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

Health-based recommended occupational exposure limit

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding adviezen over Chloortrimethylsilaan en Butylacetaten
Uw kenmerk : DGV/MBO/U-932542
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Mijnheer de Staatssecretaris,

Bij brief van 3 december 1993, nr. DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door de genoemde Minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Gezondheid en Omgeving - twee publicaties aan van de commissie over chloortrimethylsilaan en butylacetaten.
Deze publicaties heb ik heden ter kennisname aan de Minister van Volksgezondheid, Welzijn en Sport en aan de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer gestuurd.

Hoogachtend,
w.g.

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

Health-based recommended occupational exposure limit

report of the Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of The Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 2001/03OSH, The Hague, 15 November 2001

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature Preservation & Fisheries. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Samenvatting en advieswaarde

1 Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht op de werkplek waaraan beroepsmatige blootstelling kan plaatsvinden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden (MAC-waarden).

Bij de opstelling van haar advies heeft de commissie samengewerkt met de Swedish Criteria Group, een adviescommissie van de Zweedse regering.

In het voorliggende rapport bespreken de commissies de gevolgen van blootstelling aan n-, iso-, sec- en tert-butylacetaat in de lucht op de werkplek. De conclusies van de commissies zijn gebaseerd op wetenschappelijke publicaties die vóór januari 1997 zijn verschenen. Wetenschappelijke publicaties verschenen tussen 1997 en 2000 gaven de commissie geen aanleiding haar aanbevelingen te wijzigen.

2 Fysische en chemische eigenschappen

Butylacetaten zijn kleurloze, ontvlambare, naar fruit ruikende vloeistoffen. Ze zijn matig of niet oplosbaar in water en oplosbaar in ethanol en ether.

De butylacetaten komen van nature voor, maar worden ook gesynthetiseerd. Zij worden onder andere gebruikt in de voedingsindustrie als smaakstof, de cosmetische industrie, verf- en lakindustrie, voornamelijk als oplosmiddel.

3 Monitoring

Voor het meten van de concentratie van butylacetaten in de lucht op de werkplek is door het Amerikaanse NIOSH een methode beschreven die is gebaseerd op een gaschromatografische (GC-FID) analyse. Ook zijn methoden gerapporteerd die gebruik maken van persoonlijke bemonstering met diffusiebadges.

Er zijn geen methoden voor biologische monitoring beschikbaar.

4 Grenswaarden

In Nederland, Groot-Brittannië en de Verenigde Staten (ACGIH) is een grenswaarde vastgesteld van ongeveer 700 mg/m^3 (150 ppm) voor n- en isobutylacetaat, en van 950 mg/m^3 (200 ppm) voor sec- en tert-butylacetaat. Denemarken, Duitsland en Zweden hebben één grenswaarde voor alle isomeren, namelijk 710 mg/m^3 (150 ppm; Denemarken) en ± 500 mg/m^3 (100 ppm; Duitsland en Zweden).

5 Kinetiek

De commissies hebben geen kwantitatieve gegevens gevonden over de mate van opname van butylacetaten via longen en huid.

De door het lichaam opgenomen butylacetaten worden relatief snel afgebroken in azijnzuur en de respectievelijke butanolen. De halfwaardetijd, dat is de tijd die nodig is om de concentratie in het bloed te doen halveren, van n-butylacetaat is minder dan 1 minuut, terwijl van tert-butylacetaat het in de tientallen minuten loopt (tot 70 min) in ratten. Toevoeging aan bloedmonsters van mensen en ratten, leverde een halfwaardetijd op van resp. 4 en 12 minuten voor n-butylacetaat en van resp. 300 en 270 minuten voor tert-butylacetaat.

Butanolen worden in een aantal stappen enzymatisch door dehydrogenase enzymen afgebroken tot alcoholen of ketonen en uiteindelijk tot kooldioxide en zuren. tert-Butanol is een slecht substraat voor dehydrogenase enzymen en wordt daarom zeer langzaam afgebroken, in tegenstelling tot de andere butanolen.

