Butyl acetate was not sensitising to the skin after dermal exposure of either humans or animals. In the absence of specific data, by analogy to *n*-butyl acetate, no skin sensitising potential is assumed for iso-butyl acetate and *sec*-butyl acetate.

No group at extra risk was identified.

Skin

In principle, *n*-butyl acetate may be absorbed through human skin (Spasovski and Bencev 1971). However, its permeability through human skin appears to be low owing to its high vapour pressure (ACGIH 2001a). As *sec*-butyl and iso-butyl acetate have even higher vapour pressures, no "skin" notation is proposed for the three compounds.

Biological monitoring

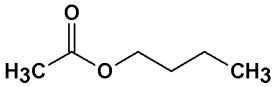
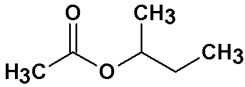
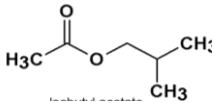
Currently, no validated method for biological monitoring is available for *n*-butyl, *sec*-butyl and isobutyl acetate.

Sampling, analysis and measurements

Analytical measurement methods are available. Sampling and measurement procedures can be performed at the corresponding levels of concentration with appropriate estimated levels of performance.

Recommendation Report

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	<i>n</i> -Butyl acetate	<i>sec</i> -Butyl acetate	Isobutyl acetate
Synonyms:	Butyl acetate; 1-butyl acetate; acetic acid, <i>n</i> -butyl ester; butyl ethanoate	2-Butyl acetate; acetic acid, secondary butyl ester; acetic acid, 1-methylpropyl ester	Acetic acid, 2-methylpropyl ester; acetic acid, isobutyl ester
Molecular formula:	C ₆ H ₁₂ O ₂	C ₆ H ₁₂ O ₂	C ₆ H ₁₂ O ₂
Structural formula:			
EC No.:	204-658-1	203-300-1	203-745-1
CAS No.:	123-86-4	105-46-4	110-19-0
Molecular weight:	116.16 g/mol	116.16 g/mol	116.16 g/mol
Boiling point:	126 °C	112.2 °C (DL-racemic)	111–118 °C
Melting point:	–77 °C		
Vapour pressure:	13.3 hPa (20 °C)	25.3 hPa (20 °C)	18 hPa (20 °C)
Water solubility:	7 g/l (20 °C)	30 g/l at 20 °C	7 g/l at 20 °C
Flash point:	24 °C (closed cup) 37 °C (open cup)	31.1 °C (closed cup) 16.7 °C (open cup)	17 °C (closed cup) 35 °C (open cup)
Density:	0.88 g/cm ³	0.87 g/cm ³	0.87 g/cm ³
Log P _{ow} :	1.82	1.51 (calculated)	1.60
Conversion factors (20 °C, 101.3 kPa):	1 ppm = 4.83 mg/m ³ 1 mg/m ³ = 0.207 ppm		

The *n*-, *sec*- and isobutyl acetates are all colourless, with a fruity odour.

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonized classification and labelling for Isobutyl acetate, *sec*-butyl acetate and *n*-butyl acetate is provided by ECHA, as summarized in Tables 1, 2, 3 and 4.

Table 1: Isobutyl acetate **and** *sec*-butyl acetate: Classification according to part 3 of Annex VI, table 3.1 (list of harmonised classification and labelling of hazardous substances of Regulation (EC) No1272/2008; Source: ECHA (2015))

Index no.	Internat. Chemical Identification	EC no.	CAS no.	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class & Category Code (s)	Hazard statement code (s)	Pictogram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)		
607-026-00-7	Isobutyl acetate	203-745-1	110-19-0	Flam.Liq. 2	H225	GHS02 Dgr	H225	EUH066		Note C
607-026-00-7	<i>sec</i> -Butyl acetate	203-300-1	105-46-4							

Table 2: Isobutyl acetate **and** *sec*-butyl acetate. Classification according to part 3 of Annex VI, table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No1272/2008; DSD classification; Source: ECHA (2015))

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
F; R11 R66	11 66	(2) 16 23 25 29 33	F	-	-

Table 3: *n*-butyl acetate: Classification according to part 3 of Annex VI, table 3.1 (list of harmonized classification and labelling of hazardous substances of Regulation (EC) No1272/2008; Source: ECHA (2015))

Index no.	Internat. Chemical Identification	EC no.	CAS no.	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class & Category Code (s)	Hazard statement code (s)	Pictogram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)		
607-025-00-1	<i>n</i> -Butyl acetate	204-658-1	123-86-4	Flam.Liq 3 STOT SE 3	H226 H336	GHS07 GHS02 Wng	H226 H336	EUH066		

Table 4: *n*-butyl acetate. Classification according to part 3 of Annex VI, table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No1272/2008; DSD classification; Source: ECHA (2015))

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
R10	10			-	-
R66	66	(2)			
R67	67	25			

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Isobutyl acetate, *sec*-butyl acetate and *n*-butyl acetate are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of this legislation.

Isobutyl acetate, *sec*-butyl acetate and *n*-butyl acetate are not carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and do not fall within the scope of this legislation.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits exist in a number of countries, as shown in the tables below. The values presented below represent examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 5: Existing OELs for isobutyl acetate; adapted from the GESTIS database (GESTIS, 2015)

EU-countries	TWA (8 hrs)		STEL (15 min)		References
	ppm	mg/m ³	ppm	mg/m ³	
Austria	100	480	100	480	GKV (2011)
Belgium	150	723			Royal Decision (2014)
Denmark	150	710	300	1420	BEK (2011)
European Union	50	241	150	723	SCOEL (2013)
Finland	150	720	200	960	MoSH (2012)
France	150	710	200	940	INRS (2012)
Germany (AGS)	62	300	124	600	BAUA (2006)
Germany (DFG)	100	480	200	960	DFG (2016)
Ireland	150	700	187	875	HSA (2011)
Poland		200		400	MLSP (2002)
Spain	150	724			INSHT (2011)
Sweden	100	500	150	700	SWEA (2011)
United Kingdom	150	724	187	903	HSE (2011)

Non-EU-countries	TWA (8 hrs)		STEL (15 min)		References
	ppm	mg/m ³	ppm	mg/m ³	
Australia	150	713			Safe Work Australia (2011)
Canada (Ontario)	150		187		Ontario Ministry of Labour (2013)
Canada (Québec)	150	713			IRSST (2010)
Japan	150				JSOH (2015)
New Zealand	150	713			HS (2013)
Singapore	150	713			GESTIS (2015)
South Korea	150	700	187	875	GESTIS (2015)
Switzerland	100	480	200	960	SUVA (2015)
USA (NIOSH)	150	700			NIOSH (2007)
USA (OSHA)	150	700			OSHA (2006)

Table 6: Existing OELs for *sec*-butyl acetate; adapted from the GESTIS database (GESTIS, 2015)

EU-countries	TWA (8 hrs)		STEL (15 min)		References
	ppm	mg/m ³	ppm	mg/m ³	
Austria	100	480	100	480	GKV (2011)
Belgium	200	964			Royal Decision (2014)
Denmark	150	710	300	1420	BEK (2011)
European Union	50	241	150	723	SCOEL (2013)
Finland	150	720	200	960	GESTIS (2015)
France	200	950			INRS (2012)
Germany (AGS)	62	300	124	600	BAUA (2006)
Ireland	200	950	250	1190	HSA (2011)
Poland		900		900	MLSP (2002)
Spain	200	966			INSHT (2011)
Sweden	100	500	150	700	SWEA (2011)
United Kingdom	200	966	250	1210	HSE (2011)
Non-EU-countries	ppm	mg/m ³	ppm	mg/m ³	References
Australia	200	950			Safe Work Australia (2011)
Canada (Ontario)	200				Ontario Ministry of Labour (2013)
Canada (Québec)	200	950			IRSST (2010)
New Zealand	200	950			HS (2013)
Singapore	200	950			GESTIS (2015)

South Korea	200	950			GESTIS (2015)
Switzerland	100	480	200	960	SUVA (2015)
USA (NIOSH)	200	950			NIOSH (2007)
USA (OSHA)	200	950			OSHA (2006)

Table 7: Existing OELs for *n*-Butyl acetate; adapted from the GESTIS database (GESTIS, 2015)

EU-countries	TWA (8 hrs)		STEL (15 min)		References
	ppm	mg/m ³	ppm	mg/m ³	
Austria	100	480	100	480	GKV (2011)
Belgium	150	723	200	964	Royal Decision (2014)
Denmark	150	710	300	1420	BEK (2011)
European Union	50	241	150	723	SCOEL (2013)
Finland	150	720	200	960	MoSH (2012)
France	150	710	200	940	INRS (2012)
Germany (AGS)	62	300	124	600	BAUA (2006)
Germany (DFG)	100	480	200	960	DFG (2016)
Hungary		950		950	MHSFA (2000)
Ireland	150	710	200	950	HSA (2011)
Latvia		200			GESTIS (2015)
Poland		200		950	MLSP (2002)
Spain	150	724	200	965	INSHT (2011)
Sweden	100	500	150	700	SWEA (2011)
United Kingdom	150	724	200	966	HSE (2011)

Non- EU-countries	ppm	mg/m ³	ppm	mg/m ³	References
Australia	150	713	200	950	Safe Work Australia (2011)
Canada (Ontario)	150		200		Ontario Ministry of Labour (2013)
Canada (Québec)	150	713	200	950	IRSST (2010)
China		200		300	GESTIS (2015)
Japan	150				JSOH (2015)
New Zealand	150	713	200	950	HS (2013)
Singapore	150	713			GESTIS (2015)
South Korea	150	710	200	950	GESTIS (2015)
Switzerland	100	480	200	950	SUVA (2015)
USA (NIOSH)	150	710	200	950	NIOSH (2007)
USA (OSHA)	150	710			OSHA (2006)

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

Butyl acetate was discovered in the 1940s by Altschul (1946). Butyl acetates can occur naturally in various plant tissues (WHO 2005). According to IAQUK (2015) butyl acetates occur naturally

- in the so-called alarm pheromones secreted by animals particularly insects, such as honey bees;
- in the atmosphere during the photochemical oxidation of other chemicals. Butyl acetate has been identified as a product of gasphase reactions of ethyl-*n*-butyl ether with hydroxyl radicals in the presence of nitric oxide. (Johnson and Andino 2001; WHO 2005).

n-Butyl acetate has been found in a wide variety of food products: bananas milk, cheese, beer, rum, brandy, wine, whisky, cocoa, black tea, coffee, roasted nuts, vinegar and honey (DECOS 2002; Maarse and Visscher 1989; WHO 2005). *n*-Butyl acetate is biosynthesised during fermentation processes and has also been identified in sunflower (*Helianthus annuus*) stems (Buchbauer et al. 1993; WHO 2005).