Butylacetaten en hun afbraakproducten zijn aangetoond in de urine en in de uitademingslucht, hoewel geen gestandaardiseerde methoden voor biologische monitoring beschikbaar zijn.

6 Effecten

Studies waarin vrijwilligers gedurende vier uur werden blootgesteld aan concentraties van 700 mg/m^3 (150 ppm) n-butylacetaat, geven aan, dat de stof slechts in zeer geringe mate irriterend is voor de mens. Het zou in incidentele gevallen allergische contactdermatitis kunnen veroorzaken. Uit onderzoek met proefdieren kon geen irritatie in de huid of sensibilisatie worden vastgesteld na een blootstelling aan n-butylacetaat. n-Butylacetaat bleek op zijn hoogst in lichte mate oogirritatie te veroorzaken bij konijnen.

Isobutylacetaat heeft vermoedelijk geen sensibiliserende eigenschappen.

De commissies hebben geen onderzoeken gevonden waarin systemische effecten konden worden toegeschreven aan blootstelling aan butylacetaten in de mens.

De commissies zijn van mening, dat zowel n- als isobutylacetaat slechts in geringe mate toxisch is via de inhalatoire, orale of dermale route.

Korte blootstelling aan 3.700 tot 7.300 mg/m^3 n-butylacetaat gedurende 4 tot 6 uur resulteerde in reversibele effecten op ogen en gedrag in ratten.

Ratten blootgesteld aan maximaal 14.520 mg/m^3 n-butylacetaat gedurende 13 weken (6 uur/dag, 5 dagen/week) vertoonden na de blootstelling geen blijvende neurotoxische effecten. Blootstelling aan 7.260 mg/m^3 veroorzaakte groeivertraging, geringe reversibele afname in activiteit van het zenuwstelsel en als gering tot matig geclassificeerde necrose van het reukepitheel. Bij blootstelling aan 2.662 mg/m^3 werden geen effecten waargenomen.

De commissies hebben geen studies kunnen vinden waarin sprake was van langdurige blootstelling of van mogelijke kankerverwekkende eigenschappen van butylacetaten. n-Butylacetaat induceerde geen mutaties in bacteriën en gist en ook geen chromosoombreuken in celkweken van fibroblasten afkomstig van Chinese hamsters.

In een onderzoek waarin zwangere vrouwelijke ratten en konijnen werden blootgesteld aan 7.260 mg/m^3 n-butylacetaat volgens een aantal blootstellingsscenario's, werden in beide soorten effecten van minder belangrijke aard in de foeten alsmede in de moeders waargenomen. Aangezien slechts één concentratie werd getest zijn de commissies van mening, dat de resultaten van dit onderzoek ontoereikend zijn voor een conclusie over de reproductietoxiciteit als gevolg van blootstelling aan n-butylacetaat.

7 Evaluatie en advies

De Commissie WGD neemt het subchronisch onderzoek met ratten als uitgangspunt voor de afleiding van de gezondheidskundige advieswaarde. In dit onderzoek zijn acute, reversibele effecten op het zenuwstelsel en effecten op het lichaamsgewicht en het

reukepitheel gevonden na blootstelling aan 7.260 mg/m^3 (1.500 ppm) n-butylacetaat gedurende 13 weken. Aangezien bij blootstelling aan 2.662 mg/m^3 (550 ppm) deze effecten niet zijn waargenomen, beschouwt de Commissie WGD deze concentratie als een “geen-waargenomen-nadelig- effect-niveau” (NOAEL).

Voor het vaststellen van een gezondheidskundige advieswaarde wordt een factor 3 voor variatie tussen soorten, een factor 3 voor interindividuele verschillen en een factor 2 voor verschillen tussen de blootstellingsduur tussen het dierexperiment en beroepsmatige blootstellingsduur (subchronisch *vs* chronisch) in beschouwing genomen. Toepassing van al deze onzekerheidsfactoren en aannemende dat de dosis die de rat opneemt via inademing gelijk is aan de dosis die de mens opneemt, wordt een gezondheidskundige waarde van 150 mg/m^3 (≈30 ppm) aanbevolen. De Commissie WGD is van mening, dat deze limietwaarde bij werkers zowel systemische effecten als irritatie voorkomt.

De Commissie WGD vindt, dat de beschikbare gegevens ontoereikend zijn voor de afleiding van een gezondheidskundige advieswaarde voor iso-, sec- en tert-butylacetaat.

8 Gezondheidskundige advieswaarde

De Commissie WGD stelt een gezondheidskundige advieswaarde voor n-butylacetaat van 150 mg/m^3 (≈30 ppm) voor, gemiddeld over een achturige werkdag.

Voor de overige butylacetaten acht de Commissie WGD het niet mogelijk een advies af te geven. Als aanvulling hierop, vermoedt de commissie dat iso- en sec-butylacetaat een vergelijkbare toxiciteitsprofiel bezitten als n-butylacetaat. tert-Butylacetaat wordt echter langzamer afgebroken dan n-butylacetaat, wat kan resulteren in hogere concentraties in het lichaam. Volgens de commissie is het daarom niet uit te sluiten dat blootstelling aan tert-butylacetaat een hoger risico op gezondheidseffecten kan geven dan de andere butylacetaten.

Executive summary

1 Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure that leads to legally-binding limit values. Based on the consequences of occupational exposure to n-, iso-, sec-, and tert-butyl acetate the DECOS recommends a health-based occupational exposure limit.

The present report on n-, iso-, sec-, and tert-butyl acetate was prepared in co-operation with the Swedish Criteria Group, which advises the Swedish government. The committees' conclusions are based on scientific publications prior to January 1997. Scientific publications between 1997 and 2000 were no reason for both committees to adjust their conclusions.

2 Physical and chemical properties

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.

3 Monitoring

Methods for the determination of the butyl acetates have been described by the National Institute for Occupational Safety and Health (NIOSH, USA), and are based on gaschromatographic (GC-FID) analysis.

Methods for personal air sampling using diffusive samplers have also been reported.

4 Limit values

In The Netherlands and the UK, the current occupational exposure limits are 700 and 710 mg/m^3 (150 ppm) for n- and isobutyl acetate, respectively, and 950 mg/m^3 (200 ppm) for both sec- and tert-butyl acetate. In the USA, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended threshold limit values of 713 mg/m^3 (150 ppm) for n- butyl acetate, 152 mg/m^3 (50 ppm) for iso- butyl acetate, and 303 mg/m^3 (100 ppm) for both sec- and tert-butyl acetate. Scandinavian countries and Germany have one occupational exposure limit for all isomers varying from 355 mg/m^3 (75 ppm) in Norway to 950 mg/m^3 (200 ppm) in Germany.

5 Kinetics

The committees could not retrieve quantitative data on the absorption of butyl acetate isomers.

Butyl acetates are quickly metabolised in the body in acetic acid and their respective butanols. The half-life time for n-butyl acetate is less then 1 minute and for n-butanol a few minutes in rats, whereas the half-life time for tert-butyl acetate is much longer (up to 70 min). When added to blood samples from men and rats, half-life times measured were respectively 4 and 12 minutes for n-butyl acetate and respectively 300 and 270 minutes for tert-butyl acetate.

When rats were exposed to 34,000 mg/m^3 (7,000 ppm; 1 hour) or to 4,800 mg/m^3 (1,000 ppm; 5 hours) n-butyl acetate via a tracheal canula, a steady-state blood level of the compound and its metabolite (n-butanol) was rapidly reached. Similar experiments in rats with tert-butyl acetate showed continuously increasing blood levels of both the parent compound and the metabolite (tert-butanol). After ending exposure, tert-butyl acetate was eliminated in two phases ($t_{½}$ 5 and 70 min), while tert-butanol levels continued to increase or remained constant depending on exposure conditions.

Acetic acid is oxidised via the citric acid cycle to carbon dioxide and water. Generally, butanols are readily metabolised by alcohol and aldehyde dehydrogenases to their respective aldehydes or ketones, their acids, and finally to carbon dioxide. Only

tert-butanol is very slowly metabolised by dehydrogenases. Ethanol inhibits or retards butyl acetate metabolism.