Isobutyl acetate occurs in natural products such as raspberries, pears, pineapples and natural cocoa aroma (Opdyke, 1978), black currants, guava, grapes, melons, peaches, strawberries, tomatoes, soy beans, plums, passion fruit, star fruit and dill herb (DECOS 2002; Maarse and Visscher 1989; WHO 2005).

sec-Butyl acetate has been found in vinegar (Maarse and Visscher 1989; WHO, 2005).

According to (WHO, 2005) butyl acetates released to the environment are likely to volatilize to the atmosphere, where they will undergo photochemical oxidation reactions with hydroxyl radicals and chlorine atoms. Butyl acetates in solution will undergo hydrolysis reactions, at a rate determined by the pH of the solution. Butyl acetates are readily biodegradable. Their physicochemical properties suggest that butyl acetates will not bind to soil or be bioaccumulated. Butyl acetates have been detected in river water, but the concentrations were not quantified. They have also been detected in air samples from industrial and chemical waste sites at concentrations up to 4.8 µg/m³. Exposure of the general population may occur from domestic sources, with *n*-butyl acetate concentrations up to 23 µg/m³ reported in household air.

5.2. Production and use information

Butyl acetate is made by dissolving acetic acid and butanol in a base of sulfuric acid (DECOS 2002; IAQ UK 2015). Isobutyl acetate is prepared from methyl isobutyl ketone, the *sec*-butyl acetate from *sec*-butyl alcohol and acetic acid anhydride (DECOS 2002).

Annual global production of butyl acetate was 528 000 tonnes in 1998, with 170 000 tonnes in the USA, Japan 50 000 tonnes; Mexico 8000 tonnes; South America 39 000 tonnes; China (Province of Taiwan), 40 000 tonnes; and Western Europe, 221 000 tonnes (CEH 1999).

Isobutyl acetate had a global industrial production of approximately 74 000 metric tonnes in 2002 (WHO 2005). In 2001, total production in China of *n*-butyl acetate was 155 thousand metric tons (ICIS 2003), which is the largest consumer of *n*-butyl acetate, accounting for 49% of the largest-volume alkyl acetates (CEH 2013).

The world consumption of *n*-butyl acetate in 2003 is estimated to be about 530 000 tonnes/year (SCA 2003).

Butyl acetates, especially *n*-butyl acetate and isobutyl acetate, are frequently used as solvents. Further uses include surface coatings, printing inks, paints/lacquers, adhesives, hardeners, anticorrosive agents, medicals, sealing agents, putty, cleaning agents, car care products, plasticizers, air care products and drilling fluids (PubChem 2015; SCA, 2003; WHO 2005).

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;
- 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;
- the production of shoe and leather glues, photographic films, plastics, safety glass; and
- in the pharmaceutical industry as an extractant (Greim 1999; HCN 2001).

Both *n*-butyl and isobutyl acetate are used in perfumery. Isobutyl acetate is also used as a component of hydraulic fluids and as a solvent in manufacturing lacquers and paint removers. *sec*-Butyl acetate also serves as a solvent for nitrocellulose and nail enamel and in the production of paper coatings (Greim 1999; HCN 2001; WHO 2005).

5.3. Occupational Exposure

Occupational exposure may occur in the industries listed in chapter 5.2, mainly by inhalation.

5.4. Routes of Exposure and uptake

The major route of occupational exposure to butyl acetates is by inhalation. According to WHO (2005) the available data are insufficient to estimate human exposure from all routes. Regarding the exposure of the general population (JECFA 1998) estimated levels of intake of *n*-butyl acetate from use as a flavoring agent in food as 170 µg/person per day in the USA and 1200 µg/person per day in Europe. This is likely to be a minor source of overall human exposure.

6. MONITORING EXPOSURE

Isobutyl acetate, *n*-butyl acetate and *sec*-butyl acetate can be monitored in the air of the workplace by applying the following methods (NIOSH 2011; DFG 2015):

- NIOSH method 1450 (esters 1)
- NIOSH method 2549 (VOCs)
- OSHA method 7 (organic vapours)
- MAK method 1 (solvent mixtures)
- MAK method 2 (solvent mixtures)
- MAK method 6 (solvent mixtures)
- MAK method 1 (lacquer aerosols)
- MAK method 2 (lacquer aerosols)
- MAK method 3 (lacquer aerosols)

In all nine methods isobutyl acetate, *n*-butyl acetate and *sec*-butyl acetate are sampled from the air in the workplace by adsorption onto a solid sorbent, followed by extraction with an organic solvent. The isobutyl acetate, *n*-butyl acetate and *sec*-butyl acetate-containing extract can then be analysed by gas chromatography (GC) using flame ionisation detection (FID) as shown in Table 8.

Table 8: Overview of sampling and analytical methods for monitoring isobutyl acetate, *n*-butyl acetate and *sec*-butyl acetate in the workplace

Method	Applicable for	Sorbent	Desorption solution	Analysis	Recovery (%)	LOQ	Concentration range	Refs.
NIOSH method 1450 (Esters 1)	Isobutyl acetate, <i>n</i> -butyl acetate and <i>sec</i> -Butyl acetate	Coconut shell charcoal	Carbon disulfide	GC-FID	98	0.9	14-440 µg/sample	NIOSH 2003
NIOSH method 2549 (VOCs)	Butyl acetate	Thermal desorption tube	Thermal	GC-MS	N.a.	100ng per tube or less	N.a.	NIOSH 1996
OSHA method 7 (organic vapours)	Isobutyl acetate, <i>n</i> -butyl acetate and <i>sec</i> -butyl acetate	Charcoal	N.a.	GC-FID	N.a.	N.a.	N.a.	OSHA 2000
MAK method 1 (solvent mixtures)	Isobutyl acetate, <i>n</i> -butyl acetate	Active charcoal	Carbon disulfide	GC-FID	97	0.027 mg/m ³	From 0.1 to 2 times the OEL set by DFG.	Kraemer 2014a
MAK method 2 (solvent mixtures)	Isobutyl acetate, butyl acetate	Active charcoal	CH ₂ Cl ₂ /CS ₂ /MeOH (60/35/5)	GC-FID	100	1 mg/m ³	N.a.	Schneider and Breuer 2014b
MAK method 6 (solvent mixtures)	Isobutyl acetate, <i>n</i> -butyl acetate	Chromosorb 106	Thermal	GC-FID/MS	97	4.1 mg/m ³	From 0.1 to 2 times the OEL set by DFG.	Tschickard 2014e
MAK method 1 (lacquer aerosols)	Isobutyl acetate, <i>n</i> -butyl acetate	Tenax GR	Thermal	GC-FID	99	Inhalable particles: absolute 0.1 mg. Solvent vapour: absolute 0.005-0.01 mg.	Inhalable particles: 20-220 mg/m ³ . Solvent vapour: 0.8-60 mg/m ³ .	Auffarth et al 2003

MAK method 2 (lacquer aerosols)	Isobutyl acetate, <i>n</i> -butyl acetate	Activated carbon	CH ₂ Cl ₂ /CS ₂ /CH ₃ OH (60:35:5)	GC-FID	99-100	Inhalable particles: absolute 0.3 mg. Solvent vapour: absolute 0.04 mg.	Inhalable particles: 20-220 mg/m ³ . Solvent vapour: 0.4-60 mg/m ³ .	Friedrich et al 2003
MAK method 3 (lacquer aerosols)	Isobutyl acetate, <i>n</i> -butyl acetate	Activated carbon	0.877 g/L 1-Chlorohexane in CS ₂	GC-FID	94-97	Inhalable particles: absolute 0.15 mg. Solvent vapour: absolute 0.0025-0.0075 mg.	Inhalable particles: 20-220 mg/m ³ . Solvent vapour: 4-60 mg/m ³ .	Dahmann et al 2003

N.a. not available

NIOSH method 1450 is a fully evaluated method and is considered an update of previous methods/issues. NIOSH method 2549 is partially evaluated.

OSHA method 7 (OSHA 2000) is a generalized version of the NIOSH method 1450 (NIOSH 2003) with slight modification.

7. HEALTH EFFECTS

7.1. Toxicokinetics (Absorption, Distribution, Metabolism, Excretion)

7.1.1. Human data

n-Butyl acetate

n-Butyl acetate is well absorbed after inhalation and oral exposure; however, no quantitative data were available. Although *n*-butyl acetate is reported to be absorbed when applied epicutaneously to humans (no details given, Spasovski and Bencev 1971), its ability to penetrate human skin appears to be low as Ursin et al (1995) reported a permeability constant of 1.6 ± 0.1 g/m²/hour, measured in living human skin obtained from female surgery patients.

After systemic uptake, *n*-butyl acetate is hydrolysed by unspecific esterases to acetic acid and *n*-butanol. An estimated 10–20 % of *n*-butyl acetate is already metabolised within the respiratory tract and is thus not systemically available (Barton et al 2000). After inhalation of 42 ppm (200 mg/m³) *n*-butyl acetate, about 50 % of the inhaled compound was found in the exhaled air (ACGIH 2001a). 4-Hydroxy-3-methoxy mandelic acid (vanilline mandelic acid) was found in the urine of mammals after exposure to *n*-butyl acetate (Bisesi 1994). However, because 4-hydroxy-3-methoxy mandelic acid is also found in the urine of unexposed persons, some authors question whether it is actually a metabolite of *n*-butanol (Greim 1999). The reported half-life of *n*-butyl acetate in human blood (in vitro) is only about 4 minutes (Essig et al 1989).

Upon inhalation, the main metabolite of *n*-butyl acetate, *n*-butanol, is also readily absorbed. Human experimental data by Åstrand et al (1976, cited in Teeguarden et al 2005) indicated 40 % pulmonary uptake or 59 % of alveolar ventilation. According to pharmacokinetic modelling, human inhalation exposure at steady-state to 190 ppm *n*-butanol leads roughly to the same *n*-butanol blood arterial concentrations (7.4 µM) as does exposure of experimental animals (rats) to 100 ppm *n*-butyl acetate (Teeguarden et al 2005).

sec-Butyl acetate

No quantitative data were available for *sec*-butyl acetate, but it can be assumed that it is absorbed after exposure by oral and inhalation routes. In the organism, *sec*-butyl acetate is hydrolysed by unspecific esterases to acetic acid and *sec*-butanol, which is further metabolised to ethyl methyl ketone and then excreted either by exhalation or in the urine or further metabolised producing 3-hydroxy-2-butanone and 2,3-butanediol (WHO 1987).

Isobutyl acetate

No quantitative toxicokinetic data were available for isobutyl acetate, but it can be assumed that it is well absorbed after inhalation and oral exposure and to a lesser extent after dermal contact. In the organism, isobutyl acetate is hydrolysed by unspecific esterases to acetic acid and isobutanol, which can be further oxidised to isobutyric acid (Greim 1999). The human blood/air partition coefficient for isobutyl acetate is 578, which is similar to that of the *n*-butyl acetate isomer (660) (Kaneko et al 1994). Small amounts of isobutyl acetate are excreted unchanged or conjugated as glucuronide (WHO 1987).

7.1.2. Animal data

n-Butyl acetate

n-Butyl acetate is well absorbed by the lung (100 % of alveolar ventilation, Teeguarden et al 2005), the gastrointestinal tract and to a lower extent by the skin in rats.

No relevant differences in distribution (Kaneko et al 1994) and metabolism (Teeguarden et al 2005) between species are known. The metabolism of the main metabolite of *n*-butyl acetate, *n*-butanol is retarded by simultaneous administration of ethanol in excess, since there is a substrate competition between both alcohols and the metabolising alcohol dehydrogenase (Groth and Freundt 1991). Essig et al (1989) measured an in vitro half-life of 12 min for *n*-butyl acetate in rat blood.

n-Butanol, is also readily absorbed at inhalation exposure. However, closed chamber inhalation studies revealed an estimated 50 % respiratory availability compared to 100 % for *n*-butyl acetate. According to pharmacokinetic modelling, inhalation exposure of experimental animals (rats) at steady state to 140 ppm *n*-butanol roughly leads to the same *n*-butanol blood arterial concentrations (7.4 µM) as does exposure to 100 ppm *n*-butyl acetate (Teeguarden et al 2005).

All acetates

All butyl acetates are absorbed by the lung, the gastrointestinal tract and to a smaller extent through the skin. Dahl et al (1987) measured the hydrolysis rates of all four isomers using esterases from a rat S9-mix. Steric factors at the site of hydrolysis such as degree of branching clearly contributed to the velocity of the reaction: *n*-butyl acetate: 77 ± 3 nmol/mg protein, isobutyl acetate: 67 ± 3 nmol/mg protein, *sec*-butyl acetate: 62 ± 3 nmol/mg protein and *tert*-butyl acetate: 42 ± 2 nmol/mg protein. Kaneko et al (1994) measured the organ/air partition coefficients for isobutyl acetate in rats for several tissues (liver: 5.06, kidney: 4.08, brain: 2.65, muscle: 2.12 and fat: 21.3) and also the blood/air partition coefficient (880).

7.1.3. In vitro data

No data were available.

7.1.4. Biological Monitoring

The chemical agent *n*-butyl acetate itself as well as its metabolites have been identified in blood, urine and exhaled air. Also, *sec*-butyl acetate and isobutyl acetate, as well as their metabolites, have been identified in blood, urine and exhaled air. However, due to the short half-life of 4 min and the *non*-specific nature of metabolites for use in biomonitoring, determinations are not reasonably technically possible.

7.2. Acute toxicity

7.2.1. Human data

All three butyl acetate isomers are known to cause irritation of the eyes, nose and throat after inhalation. Von Oettingen (1960) stated isomers with lower boiling points to be generally less toxic.

n-Butyl acetate

Reported symptoms after short-term inhalation exposure to *n*-butyl acetate were irritation of the nose, the throat and the eyes (Flury and Wirth 1933, Nelson et al 1943,

Iregren et al 1993) (for further details, see Section 7.4). After severe overexposure, weakness, drowsiness and unconsciousness were observed (ACGIH 2001a).

Patients with toxic encephalopathy with subjective hypersensitivity to chemicals and smell intolerant patients were exposed to up to 57 mg/m³ (11 ppm) of *n*-butyl acetate for up to 2 hours. No dose related changes in neurological performance tests could be demonstrated (Österberg et al 2000, 2003).

sec-Butyl acetate

Based on some unpublished data, ACGIH (2001b) reported that the irritating effect of *sec*-butyl acetate vapour is slightly less than that of *n*-butyl acetate (no further details given). This finding is supported by a statement of von Oettingen (1960), who reported butyl acetate isomers with lower boiling points to be generally less toxic.

Isobutyl acetate

No further human data were available.

7.2.2. Animal data

n-Butyl acetate

The published data on LC₅₀ values of *n*-butyl acetate are highly inconsistent. The reported LC₅₀ values for rats (4 hours) vary between 160 ppm (773 mg/m³) and > 9 000 ppm (43 478 mg/m³) (HCN 2001). In some inhalation studies, the animals were exposed to *n*-butyl acetate vapour and in others to *n*-butyl acetate aerosol (ACGIH 2001a). Thus, ACGIH (2001a) stated that the differences in toxicity might be due to the particle size. However, the LC₅₀ values of these aerosol studies were not reproducible. Possibly oral uptake of the aerosol particles (e.g. by licking of the fur) might have contributed to the lethality. All studies performed according to OECD guideline 403 revealed 4-hour LC₅₀ values of > 4 000 ppm in rats (Greim 1999). The LC₅₀ in mice was 1 260 ppm (6 100 mg/m³) (ECB 1995). Acute toxic symptoms after single exposure to *n*-butyl acetate are irritation effects on eyes, nose and respiratory tract. In higher concentrations, it produces severe damage to the lung (haemorrhagia, oedema and congestion), which is the main cause of death, as well as central nervous effects leading to narcosis. In early studies of Flury and Wirth (1933), 6 hours of exposure to *n*-butyl acetate caused anaesthesia in mice and cats at concentrations of 6 210 and 6 830 ppm, respectively (30 000 and 33 000 mg/m³). Both species recovered within 30 min. After single exposures to 3 000–6 000 ppm (14 500–29 000 mg/m³) in a neurotoxicity test on rats, decreased motor activity and response to stimuli were determined (Bernard and David 1994).

Reported LD₅₀ values after oral ingestion were 10 700–14 130 mg/kg for rats, 7 060 mg/kg for mice, 4 700 for guinea pigs and 3 200–7 437 mg/kg for rabbits (ECB 2000). Dermal LD₅₀ values were > 8 000 mg/kg for guinea pigs and > 17 600 mg/kg for rabbits (Greim 1999).

sec-Butyl acetate

According to an unpublished report by Roudabush (1970), all rats survived inhalation exposure to 3 500 ppm (17 000 mg/m³) *sec*-butyl acetate for 6 hours, while all rats exposed to 24 000 ppm (116 000 mg/m³) for 4 hours died. The oral LD₅₀ is 3 200–6 400 mg/kg in rats (Greim 1999).

For *sec*-butanol, the 4-hour LC₅₀ value in rats is 8 000–16 000 ppm (25 000–49 000 mg/m³) for inhalation exposure (ECETOC 2003). The oral LD₅₀ for rats varies between 2 200 mg/kg (Shell 1994) and 6 500 mg/kg and is 4 900 mg/kg for rabbits (Greim 1999). The dermal LD₅₀ in rabbits is > 2 000 mg/kg (Shell 1994).

Isobutyl acetate

Inhalation exposure of rats to 8 000 ppm (38 600 mg/m³) for 4 hours caused death in 4 of 6 animals, while after exposure to 16 000 ppm (77 300 mg/m³) all rats (6/6) died (Smyth et al 1962). Oral LD₅₀ values for rats and rabbits are 13 400 mg/kg (Smyth et al 1962) and 4 763 mg/kg (Munch, 1972), respectively. The dermal LD₅₀ in rabbits is ≥ 20 ml/kg (17 400 mg/kg; Smyth et al 1962). In summary, these data suggest a low acute toxicity of isobutyl acetate.

7.2.3. In vitro data

There are no data available.

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

n-Butyl acetate

After chronic exposure of workers to unknown concentrations of *n*-butyl acetate in combination with other solvents, conjunctival irritation, feeling of chest constriction and coughing were observed. No quantitative conclusion for single substance exposure to *n*-butyl acetate can be derived from these reports (ACGIH 2001a). Irritation to the eyes, nose and throat were demonstrated after repeated inhalation exposure to *n*-butyl acetate (Iregren et al 1993).

Iregren et al (1993) tested the irritating potential of *n*-butyl acetate in *non*-smoking, not occupationally exposed volunteers in a series of three different chamber studies. In the experiments, there was no significant effect on CNS symptoms (headache, vertigo, nausea and tiredness), tear film break-up time and conjunctival epithelial damage. The first group of volunteers (n = 24, experiment I) was exposed to concentrations of 350, 700, 1050 and 1400 mg/m³ (72.5, 145, 220 and 290 ppm). Exposure lasted 20 minutes, and each participant was exposed to the four concentrations with 24 hours in between exposures. In this experiment, the following effect measures were employed: magnitude estimation of irritation, category scales of irritations (eyes, nose, throat, skin, breathing difficulties, and sensation of bad smell) and category scales of CNS effects (headache, vertigo, nausea, tiredness). Under these conditions, changes in categorical ratings of irritation from baseline level before exposure were not significant for any of the items read. However, subjects reported borderline statistical significant "irritation to the throat" (p=0.05) and "difficulties in breathing" (p=0.06), whereas "sensation of a bad smell" (p<0.05) was statistical significant. The trends towards increasing effects with increasing exposure level were only weak, and there were no significant differences in effect size between any of the exposure concentrations and the baseline level before exposure. The psychophysical function relating total perceived irritation in this experiment did fit very well with empirical data (R² = 0.999). The exponent of the power function (0.328) suggested that odour plays a role in the irritation rating.