The parent compounds and their metabolites were identified in urine and exhaled breath. However, no validated methods for biological monitoring are available.

6 Effects

Studies, in which volunteers were exposed for four hours to concentrations of 700 mg/m^3 (≈150 ppm), indicate that n-butyl acetate is only minimally irritating to humans. It may occasionally cause allergic contact dermatitis. Isobutyl acetate probably has no sensitising properties. In animal experiments, n-butyl acetate had no skin irritant properties and did not act a sensitiser. n-Butyl acetate appeared to be at most slightly irritating to the eyes of rabbits.

The committees could not find any case-control or epidemiological studies in which systemic effects could be attributed to exposure to butyl acetates.

Mortality data from animal experiments with acute inhalatory exposure to n-butyl acetate are conflicting. However, the committees consider n-butyl acetate, as well as isobutyl acetate, to be of low toxicity via the inhalatory, oral, and dermal route. Acute exposure to non-lethal n-butyl acetate levels of 3,700-7,300 mg/m^3 (800-1,575 ppm) for four to six hours resulted in transient effects on the eyes and behaviour.

Subchronic exposure to up to 14,520 mg/m^3 (3,000 ppm) n-butyl acetate for 13 weeks (6 hrs/day, 5 days/week) did not induce persistent neurotoxic effects in rats. Exposure to 7,260 mg/m^3 (1,500 ppm) caused growth retardation, minimal reduced activity on the nervous system, and minimal to mild olfactory epithelial necrosis. No effects were observed at 2,662 mg/m^3 (550 ppm).

The committees did not find long-term and carcinogenicity studies concerning butyl acetates. n-Butyl acetate did not induce mutations in bacteria and yeast nor showed clastogenic effects in Chinese hamster fibroblasts. With respect to the other isomers, the committees did not find data on genotoxicity.

In a study, in which pregnant female rats and rabbits were exposed to 7,260 mg/m^3 (1,500 ppm) n-butyl acetate according to a number of exposure schemes, minor developmental effects in the fetuses and minor reproductive effects in mothers were observed, in both species. Since only one concentration was tested, the committees consider these results to be inconclusive with respect to developmental toxicity induced by n-butyl acetate.

7 Evaluation and advice

DECOS takes the subchronic rat study as a starting point in deriving a health-based recommended occupational exposure limit (HBR-OEL). In this study, acute transient effects on the nervous system, effects on body weight and on the olfactory epithelium were found following exposure to n-butyl acetate concentrations of 7,260 mg/m^3 (1,500 ppm) for 13 weeks. No effects were observed at 2,662 mg/m^3 (550 ppm), which is considered to be a NOAEL.

For the assessment of a HBR-OEL, DECOS has taken the following considerations into account: a factor of 3 for intraspecies variation, a factor of 3 for interspecies variation, and a factor of 2 for the extrapolation from a subchronic to chronic situation. Application of this overall uncertainty factor of 18 and assuming that the dose inhaled by rats is equivalent to the dose inhaled by humans, a HBR-OEL of 150 mg/m^3 (≈30 ppm) for n-butyl acetate is recommended. This level is considered to protect workers against systemic effects and irritation.

DECOS considers the available data to be insufficient to recommend an HBR-OEL for iso-, sec- and tert-butyl acetates. As an aditional consideration, DECOS assumes that iso- and sec-butyl acetate show comparable toxicity as n-butyl acetate. Tert-butyl acetate is, however, broken down more slowly, which may lead to higher concentrations in the body and, therefore, may result in more hazardous effects.

8 Health-based recommende occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for n-butyl acetate of 150 mg/m^3, as an eight-hour time weighted average.

DECOS considers the available data to be insufficient to recommend an HBR-OEL for iso-, sec- and tert-butyl acetate.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (Annex A). The purpose of the committee's evaluation is to set a health-based recommended occupational exposure limit for the atmospheric concentration of the substance, provided the database allows the derivation of such a value.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister on the feasibility of using the health-based limits as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure, the Minister of Social Affairs and Employment sets the legally-binding OEL.