In the second experiment, volunteers (n = 23) were exposed to 70 (as "control" level) and 1400 mg/m³ (14.5 and 290 ppm) *n*-butyl acetate twice for 20 min at intervals of 7 days. In this experiment, measurements of pulmonary function (respiratory frequency, total lung capacity, airway resistance, forced expiratory volume in 1 second (FEV₁), vital capacity, forced vital capacity (FVC), maximal expiratory flow, specific airway resistance, closing volume) and objective eye irritation (blinking frequency, eye redness, lipid layer thickness, tear film break up time, conjunctival epithelial damage) were done besides subjective scaling of CNS effects and irritation. Subjective ratings for irritation of all sites except skin differed significantly between 1 400 mg/m³ and the control (70 mg/m³). The rated levels of irritation were, however, very low also in this experiment, and the subjects tended to use only the extreme lower end of the scales. The blinking frequency

was unchanged during the control exposure (12/min). However, at 290 ppm (1400 mg/m³), the frequency rose from 9/min to 12/min (p=0.02). The authors stated that interpretation of the results was difficult since the difference found was mainly due to a difference in baseline levels before exposure. No substantial effects on the lipid layer of the eyes were observed after the 20 min exposures. There were only minor changes in pulmonary functions at 1400 mg/m³; FEV₁ was unchanged during the exposure and FVC was slightly lower (-1.4% P<0.05) at 20 min of exposure. Yet, bronchial responsiveness was significantly increased after exposure to 1400 mg/m³.

In the third part of the study, 12 subjects were exposed to 70 (control) and 700 mg/m³ of *n*-butyl acetate (14.5 and 145 ppm) for 4 hours with 7 days in between exposures. Significant effects at 700 mg/m³ were observed for subjective throat irritation, difficulties in breathing and sensation of a bad smell, but there was no significant difference in ocular and nasal irritation. The results of pulmonary function measures (the same as in the 2nd experiment) were unchanged during the exposure except for an increase in bronchial responsiveness and the maximum expiratory flow at 25% at the end of the exposure. Eye redness was increased in 50 % of the subjects following exposure to 700 mg/m³ as compared to 17 % during control conditions.

sec-Butyl acetate

No data were available for *sec*-butyl acetate and its metabolites.

Isobutyl acetate

No data were available for isobutyl acetate and its metabolites.

7.3.2. Animal data

Inhalation

n-Butyl acetate

Several animal studies on repeated dose toxicity of *n*-butyl acetate have been performed. In an older study of Smyth and Smyth (1928) inhalation of 1 000 ppm (4 830 mg/m³) *n*-butyl acetate for 28 exposures (6 days/week, 4 hours/day) did not show any effects on blood counts, urine samples or necropsy data in guinea pigs.

Flury and Wirth (1933) reported irritation of respiratory passages, weakness and weight loss in cats after exposure to 4 200 ppm (20 290 mg/m³) *n*-butyl acetate over a period of 6 days (6 hours/day). Changes in blood cell morphology were observed at concentrations of \geq 3 100 ppm (14 976 mg/m³).

In a reproductive toxicity study, rats and rabbits were exposed to 1 500 ppm (7 246 mg/m³) *n*-butyl acetate for several days during gestation. At this concentration food consumption and consequently body weights of the rat dams were reduced. No signs of toxicity occurred in the rabbits (for further details, see Section 7.8; Hackett et al 1983).

In a subchronic inhalation study performed by David et al (1998), the neurotoxicity of *n*-butyl acetate at concentrations of 0, 500, 1 500 and 3 000 ppm (0, 2 415, 7 245, 14 490 mg/m³; 6 hours/day, 5 days/week) was tested in both food-restricted (13 weeks) and ad libitum fed rats (14 weeks). Endpoints for neurotoxicity testing were a functional observed battery (FOB), motor activity, neuro-histopathology (ad libitum fed rats) and schedule-controlled operant behaviour (SCOB, food-restricted rats). During the experiment, no spontaneous mortality occurred in any of the groups. According to the authors, the only sign of systemic toxicity was a significantly reduced body weight in the ad libitum fed rats at concentrations of 1 500 and 3 000 ppm *n*-butyl acetate. No treatment-related histopathological effects were detected. At 3 000 ppm and beginning

on the second day also at 1 500 ppm, rats were less active and movement and response to stimuli were slowed down (both feeding groups). No signs of neurobehavioural effects and no systemic toxicity were determined 30–60 min after cessation of exposure. Besides the described transient effects of sedation and hypoactivity, there was no evidence of neurotoxicity.

In a second study by David et al (2001) with analogous experimental design (all rats fed ad libitum), *n*-butyl acetate vapour equally led to reduced activity levels and decreased body weights at concentrations of 1 500 and 3 000 ppm. Due to the body weight loss, the organ weights of liver and kidney were reduced, but no systemic or organ specific toxicity was noted. Haematocrit, haemoglobin and erythrocyte counts, while still in the normal range, were increased compared to controls. At $\geq 1\ 500$ ppm, necrosis of the olfactory epithelium along the dorsal medial meatus was detected. The severity of the olfactory lesions was dose dependent. At 3 000 ppm, signs of irritation of the glandular stomach and necrosis of the *non*-glandular stomach were reported in females. No effects were observed at 500 ppm (NOAEC).

n-Butanol is the major metabolite of *n*-butyl acetate and is considered responsible for the systemic toxicity of the acetate. From absorption studies on the two substances and pharmacokinetic modelling (Teegarden et al 2005) it may be concluded that exposure to 100 ppm *n*-butyl acetate and 140 ppm *n*-butanol (rats) or 190 ppm *n*-butanol (humans), results in roughly identical blood concentrations of *n*-butanol. From this and from the toxicity data on *n*-butanol (Greim 1999) it may be concluded that no systemic effects are to be expected at non-irritating concentrations of *n*-butyl acetate at the workplace

sec-Butyl acetate

No data were available for *sec*-butyl acetate.

Isobutyl acetate

No data were available for isobutyl acetate.

SD rats (5 per sex and group) were exposed to isobutanol at 750, 1 500 and 3 000 ppm (2 272, 4 545 and 9 091 mg/m³) for 2 weeks (6 hours/day, 5 days/week). Animals exposed to 750 ppm were less sensitive against external stimuli than animals of the higher exposure groups. At $\geq 1\ 500$ ppm, isobutanol caused laboured breathing and signs of central nervous depression, but no pathological findings were reported (CMA 1996).

Inhalation exposure of SD rats (10 rats per sex and group) to isobutanol at 0, 770, 3 100 and 7 700 mg/m³ (0, 254, 1 023 and 2 541 ppm) for 14 weeks (6 hours/day, 5 days/week) revealed a NOAEC of 3 100 mg/m³. At 7 700 mg/m³, female rats had slightly but significantly increased red blood cell counts (Li et al 1999).

Oral

n-Butyl acetate

No data were available.

sec-Butyl acetate

No data were available.

Isobutyl acetate

No data were available for isobutyl acetate.

In a 90-day study performed according to OECD guideline 408, male and female Wistar rats (10 per sex and group) were given isobutanol in the drinking water at concentrations of 1 000, 4 000 and 16 000 mg/l (averaged daily doses: 80, 340 and 1 450 mg/kg/day for rats of both sexes). The NOAEL was 1 450 mg/kg/day (Schilling et al 1997).

In an older study, 30 male and 30 female CD rats per group were given isobutanol by gavage at 0, 100, 316 and 1 000 mg/kg/day for 13 weeks. At 1 000 mg/kg/day, hypoactivity, ataxia, salivation, laboured breathing and hypothermia occurred. The NOAEL in this study was 316 mg/kg/day (TRL 1987).

The observed discrepancies of these studies might result from the different study designs (drinking water vs. gavage application). Furthermore, rats of different strains might have different susceptibilities.

Oral application of 4 500 mg/kg acetic acid for 30 days caused gastric lesions in rats (Leung and Paustenbach 1990).

Dermal

No data were available.

7.3.3. Combination effects

The main metabolites of *sec*-butyl acetate, *i.e.* *sec*-butanol and methyl ethyl ketone, caused an increase in the activity of several enzymes in the rat (Traiger *et al* 1989). Furthermore, both compounds markedly increased CCl₄-induced hepatotoxicity in rats.

Methyl ethyl ketone increases the neurotoxic effects of *n*-hexane, 2,5-hexanedione and related compounds, although it does not exert neurotoxicity itself. Therefore, *sec*-butyl acetate may also influence the neurotoxic effects of certain chemicals. However, no such effects have yet been reported (ECETOC 2003).

7.3.4. In vitro data

No data were available.

7.4. Irritancy and corrosivity

7.4.1. Human data

n-Butyl acetate

Accepted odour thresholds according to AIHA (1997) were 0.31 ppm (1.5 mg/m³; detection) and 0.68 ppm (3.3 mg/m³; recognition). Other values not considered adequate by these authors were in the range of 0.63 to 368 ppm (3.0–177.8 mg/m³).

Repeated exposure of workers to *n*-butyl acetate was associated with mild irritation, cracking and defatting of the skin (ACGIH 2001a).

Flury and Wirth (1933) tested the irritating potential of *n*-butyl acetate after inhalation at concentrations of 1 000 mg/m³ and 10 000 mg/m³ (210 and 2 100 ppm) in 2–4 test persons. The subjects were exposed for 5 min in an inhalation chamber, 3 min after spraying and evenly distributing *n*-butyl acetate. Noted effects of *n*-butyl acetate were irritation to the eyes, nose, throat and oesophagus, reportedly weak at 210 ppm and moderate at 2 100 ppm. The authors observed adaptation over time.