1.2 Committees and procedure

This document is a co-production of DECOS and the Swedish Criteria Group (SCG) at the Swedish National Institute of Occupational Health. It is a result of an agreement between both groups to prepare jointly criteria documents which can be used by the regulatory authorities in the Netherlands and in Sweden. The members of DECOS and

SCG are listed in Annex B. The first draft document has been prepared by H Stouten and W Bogaerts, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, Zeist, the Netherlands, and was first reviewed by DECOS, hereafter called the committee, and thereafter by SCG.

In 1997, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commended on the draft are listed in Annex C. DECOS has taken these comments into account in deciding on the final version of the report.

1.3 Data

For preparing the present document a number of review articles were used:

- Bisesi MS. Esters. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. 4th ed. New York: J. Wiley & Sons, 1994: 2967-3118 (Toxicology; Vol IID) (Bis94).
- Opdyke DLJ. Monographs on fragrance raw materials. Isobutyl acetate. Food Cosmet Toxicol 1978; 16: 795-6 (Opd78).
- Opdyke DLJ. Monographs on fragrance raw materials. Butyl acetate. Food Cosmet Toxicol 1979; 17: 515-9 (Opd79).
- Syracuse Research Corp: Center for Chemical Hazard Assessment. Information profiles on potential occupational hazards. Volume 1. Single chemicals. n-Butyl acetate. Springfield VA, USA: National Technical Information Service, 1979; rep no PB81-147993 (Syr79).
- Toy NJ. Final report on the safety assessment of ethyl acetate and butyl acetate. J Am Coll Toxicol 1989; 8: 681-705 (Toy89)
- Zaleski J. Butyl acetates. In: Thurman RG, Kaufman FC, eds. Ethel Browning's toxicity and metabolism of industrial solvents. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers BV, 1992: 247-55 (Alcohols and ethers; Vol 3) (Zal92).

In addition, literature was retrieved from the on-line databases 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.

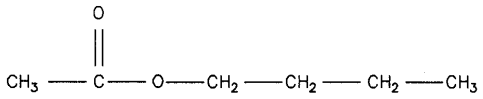
Before finalising the document, the committee performed an additional literature search in Medline (January 1995-November 2000) and Toxline (January 1995-September 2000). Where relevant, these additional data are incorporated in the text. The results of this search were no reason for the committee to adjust the recommendations made in the draft report published in 1997.

Chapter **2**

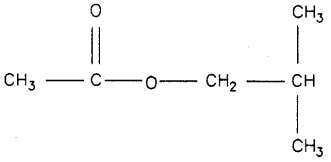
Identity, properties, and monitoring

2.1 Identity

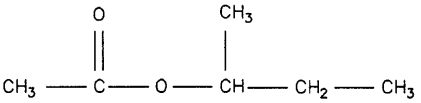
2.1.1 Structures



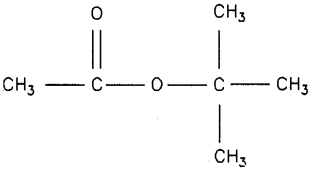
n-butyl acetate



isobutyl acetate



sec-butyl acetate



tert-butyl acetate

2.1.2 Chemical identity (Stu97, Zal92)

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-dimethylethyl 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 (NLM96, Stu97, Zal92)

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 (20 °C, 101.3 kPa)	1 ppm = 4.83 mg/m^3 1 mg/m^3 = 0.207 ppm[a]

[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) (Kru88), 0.92 (Dev90), and 1.88 mg/m^3 (Amo83) (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 (20ºC/4ºC)	0.9
vapour pressure (20ºC)	1.07 kPa
vapour density (air=1)	4.0
relative density of saturated vapour/air mixture (air=1; 20ºC)	1.03
flash point	closed cup: 24 °C; open cup: 37 °C
explosive limits, vol% in air	1.2-7.5
solubility in water (20ºC)	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 (20ºC/4ºC)	0.9
vapour pressure (20ºC)	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	1.1
vapour/air mixture (air=1; 20ºC)	
flash pointclosed 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	solvents soluble in ethanol, ether
partition coefficient log K_{ow}	1.38

2.3 EU Classification and labelling (Ano00)

According to the 25th Amendment of Annex 1 of Directive 67/548/EEC, n-butyl acetate is classified as “flammable”, “repeated exposure may 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 (appropiate wording to be specified by the manufacturer

2.4 Validated analytical methods

2.4.1 Environmental monitoring

NIOSH methods are available for measuring the respective butyl acetates (Ell84). 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 (DeB87, Gen87, Kri87, Sal87).