In a study performed by Nelson et al (1943), 10 healthy volunteers were exposed to *n*-butyl acetate for 3–5 min. The test persons themselves subjectively scored the extent of irritation (none, weak, severe). At 200 ppm (966 mg/m³), irritation of the throat was reported, while irritating effects on eyes and nose occurred at 300 ppm (1449 mg/m³), together with a severe throat irritation.

In a study on anosmic patients, a threshold value of 3 650 ppm (17 633 mg/m³) for nasal irritation was determined for an exposure duration of 2 seconds (Abraham et al 1996) suggesting an important influence of the smell on the subjective sensation of irritation.

sec-Butyl acetate

A threshold value of 3 950 ppm (19 082 mg/m³) for nasal irritation caused by *sec*-butyl acetate was determined after inhalation exposure for 2 seconds in a study on anosmic patients (Abraham et al 1996).

Isobutyl acetate

No data were available.

7.4.2. Animal data

Skin

n-Butyl acetate

Only minimal irritation occurred 24 hours after application of 0.01 ml undiluted *n*-butyl acetate to the clipped skin of rabbits (Gad et al 1986). Also, no irritating effects on the skin of guinea pigs were observed after treatment with up to 10 ml *n*-butyl acetate (Greim 1999).

sec-Butyl acetate

No data were available.

Isobutyl acetate

Uncovered application of 0.01 ml undiluted isobutyl acetate for 24 hours to the shaved skin of rabbits did not cause irritation (Smyth et al 1962), while occlusive application of

pure isobutyl acetate caused moderate irritation of the intact or abraded skin of rabbits after 24 hours (unpublished results, Opdyke 1978).

Eyes

n-Butyl acetate

Grant (1986) reported superficial but reversible injury after instillation of liquid *n*-butyl acetate into the rabbit eye (no further details), and only mild ocular irritation occurred in a Draize test in rabbits (Kennah et al 1989). Inhalation exposure to either 500 ppm (2 415 mg/m³; guinea pigs: 10 days, rabbits: 20 days) or 1 000 ppm (4 830 mg/m³; guinea pigs and rabbits: 4 days) did not cause corneal or conjunctival injury (no further details given, Grant 1986).

sec-Butyl acetate

No data were available.

Isobutyl acetate

Instillation of up to 0.5 ml undiluted isobutyl acetate into the rabbit eye resulted in moderate inflammation (Smyth et al 1962).

Respiratory tract

n-Butyl acetate

The RD₅₀ (concentration causing a 50 % depression of the respiratory rate due to sensory irritation of the respiratory tract) of *n*-butyl acetate was 733 ppm (3 540 mg/m³) in Swiss OF1 mice (Alarie et al 1998).

sec-Butyl acetate

No data were available.

Isobutyl acetate

The RD₅₀ (concentration causing a 50 % depression of the respiratory rate due to sensory irritation of the respiratory tract) of isobutyl acetate was 818 ppm (3 950 mg/m³), and the RD₅₀ of isobutanol was 1 819 ppm (5 512 mg/m³) in Swiss-OF1 mice (Alarie et al 1998).

7.4.3. In vitro data

No data were available.

7.5. Sensitisation

7.5.1. Human data

n-Butyl acetate

No irritating or sensitising effects on the skin were observed after dermal exposure to 4 % *n*-butyl acetate in petrolatum as well as after repeated exposure to nail polish containing 25.5 % *n*-butyl acetate. The same results were obtained after repeated insult patch testing (9 × 24 hours within 3 weeks) with 0.5 ml pure liquid (Greim 1999, ACGIH

2001a). Only one person who was occupationally exposed to *n*-butyl acetate and one patient suffering from dermatitis showed positive results (Greim 1999). Because sensitisation tests were negative in all other test persons, *n*-butyl acetate seems to have no relevant skin sensitising potential.

sec-butyl acetate

No data were available.

Isobutyl acetate

Negative results on sensitisation of isobutyl acetate were obtained in a 48-hour closed patch test and in a maximisation test on 28 human volunteers with 2 % isobutyl acetate in petroleum (Opdyke 1978).

7.5.2. Animal data

n-Butyl acetate

No sensitising potential of *n*-butyl acetate was determined in a maximisation test in guinea pigs (no further details given, Magnusson and Kligman 1969) or in a mouse ear-swelling test after topical application of 100 µl *n*-butyl acetate (dissolved in 70 % ethanol) on the abdominal skin (induction) followed by application of 50 µl *n*-butyl acetate onto one ear (challenge) (Gad et al 1986).

sec-Butyl acetate

No data were available.

Isobutyl acetate

Isobutyl acetate did not show any sensitising potential in a maximisation test performed on guinea pigs according to OECD guideline 406, (no further details, Huels AG 1988).

No information is given for the sensitising potential of isobutanol or acetic acid.

7.5.3. In vitro data

There are no in vitro data on sensitisation.

7.6. Genotoxicity

7.6.1. Human data

No data were available.

7.6.2. Animal data

No data were available.

7.6.3. In vitro

n-Butyl acetate

n-Butyl acetate revealed no genotoxic effects in *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, TA1537) at concentrations of 33–10 000 µg/plate (Zeiger et al 1992) and in *Escherichia coli* (Shimizu 1985) both with and without activation. Negative results were obtained at all tested concentrations in a yeast assay (D61.M) and after incubation of Chinese hamster lung (CHL) cells with *n*-butyl acetate (Greim 1999).

sec-butyl acetate

No relevant data were reported on *sec*-butyl acetate. The genotoxic activities of its metabolites *sec*-butanol and methyl ethyl ketone were tested in a study by Brooks et al (1988). Both *sec*-butanol and the ketone gave negative results in an Ames test (TA98, TA100, TA1535, TA1537, TA1538), in a yeast mitotic gene conversion assay (JD1) and in cultured mammalian cells (rat liver cells, Chinese hamster ovary (CHO) cells). Furthermore, an Ames test with *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538), performed by von der Hude et al (1988) gave negative results for acetic acid. Therefore, a genotoxic potential of *sec*-butyl acetate is unlikely.

Isobutyl acetate

Testing the genotoxicity of isobutyl acetate in *Salmonella typhimurium* (TA98, TA100, TA153, TA1537, TA1538) with or without metabolic activation revealed no mutagenic potential up to the highest concentrations tested (5 mg/plate, Bayer 1997). Besides, in V79 hamster cells, no chromosomal aberrations were caused with up to 2 500 µg/ml. At this concentration, the mitotic index was already at 50 % (BAU 1996).

7.7. Carcinogenicity

7.7.1. Human data

No data were available.

7.7.2. Animal data

n-Butyl acetate and *sec*-butyl acetate

No data were available.

Isobutyl acetate

No data were available for isobutyl acetate.

The tumour incidences in Wistar rats were increased in an inadequately conducted and poorly reported gavage study on isobutanol (Gibel et al 1974, 1975). Reported toxic symptoms as well as reduced survival of the dosed animals suggested that the only tested dose was above the maximum tolerated dose (MTD) (Greim 1999). Thus, no assessment can be made on the basis of this study.

No animal data on carcinogenic effects of acetic acid were available.

7.8. Reproductive toxicity

7.8.1. Human data

No data were available.

7.8.2. Animal data

7.8.2.1. Fertility

n-Butyl acetate

No dose-related effects on the epididymal or testicular sperm count in rats were observed in a 13-week inhalation study with *n*-butyl acetate (David et al 2001) (for further details, see Section 7.3).

sec-Butyl acetate

No data were available for *sec*-butyl acetate itself. Its main metabolite *sec*-butanol, tested in a two-generation study in rats, did not show adverse effects on the fertility of rats at oral doses of about 4 500 mg/kg/day (Cox et al 1975).

Isobutyl acetate

No data were available for isobutyl acetate itself.

In an unpublished two-generation study, rats (30 per sex and group) were exposed by inhalation to isobutanol at 0, 1 500, 3 100 and 7 700 mg/m³ (0, 495, 1 023 and 2 541 ppm) for 10 weeks prior to mating (6 hours/day, 5 days/week). Females were exposed until gestation day (gd) 20 and again from lactation day 5 until lactation day 28. Inhalation exposure of the pups (F₁ generation) continued until mating (10 weeks). No systemic toxicity and no effects on fertility occurred at any concentration (WIL Research Laboratories 2003).

7.9. Developmental toxicity

n-Butyl acetate

In a reproductive toxicity study, rats (n = 40) and rabbits (n = 30, artificially inseminated) were exposed to *n*-butyl acetate at 1 500 ppm (7 246 mg/m³) for several days during gestation (7 hours/day) (Hackett et al 1983). Of the rats, group 1 was exposed to filtered air (control), group 2 was exposed to *n*-butyl acetate on gestational day (gd) 7–16, group 3 on gd 1–16 and group 4 was exposed on 5 days per week for 3 weeks prior to mating and again on gd 1–6. Rabbits were exposed to filtered air (control, group I) or to *n*-butyl acetate either on gd 1–19 (Group II) or on gd 7–19 (Group III). Maternal toxicity was observed in all exposed animals, manifest in reduced food consumption (rats and rabbits) and reduced body weights (rats). No malformations, increased numbers of resorptions or deaths occurred in rabbits in any of the exposed groups. The incidences of some morphologic variations were increased in rabbits of group III. In rats, signs of minor developmental toxicity were detected. Foetal growth (crown-rump length, body weight) was reduced in all exposure groups, which could be due to the observed reduced body weight of the dams. Reduced pelvic ossification occurred in foetuses of groups 2 and 3 and dilated ureters occurred in group 4. The only significant foetal effect of *n*-butyl acetate was an increase in the incidence of rib dysmorphology in rats (wavy, fused and bifid ribs). This effect was found in all exposed groups of rats. Because the observed findings were only variations and no malformations, the authors concluded that they were not due to teratogenic effects (Hackett et al 1983). Furthermore, the detected developmental effects might be due to the maternal toxicity.

This was confirmed by a more recent study. The developmental toxic potential of *n*-butyl acetate was examined in Sprague-Dawley rats in a whole-body inhalation study (6 hours/day, gd 6–20) with nominal exposure concentrations of 0, 500, 1 000, 2 000 and 3 000 ppm (2 415, 4 830, 9 660, 14 490 mg/m³). Maternal toxicity was evident at 1 000 ppm and above (reduced food consumption, decreased weight gain at higher concentrations). Foetal weight was reduced at 3 000 ppm. The authors concluded that *n*-butyl acetate is not a selective developmental toxicant (Saillenfait et al 2007).

The developmental toxicity of *n*-butanol, the major metabolite of *n*-butyl acetate, was investigated by Nelson et al (1989). In this study, rats were exposed to 0, 3 500, 6 000 and 8 000 ppm *n*-butanol on gd 1–19 for 7 hours per day. Foetal body weights were reduced at $\geq 6\,000$ ppm. At 8 000 ppm (25 000 mg/m³), the incidence of skeletal alterations was increased. For *n*-butanol, no effects were observed at 3 500 ppm (11 000 mg/m³).

sec-Butyl acetate

No data on the developmental toxicity of *sec*-butyl acetate were available. However, inhalation studies with its main metabolite *sec*-butanol were performed in rats at concentrations of 0, 3 500, 5 000, 7 000 ppm (0, 11 000, 15 700 and 22 000 mg/m³) (Nelson et al 1989). Exposure on gd 1–19 (7 hours/day) resulted in an increased number of resorptions at 7 000 ppm. Furthermore, exposure to *sec*-butanol produced decreased foetal body weights and a reduced number of live foetuses at $\geq 5\,000$ ppm (15 700 mg/m³). Maternal toxicity manifested in reduced food consumption and decreased weight gain of the dams at all concentrations tested. At $\geq 5\,000$ ppm, narcosis of the dams occurred. For *sec*-butanol, a NOAEC of 3 500 ppm (11 000 mg/m³) was determined for developmental toxicity and the NOAEC for maternal toxicity was below 3 500 ppm.

A "low level of developmental toxicity" occurred after inhalation exposure to methyl ethyl ketone at 3 000 ppm (9 000 mg/m³), but the significance of this finding is questionable (ECETOC 2003).

No developmental effects occurred in two filial generations (F₁, F₂) at approximately 1 500 mg/kg/day *sec*-butanol (NOAEL) in an oral two-generation reproductive toxicity study (no further details, Cox et al 1975).

Isobutyl acetate

No data were available for isobutyl acetate, but a study with isobutanol was performed on rats and rabbits (Klimisch and Hellwig 1995). Inhalation exposure to 500, 2 500 and 10 000 mg/m³ (105, 520, 2 070 ppm) during gestation (gd 6–15 rats, gd 7–19 rabbits) induced no foetotoxic effects in either rats or rabbits. Also, no teratogenicity of isobutanol was observed at these concentrations and no maternal toxicity occurred.

There were no studies on the developmental toxicity of acetic acid. However, there were no signs of foetotoxic or teratogenic effects of several alkyl acetates even at high concentrations (e.g. *n*-propyl acetate at 13 000 ppm, Flury and Wirth 1933). In a study on rabbits fed 1 600 mg/kg apple cider vinegar (assuming 5 % acetic acid = approximately 80 mg/kg) on gd 6–18, neither maternal nor foetal effects were observed (FDA 1977).

7.10. Mode of Action and adverse outcome pathway considerations

The main effect of butyl acetates is local irritation, as evidenced in humans and in experimental animals. This effect might, on the one hand, be caused by the compounds itself and, on the other hand, by the product of hydrolysis, acetic acid.

7.11. Lack of specific scientific information

For OEL setting there is no lack of specific scientific information.

8. GROUPS AT EXTRA RISK

There are no specific indications for the existence of groups at extra risk.

9. REFERENCES

- Abraham MH, Andonian-Haftvan J, Cometto-Muniz JE, Cain WS (1996). An analysis of nasal irritation thresholds using a new solvation equation. *Fundam Appl Toxicol* 31:71-76, cited in Greim 1999.
- ACGIH, American Conference of Governmental Industrial Hygienists (2001a). *n*-Butyl acetate. In: *Threshold limit values for chemical substances and physical agents and biological exposure indices*, 2001. ACGIH, Cincinnati, OH, USA.
- ACGIH, American Conference of Governmental Industrial Hygienists (2001b). *sec*-Butyl acetate. In: *Threshold limit values for chemical substances and physical agents and biological exposure indices*. ACGIH, Cincinnati, OH, USA.
- AIHA, American Industrial Hygiene Association (1997). *Odor thresholds for chemicals with established occupational health standards*. American Industrial Hygiene Association, Fairfax, VA, USA.
- Alarie Y, Schaper M, Nielsen GD, Abraham MH (1998). Structure-activity relationships of volatile organic chemicals as sensory irritants. *Arch Toxicol* 72:125-140.
- Altschul R (1946). The reversible esterification of carboxylic acids with isobutene and trimethylethylene. Quantitative studies and synthetic applications. *J Am Chem Soc* 68(12):2605-2609.
- Auffarth J, Hebisch R, Rentel K-H (2003). Lacquer aerosols. Method number 1. In: Kettrup A, Angerer J, Greim H (eds), *Analyses of Hazardous Substances in Air*, Vol 8, 135-148, Wiley-VCH, Weinheim.
<http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lackaere0008a/pdf>
- Barton HA, Deisinger PJ, English JC, Gearhart JM, Faber WD, Tyler TR, Banton MI, Teeguarden J, Andersen ME (2000). Family approach for estimating reference concentrations/doses for series of related organic chemicals. *Toxicol Sci* 54:251-261.
- BAUA, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (2006). TRGS 900 "Arbeitsplatzgrenzwerte". BAUA, Germany
<http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/TRGS-900.html>
- BAU, Bundesanstalt für Arbeitsschutz (1996). Prüfung exemplarisch ausgewählter Altstoffe auf eine cytotogenetische Wirkung in vitro: Induktion von Chromosomenaberrationen. Fraunhofer-Institut für Toxikologie und Aerosolforschung, Bericht Nr. F 1250, cited in Greim 1999.
- Bayer (1997). IUCLID, International Uniform Chemical Information Database, data sheet, isobutyl acetate, 28.01.1997, unpublished, cited in Greim 1999.
- BEK (2011). Bekendtgørelse om ændring af bekendtgørelse om grænseværdier for stoffer og materialer, BEK nr 1134 af 01/12/2011 (Gældende), Beskæftigelsesministeriet, Arbejdstilsynet, j.nr. 2011007144, Denmark,
<https://www.retsinformation.dk/pdfPrint.aspx?id=139131>
- Bernard LG, David RM (1994). *n*-Butyl acetate: an acute inhalation neurotoxicity study in the rat. Toxicologic Sciences Laboratory, Eastman Kodak Company, Rochester, NY, August 19, 1994, cited in ACGIH 2001a
- Bisesi MS (1994). Esters. In: Clayton GD, Clayton FE. *Patty's industrial hygiene and toxicology*, Vol. II, Part D, Toxicology. 4th Ed., John Wiley & Sons, Inc., New York, 2984-2985, cited in ACGIH 2001a

- Brooks TM, Meyer AL, Hutson DH (1988). The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis* 3:227-231, cited in WHO 2005.
- Buchbauer G, Jirovetz L, Wasicky M, Nikiforov A (1993) Headspace analysis of aroma constituents of sunflower stems. *Fresen J Anal Chem* 347(10-11):465-467
- CEH, Chemical Economics Handbook (2013). CEH. Alkyl acetates, published December 2013, accessed in October 2015.
<https://www.ihs.com/products/alkyl-acetates-chemical-economics-handbook.html>
- CEH, Chemical Economics Handbook (1999). CEH marketing research report, Oxo Chemicals. Menlo, CA, SRI International, Chemical Economics Handbook (CEH), cited in WHO, 2005.
- CMA, Chemical Manufacturers Association (1996). Exposure concentration range-finding study for a subchronic inhalation neurotoxicity study of isobutanol administered by whole-body inhalation to CD rats, with cover letter dated 3/14/96. NTIS/OTS 0558856, EPA/OTS 44624, NTIS, Springfield, VA, cited in Greim 1999.
- Cox GE, Bailey DE, Morgareidge K (1975). Toxicity studies in rats with 2-butanol including growth, reproduction, and teratologic observation. Mölndal, Astra Nutrition, Food and Drug Research Laboratories (LaB No. 2093; with TSE 8(e) cover note dated 11 May 1992 by Shell Oil, Houston, TX), cited in WHO 2005.
- Dahl AR, Miller SC, Petridou-Fischer J, (1987). Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. *Toxicol Lett* 36:129-136.
- Dahmann D, Fricke H-H, Moecklinghoff K (2003). Lacquer aerosols. Method number 3. In: Kettrup A, Angerer J, Greim H (eds), *Analyses of Hazardous Substances in Air*, Vol 8, 163-176, Wiley-VCH, Weinheim.
<http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lackaere0008c/pdf>
- David RM, Tyler TR, Ouellette R, Faber WD, Banton MI, Garman RH, Gill MW, O'Donoghue JL, (1998) Evaluation of subchronic neurotoxicity of *n*-butyl acetate vapor. *Neurotox* 1998 Dec;19(6):809-22
- David RM, Tyler TR, Ouellette R, Faber WD, Banton MI, (2001). Evaluation of subchronic toxicity of *n*-butyl acetate vapour *Food Chem Toxicol* 39:877-886
- DECOS, Dutch Expert Committee on Occupational Safety (2002). DECOS and SCG Basis for an Occupational Standard, *n*-, iso-, *sec*-, and tert-Butyl acetate, Hans Stouten and Wim Bogaerts. Nr. 2002:11. Arbetslivsinstitutet. National Institute for Working Life.
https://gupea.ub.gu.se/bitstream/2077/4282/1/ah2002_11.pdf
- DFG, Deutsche Forschungsgemeinschaft (2016). List of MAK and BAT Values 2016: Maximum Concentrations and Biological Tolerance Values at the Workplace. Chapter II List of Substances. Wiley-VCH, Weinheim.
<http://onlinelibrary.wiley.com/book/10.1002/9783527805983>
- ECB, European Chemicals Bureau (1995). IUCLID, International Uniform Chemical Information Database, data sheet, *n*-butyl acetate, 23.10.95, cited in Greim 1999
- ECB, European Chemicals Bureau (2000). IUCLID, International Uniform Chemical Information Database. Edition II. EUR 19559 EN, European Commission
- ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals (2003). *sec*-Butanol. JACC Report No. 43. Brussels, Belgium