Butyl acetates can be determined by infrared and UV spectroscopy, gas chromatography, gas chromatography/mass spectrometry, and headspace gas chromatography (Toy89, Wel89).

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 (Düb89).

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 (Fra88, Spi82, Str92, Ueh87).

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

Chapter 3

Sources

3.1 Natural occurrence

The n-butyl, isobutyl, and tert-butyl acetates occur naturally among other esters in bananas and related fruits (Bis94). 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 (Maa89). Isobutyl acetate occurs in natural products such as raspberries, pears, pineapples and natural cocoa aroma (Opd78), black currants, guava, grapes, melons, peaches, strawberries, tomatoes, soy beans, plums, passion fruit, star fruit and dill herb (Maa89).

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 (Zal92).

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 (Zal92).

tert-Butyl acetate is only slowly and incompletely formed from its alcohol and acetic acid; it is mainly produced from acetic acid and isobutylene (Zal92).

Technical grades of butyl acetates contain butyl alcohol as an impurity; small amounts of water may also be present (Syr79). 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 (Zal92).

In cosmetic grade butyl acetate, lesser amounts of n-butyl alcohol, isobutyl alcohol and traces of n-propyl acetate and isobutyl acetate are present (Toy89).

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 tonnes of n-butyl acetate and 1,275 tonnes of isobutyl acetate in 1979 (Doo86).

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 (Zal92). 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 (Toy89);
- the food industry as a component in synthetic flavours, as a component used in articles used for food packaging, and also as a dilutent for dyes in inks for marking vegetables and fruits (Zal92);
- the production of artificial leather, shoe and leather glues, photographic films, plastics, and safety glass (Zal92);
- the pharmaceutical industry as an extractant (Zal92).

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 (Zal92).

Chapter **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 (Ber93).

In a German field study, in selected representative households, low levels of n-butyl acetate were found (n.d.-23 µg/m^3). In winter, the total concentration of volatile organic compounds was 2-3 times higher than during summer (Sei89).

In a Swiss study of new and recently renovated buildings, a concentration of 549 µg/m^3 was measured. Butyl acetate was found to be offgassed from a sealing wax on a cork floor (Rot92).

Concentrations of 0.1 and 4.8 µg/m^3 emanating from US industrial and chemical waste disposal sites have been reported (Pel82).

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 (Ber93). 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 (Maa89).

sec-Butyl acetate was found in vinegar at concentrations of 43-67 mg/kg (Maa89).

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% (Wil95).

Table 1 Occupational air levels (personal air sampling).

work	isomer	mean concentration in mg/m^3 (ppm)	concentration range in mg/m^3	reference
paint industry	n-butyl acetate	-	13, 17[a]	Pet87
paint industry	n-butyl acetate	9.7 (2.0)	0-200	Wan93
paint industry	n-butyl acetate	9 (1.9)[b]	1-1680	Lun85
paint industry	n-butyl acetate		up to 330	
	isobutyl acetate		up to 110	Bel82
glue manufacture	n-butyl acetate		up to 17	Wal84
painter's workplace	isobutyl acetate	-	4-58	Doo86
lacquering furniture	n-butyl acetate	—	0.3-120	
	isobutyl acetate		0.2-486	Doo86
lacquering brushes (dipping)	n-butyl acetate	-	4-50	Doo86
indoor painting (brushing, rolling)	butyl acetate	-	2-6	Sch85
indoor painting (rolling water-based paint)	butyl acetate	0.006 (0.001)	up to 0.030	Nor95
spray painting	butyl acetate	-	54, 65[c]	Sch85
spray painting	butyl acetate	-	22.3-76.5	Tri91
spray painting	butyl acetate	33 (6.8)	up to 629	Kur82
spray painting	butyl acetate	9 (1.9)	-	Ale88
spray painting	n-butyl acetate	19 (3.9)	5.2-48.3	Wil95
spray painting	n-butyl acetate	-	16.5-180	
	isobutyl acetate	-	37.6-134.0	DeM88
spray painting	butyl acetate	11.7 (2.4)	2-23	Win92
fingernail sculptors	butyl acetate	1.9±2.4 (0.4±0.5)	< 0.5-11.2	Hii87
screen printers:	butyl acetate			Sam82
- 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.