- ECHA, European Chemicals Agency (2015) ECHA inventory database. *sec*-Butyl acetate. Accessed 23-10-2015
<http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/120101>
- ECHA, European Chemicals Agency (2015) ECHA inventory database. Isobutyl acetate. Accessed 23-10-2015.
<http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/24499>
- ECHA, European Chemicals Agency (2015) ECHA inventory database. *n*-Butyl acetate. Accessed 23-10-2015.
<http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/56478>
- Ernstgård L, Iregren A, Sjögren B, Johanson G (2006) Acute effects of exposure to vapours of acetic acid in humans. *Toxicol Lett.* 2006 Aug 1;165(1):22-30. Epub 2006 Feb 21
- Essig KM, Groth G, Freundt KJ (1989). Different elimination of *n*-butyl acetate and *t*-butyl acetate. Abstr. No. 87. *Arch Pharmacol, Suppl.* 340, R33, cited in HCN 2001.
- FDA, Food and Drug Administration (1977). Evaluation of the health aspects of acetic acid, sodium acetate, and sodium diacetate as food ingredients. Report No. FDA/BF-78/16. NTIS Doc. No. PB-274670, NTIS, Springfield, VA, cited in Greim 1999.
- Flury F, Wirth W (1933). Zur Toxikologie der Lösungsmittel. *n*-Butylacetat. *Arch Gewerbepathol Gewerbehyg* 5:28-34.
- Friedrich C, Henning M, Lichtenstein N (2003). Lacquer aerosols. Method number 2. In: Kettrup A, Angerer J, Greim H (eds), *Analyses of Hazardous Substances in Air, Vol 8*, 149-161, Wiley-VCH, Weinheim.
<http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lackaere0008b/pdf>
- Gad SC, Dunn BJ, Dobbs DW, Reilly C, Walsh RD (1986). Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). *Toxicol Appl Pharmacol* 84:93-114.
- GESTIS (2015). GESTIS database on hazardous substances. IFA Institut für Arbeitssicherheit der Deutschen Gesetzlichen Unfallversicherung, Germany
<http://limitvalue.ifa.dguv.de/>
- Gibel W, Lohs KH, Wildner GP, Schramm T. (1974) Experimental studies on the carcinogenic effect of higher alcohols using 3-methyl-1-butanol, 1-propanol and 2-methyl-1-propanol as examples *Z Exp Chir.* 1974; 7(4):235-9. German
- Gibel VW, Lohs KH, Wildner GP (1975). Experimentelle Untersuchungen zur kanzerogenen Wirkung von Lösungsmitteln am Beispiel von Propanol-1, 2 Methylpropanol-1 und 3-Methylbutanol-1. *Arch Geschwulstforsch* 45:19-24, cited in Greim 1999.
- GKV (2011). BGBl. II Nr. 429/2011. Verordnung des Bundesministers für Arbeit, Soziales und Konsumentenschutz über Grenzwerte für Arbeitsstoffe sowie über krebserzeugende und über fortpflanzungsgefährdende (reproduktionstoxische) Arbeitsstoffe, Grenzwerteverordnung (DKV), Austria,
<http://www.arbeitsinspektion.gv.at/NR/rdonlyres/F173280B-D4FB-44D2-8269-8DB2CB1D2078/0/GKV2011.pdf>
- Grant WM (1986). *Toxicology of the eye.* Thomas CC, Springfield, IL, cited in ACGIH 2001a.

- Greim H (1999). 1-Butylacetat. 2-Butylacetat. iso-Butylacetat. Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, 28. Lfg., Wiley-VCH, Weinheim. Groth G, Freundt KJ (1991). Blutalkohol unter Anwesenheit von *n*-Butylacetat. Blutalkohol 28:166-173, cited in HCN 2001.
- Hackett PL, Brown MG, Buschbom RL, Clark ML, Miller RA, (1983). Teratogenic study of ethylene and propylene oxide and *n*-butyl acetate. National Institute for Occupational Safety and Health. Contract Report No. 210-80-0013, NTIS Pub. No. PB83-258-038. National Technical Information Service, Springfield, VA, cited in ACGIH 2001a.
- HCN, Health Council of the Netherlands (2001). Health-based reassessment of administrative occupational exposure limits - *n*-, iso-, *sec*-, and tert-butyl acetate. Publ. No. 2001/03OSH. Dutch Expert Committee on Occupational Standards, The Hague.
- HSA, Health and Safety Authority (2011). 2011 Code of Practice for the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No. 619 of 2001), HAS, Ireland.
- HS, Health and Safety (2013). Workplace Exposure Standards and Biological Exposure Indices Effective from February 2013 7th Edition. HS, The Ministry of Business, Innovation and Employment, New Zealand,
<http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices/workplace-exposure-standards-and-biological-indices-2013.pdf>
- HSE, Health and Safety Executive (2011). EH40/2005 Workplace exposure limits (Second edition), HSE, UK,
<http://www.hse.gov.uk/pUbns/priced/eh40.pdf>
- IAQUK, Indoor Air Quality UK (2015). IAQUK Resources - Butyl Acetate. Accessed October 2015.
<http://www.iaquk.org.uk/ResourcesButlyAcetate.html>. ICIS, Independent Chemical Information Services (2003). China report chemical product trends, *n*-butanol, by SRI Consulting 2003. Accessed October 2015.
<https://www.icis.com/Assets/GetAsset.aspx?ItemID=13727>
- INRS, Institut National de Recherche et de Sécurité (2012). Valeurs limites d'exposition professionnelle aux agents chimiques en France, INRS), France,
<http://www.inrs.fr/media.html?refINRS=ED%20984>
- INSHT, Instituto Nacional de Seguridad e Higiene en el Trabajo (2011). Limites de Exposicion profesional para agentes quimicos en Espana. INSHT, Spain,
http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_Limite/limites2011/Limites2011web.pdf
- Iregren A, Löf A, Toomingas A, Wang Z (1993). Irritation effects from experimental exposure to *n*-butyl acetate. Am J Ind Med 24 :727-742.
- IRSST, Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail Canada (2010). IRSST, Québec, Canada,
<http://www.irsst.qc.ca/en/-RSST62-53-3.html>
- JECFA, Joint FAO/WHO Expert Committee on Food Additives (1998) Safety evaluation of certain food additives and contaminants. Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids. 49th meeting of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization (WHO Food Additives Series 40).
- Johnson D, Andino JM (2001). Laboratory studies of the OH initiated photooxidation of ethyl-*n*-butyl ether and di-*n*-butyl ether. Int J Chem Kinet 33(5):328-341.

- JSOH, Japan Society for Occupational Health (2015). Recommendation of Occupational Exposure Limits (2014–2015), JSOH, Japan, *J Occup Health* 56: 401–420.
- Kaneko T, Wang PY, Sato A (1994). Partition coefficients of some acetate esters and alcohols in water, blood, olive oil, and rat tissues. *Occup Environ Med* 51:68-72, cited in HCN 2001.
- Kennah HE, Hignet S, Laux PE, Dorko JD, Barrow CS (1989). An objective procedure for quantitating eye irritation based upon changes of corneal thickness. *Fundam Appl Toxicol* 12:258-268.
- Klimisch H-J, Hellwig J (1995). Studies on the prenatal toxicity of 3-methyl-1-butanol and 2-methyl-1-propanol in rats and rabbits following inhalation exposure. *Fundam Appl Toxicol* 27:77-89.
- Kraemer M (2014). Solvent mixtures. Method number 1 (Lösemittelgemische; Air Monitoring Methods in German language). In: Parlar H, Hartwig A (eds), *Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 1, Luftanalysen*, 18. Lieferung, Wiley-VCH, Weinheim.
<http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lmix001d0018/pdf>
- Larsen ST, Nielsen GD (2012) Acute airway irritation of methyl formate in mice. *Arch Toxicol* 86:285-292.
- Leung HW, Paustenbach DJ (1990). Organic acids and bases: review of toxicological studies. *Am J Ind Med* 18:717-735.
- Li AA, Thake DC, Kaempfe TA, Branch DK, O'Donnell P, Speck FL, Tyler TR, Faber WD, Jasti SL, Ouellette R, Banton MI (1999). Neurotoxicity evaluation of rats after sub-chronic inhalation exposure to isobutanol. *Neurotoxicol* 20:889-900, cited in WHO 2005.
- Maarse H, Visscher CA (eds.) *Volatile compounds in food: qualitative and quantitative data*. 6th ed. Zeist, The Netherlands: TNO-CIVO Food Analysis Institute, (1989): 1127 (Vol I, products 1-66).
- Magnusson B, Kligman AM (1969). The identification of contact allergens by animal assay. *J Invest Dermatol* 52:268-276.
- MHSFA, Ministry of Health, Social and Ministry of Family Affairs (2000). 25/2000. (IX. 30.) EüM-SzCsM együttes rendelet a munkahelyek kémiai biztonságáról, MHSFA, Hungary,
http://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0000025.EUM
- MLSP, Ministry of Labour and Social Policy (2002). The Ordinance of the Minister of Labour and Social Policy on the Maximum Admissible Concentrations and Intensities of Harmful to Health Agents in the Working Environment. Rozporządzenie ministra pracy i polityki spo,ecznej Z dnia 29 listopada 2002 r, MLSP, Poland,
http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/legaldocument/wcms_151572.pdf
- MoSH, Ministry of Social Affairs and Health (2012). HTP-värden 2012.Koncentrationer som befunnits skadliga. Social- och hälso vardsministeriets publikationer 2012:6, MoS), Finland,
http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf
- Munch JC (1972). Aliphatic alcohols and alkyl esters: narcotic and lethal potencies to tadpoles and to rabbits. *Ind Med Surg* 41:31-33, cited in ECB 2000.
- Nelson KW, Ege JF, Ross M, Woodman LE, Silverman L (1943). Sensory response to certain industrial solvent vapors. *J Ind Hyg Toxicol* 25:282-285.