Chapter 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 (Kan94). Some rat tissue/blood partition coefficients for these acetates are presented in Table 2.

Table 2 Some rat tissue/blood partition coefficients for n-butyl and isobutyl acetate[a] (Kan94).

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)

When a single dose of ^{14}C-labelled n-butyl acetate (in 0.9% NaCl) of ≈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 ($t_{½}$ 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 ($t_{½}$ ≈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 (Dei97).

Nembutal-anaesthetised rats were exposed for one hour to 33,880 mg/m^3 of n-butyl acetate via a tracheal canula. 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 (Ess89).

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 (Gro91). 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 (Ess89). 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 experiment. During exposure to 4,356 mg/m^3 for 4¼ 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 (Gro94).

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 (Dah87, Lon77). 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 (Dei97). *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 (Ess89).

The acetic acid is oxidised via the citric acid cycle to carbon dioxide and water. Iso-butanol 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 (WHO87).

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 (WHO87).

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 (WHO87).

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 (Gro91).

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 (Iva78).

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 (Pen95).

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) (Pen95).

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 (Ano92).

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 ($t_{½}$ 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 ($t_{½}$ approx. 1 min).

When rats were exposed to n-butyl acetate via a tracheal canula 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 ($t_{½}$: 3 and 4-12 min, respectively). Biotransformation of tert-butyl acetate *in vitro* is far more slowly ($t_{½}$: 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.

Chapter 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) (Nel43). 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.* (1993). 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 (Ire93).

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 encephalopathy experienced significantly more irritation than the control group (Ørb98). 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) (Toy89).

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) (Roe80). The committee assumes that with butyl acetate is mentioned 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 by Opd78).

sec-Butyl acetate, tert-butyl acetate.

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 hypersensitivity 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 Ørb98, 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 (Öst00).

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 (Smy54). 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) (BRR87, Mye92).

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 (Say36). 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 (Ano92). 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 (Smy54).

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; ECE92). 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 (BRR87, Mye92). 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) (Ken89).

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 (Gad86).

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; Mul84; see also Bos92). 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 (Kor94).

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; Shu96; Ano96).

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) (Smy62). 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 by Opd78).

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) (Smy62).

With respect to respiratory tract irritation, an RD_{50} of 3,890 mg/m^3 (≈ 800 ppm) has been found in mice (see also n-butyl acetate; Mul84; see also Bos92).

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. Edema was absent at all observation intervals. No ulceration, necrosis, or any other evidence of tissue destruction was seen at any of the observation intervals (DeG97a).

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 (DeG97b). 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 (Kay53).

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 (Hof97).

With respect to tert-butyl acetate, only one study on respiratory tract irritation has been found. The RD_{50} was ≈76,000 mg/m^3 (≈15,750 ppm) (see also n-butyl acetate; Mul84; see also Bos92).

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 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 (Deb86), 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 Nor97). 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.* (1997) could not find explanations for inconsistent results from exposure to earosolised n-butyl acetate.