- Nelson BK, Brightwell WS, Khan A, Burg JR, Goad PT (1989). Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fundam Appl Toxicol* 12:469-479.
- Nielsen GD, Wolkoff P, Alarie Y (2007) Sensory irritation: risk assessment approaches. *Regul Toxicol Pharmacol* 48:6-18.
- NIOSH (1996) NIOSH method 2549. Issue 1 15 May 1996. Volatile organic compounds (screening). <https://www.cdc.gov/niosh/docs/2003-154/pdfs/2549.pdf>
- NIOSH (2003) NIOSH method 1450. Issue 3 March 2003. Esters 1. <http://www.cdc.gov/niosh/docs/2003-154/pdfs/1450.pdf>
- NIOSH (2007). Pocket guide to chemical hazards department of health and human services. Centers for Disease Control and Prevention National Institute for Occupational Safety and Health, National Institute for Occupational Safety and Health (NIOSH), USA, <http://www.cdc.gov/niosh/docs/2005-149/pdfs/2005-149.pdf>
- NIOSH (2011) Pocket guide to chemical Hazards on *sec*-Butyl acetate. Accessed on 27-10-2015. <http://www.cdc.gov/niosh/npg/npgd0073.html>
- Pocket guide to chemical Hazards on isobutyl acetate. Accessed on 27-10-2015. <http://www.cdc.gov/niosh/npg/npgd0351.html>
- Pocket guide to chemical Hazards on *n*-Butyl acetate. Accessed on 27-10-2015. <http://www.cdc.gov/niosh/npg/npgd0072.html>
- Ontario Ministry of Labour (2013). Current Occupational Exposure Limits for Ontario Workplaces Required under Regulation 833, Canada, http://www.labour.gov.on.ca/english/hs/pdf/ontario_oels.pdf
- Opdyke DLJ (1978). Monographs on fragrance raw materials. Isobutyl acetate. *Food Cosmet Toxicol* 16:795-796, cited in WHO 2005, HCN 2001, Greim 1999.
- OSHA (2000). OSHA method 7. Organic Vapors. <https://www.osha.gov/dts/sltc/methods/organic/org007/org007.html>
- OSHA (2006). Air Contaminants, Occupational Safety and Health Administration (OSHA), USA, <https://www.osha.gov/dsg/annotated-pels/tablez-1.html>
- Österberg K, Orbæk P, Karlson B, Åkesson B, Bergendorf U (2003). Annoyance and performance during the experimental chemical challenge of subjects with multiple chemical sensitivity. *Scand J Work Environ Health* 29:40-50.
- Österberg K, Orbæk P, Karlson B, Seger L, Åkesson B, Bergendorf U (2000). Psychological test performance during the experimental challenge to toluene and *n*-butyl acetate in cases of solvent-induced toxic encephalopathy. *Scand J Work Environ Health* 26:219-226.
- PubChem (2015). Open chemistry database. Compound Summary for CID 31272. Butyl acetate. Manufacturing and use. Accessed October 2015. http://pubchem.ncbi.nlm.nih.gov/compound/Butyl_acetate#section=U-S-Production
- Roudabush RL (1970). Toxicity and health hazard summary of *sec*-butyl acetate. Rochester, NY, Eastman Kodak Company, Laboratory of Industrial Medicine (available from the National Technical Information Service, Springfield, VA. Order No. OTS00556683), 2970, cited in WHO 2005.

- Royal Decision (Koninklijk besluit) (2014). Revised version valid for after July 2014. In dutch. Koninklijk besluit van 11 maart 2002 betreffende de bescherming van de gezondheid en de veiligheid van de werknemers tegen de risico's van chemische agentia op het werk, Belgium, https://www.google.it/?gfe_rd=cr&ei=2v00Vb7xC6fD8ges7oHQAaw&gws_rd=ssl#q=Koninklijk+besluit+van+11+maart+2002+betreffende+de+bescherming+van+de+gezondheid+en+de+veiligheid+van+de+werknemers+tegen+de+risico%E2%80%99s+van+chemische+agentia+op+het+werk
- Safe Work Australia (2011). Workplace exposure standards for airborne contaminants date of effect: 22 December 2011, Australia, [http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace Exposure Standards for Airborne Contaminants.pdf](http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace%20Exposure%20Standards%20for%20Airborne%20Contaminants.pdf)
- Saillenfait AM, Gallissot F, Sabate JP, Bourges-Abella N, Muller S (2007). Developmental toxic effects of ethylbenzene or toluene alone and in combination with butyl acetate in rats after inhalation exposure. *J Appl Toxicol* 27:32-42.
- SCA, The Swedish Chemical Agency (2003). On *n*-Butyl acetate. Accessed October 2015. http://apps.kemi.se/flodessok/floden/kemamne_eng/n-butylacetat_eng.htm
- Schilling K, Kayser M, Deckardt K, Kuttler K, Klimisch H-J (1997). Subchronic toxicity studies of 3-methyl-1-butanol and 2-methyl-1-propanol in rats. *Human Exp Toxicol* 16:722-726.
- Schaper M (1993) Development of a database for sensory irritants and its use in establishing occupational limits. *Am Ind Hyg Assoc J* 54:488-544.
- Schneider W, Breuer D (2014). Solvent mixtures. Method number 2 (Lösemittelgemische; Air Monitoring Methods in German language). In: Parlar H, Hartwig A (eds), *Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 1, Luftanalysen*, 18. Lieferung, Wiley-VCH, Weinheim. <http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am01mix002d0018/pdf>
- SCOEL (2013). Recommendation from the Scientific Committee on Occupational Exposure Limits for *n*-Butyl acetate, *sec*-Butyl acetate and Isobutyl acetate. SCOEL/SUM/184
- Shell (1994). Toxicity studies of secondary butyl alcohol with cover letter dated 12/23/94. NTIS/OTS 0557575, EPA/OTS 8695000062, NTIS, Springfield, VA, cited in Greim 1999.
- Shimizu H, Suzuki Y, Takemura N, Goto S, Matsushita H (1985). The results of microbial mutation test for forty-three industrial chemicals. *Japanese J Ind Health* 27:400-419.
- Smyth HF, Carpenter CP, Weil CS, Pozzani UC, Striegel JA (1962). Range-finding toxicity data: List VI. *Ind Hyg J* 23:95-107.
- Smyth HF, Smyth HF (1928). Experiments with certain lacquer solvents. *J Ind Hyg* 10:261-271, cited in ACGIH 2001a.
- Spasovski M, Bencev I (1971). An exposure test for butyl acetate. *Trudove na Naucnoisledovateliskija Institu po Ohrana na Truda i Profesionalni Zaboljavanja* 20:235-242, cited in ACGIH 2001a.
- SUVA, Schweizerische Unfallversicherungsanstalt (2015). SUVA, Grenzwerte am Arbeitsplatz 2015. MAK-Werte, BAT-Werte, Grenzwerte für physikalische Einwirkungen, Switzerland, [https://extra.suva.ch/suva/b2c/b2c/start.do;jsessionid=1SNHbj-0PppEIAFvO7Ks0eUouc2-TQFykRoe_SAPdq5f-GW926vKwRXNGAkQrfkO;saplb_*= \(J2EE505057620\)505057650](https://extra.suva.ch/suva/b2c/b2c/start.do;jsessionid=1SNHbj-0PppEIAFvO7Ks0eUouc2-TQFykRoe_SAPdq5f-GW926vKwRXNGAkQrfkO;saplb_*= (J2EE505057620)505057650)

- SWEA, Swedish Work Environment Authority (2011). The Swedish Work Environment Authority's provisions and general recommendations on occupational exposure limit values, Swedish Work Environment Authority (SWEA), Sweden, <http://www.av.se/dokument/inenglish/legislations/eng1118.pdf>
- Teeguarden JG, Deisinger PJ, Poet TS, English JC, Faber WD, Barton HA, Corley RA, Clewell HJ (2005). Derivation of a human equivalent concentration for *n*-butanol using a physiologically based pharmacokinetic model for *n*-butyl acetate and metabolites *n*-butanol and *n*-butyric acid. *Toxicol Sci* 85:429-446.
- Traiger GJ, Bruckner JV, Jiang WD, Dietz FK, Cooke PH (1989). Effect of 2-butanol and 2-butanone on rat hepatic ultrastructure and drug metabolizing enzyme activity. *J Toxicol Environ Health* 28:235-248.
- TRL, Toxicity Research Laboratories (1987). Rat oral subchronic toxicity study final report. Compound: Isobutyl alcohol. Muskegon MI, Toxicity Research Laboratories, Ltd (TRL Study No. 032-002), cited in WHO 2005.
- Tschickardt M (2014). Solvent mixtures. Method number 6 (Lösemittelgemische; Air Monitoring Methods in German language). In: Parlar H, Hartwig A (eds), *Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 1, Luftanalysen*, 18. Lieferung, Wiley-VCH, Weinheim. <http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lmix006d0018/pdf>
- Ursin C, Hansen CM, van Dyk JW, Jensen PO, Christensen IJ, Ebbelhoej J (1995). Permeability of commercial solvents through living human skin. *Am Ind Hyg Assoc J* 56:651-660.
- von der Hude W, Behm C, Guertler R, Basler A (1988). Evaluation of the SOS chromotest. *Mutat Res* 203:81-94.
- von Oettingen WF (1960). The aliphatic acids and their esters: toxicity and potential dangers. *Arch Ind Health* 21:28-65, cited in ACGIH 2001b.
- WHO, World Health Organization (1987). Butanols - four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol, Environmental Health Criteria 65. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, cited in HCN 2001.
- WHO, World Health Organization (2005). Concise International Chemical Assessment Document No. 64. Butyl acetates. World Health Organization, Geneva.
- WIL Research Laboratories (2003). An inhalation two-generation reproductive toxicity study of isobutanol in rats. Sponsored by the Oxo-Process Panel of the American Chemistry Panel, Arlington, VA. Ashland, OH, WIL Research Laboratories (Study No. WIL-186013), cited in WHO 2005.
- Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen* 19 (Suppl. 21) :2-141.

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