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	Deb86
	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	Nac87
	29,200 mg/m^3	4 h	0/10 dead	(n=5/sex) whole body; dynamic inhalation system;	
	13,890 mg/m^3	4 h	0/10 dead	evaporation	
	9,345 mg/m^3	4 h	0/10 dead	LC_{50} >32,000 mg/m^3	
rat	1,305 mg/m^3	4 h	0/10 dead	(n=5/sex/group) whole body; dynamic inhalation system;	Nac87
	2,490 mg/m^3	4 h	10/10 dead	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	BAS88a
rat	21,395 mg/m^3	4 h	0/10 dead	head-nose only; dynamic inhal. system; atomiser	BAS88b
rat	2,005 mg/m^3	4 h	0/10 dead	head-nose only; dynamic inhal. system; atomiser	BAS88c
	21,395 mg/m^3	4 h	0/10 dead		
rat	21,395 mg/m^3	4 h	0/10 dead	head-nose only; dynamic inhal. system; evaporation	BAS88d
rat	3,990 mg/m^3	4 h	3/10 dead	(n=5/sex/group) whole body; dynamic inhalation system;	Nac93
	5,730 mg/m^3	4 h	5/10 dead	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; dynamic inhal. system;	Nac94
	6,505 mg/m^3	4 h	0/10 dead	different atomisers under varying conditions (pressure,	
	6,650 mg/m^3	4 h	0/10 dead	humidity) testing new and old (latter two data)	
	6,995 mg/m^3	4 h	0/10 dead	production material	
	7,260 mg/m^3	4 h	0/10 dead	LC_{50} >42,930 mg/m^3	
	23,430 mg/m^3	4 h	0/10 dead		
	42,930 mg/m^3	4 h	0/10 dead		
	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}	NIO96
mouse	6,000 mg/m^3	2 h		LC_{50}	NIO96
guinea pig	16,000 mg/m^3	5 min	irritation		Say36
		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		

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, discolouration 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 (Nac87, Nac93). Discolouration 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 (Nac94).

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 (Ber94).

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 (Kor94).

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	reference
rat, male	14.5 mL/kg bw	oral	LD_{50}	BRR87, Mye92
rat, female	12.2 mL/kg bw	oral	LD_{50}	BRR87, Mye92
rat	14.1 g/kg bw	oral	increase in serum ornithine	Smy54
mouse	7.1 g/kg bw	oral	LD_{50}	NIO96
mouse	1.2 g/kg bw	ip	LD_{50}	NIO96
rabbit	2.2 g/kg bw	oral	ND_{50} [a]	Mun72
rabbit	7.7 g/kg bw	oral	LD_{50}	Mun72
rabbit, male and female	16.0 mL/kg bw	dermal	no deaths	BRR87, Mye92
guinea pig	1 mL/3.1 cm^2	dermal	no pathological changes in the skin. No alterations in morphology of liver and kidneys.	Kro79
guinea pig	1.5 g/kg bw	ip	LD_{50}	DiV74
guinea pig	750 mg/kg bw	ip	carbamyl transferase activity	DiV74

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

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.

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	Smy62
rat	14.0 g/m^3	6 h	inhalation	No toxicity symptoms	Bis94
	100.0 g/m^3	2.5 h	inhalation	LD_{100}	Bis94
rat	13.4 g/kg bw	-	oral	LD_{50}	Smy62
rat	15.0 g/kg bw	-	oral	LD_{50}	Smy62
rabbit	4.3 g/kg bw	-	oral	ND_{50} [a]	Mun72
rabbit	4.8 g/kg bw	-	oral	LD_{50}	NIO96
rabbit	>20.0 g/kg bw	-	dermal	LD_{50}	NIO96

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

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) (Rou70).

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. Postmortem examination showed some evidence of pulmonary congestion and haemorrhage only (observation time 14 days) (Kay53). 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) (Ben97).

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 (DeG97c). 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 (±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) (Kay53).

An oral LD_{50} of 3.8 mL/kg bw (±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) (Kay53). 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 (DeG97d).

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 (Ano92).

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 (Ano92).

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 ± 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 (Ber95).

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 discolouration 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 microscopical 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 (Ber96a).

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 wk 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 postexposure 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 wk 6 onwards (overall decrease 9%). Mean body weight gain was affected occasionally (male, wk 9, 14; female, wk 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 (Ber96b; see also Dav98).

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.

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.

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	-/-	Zei92
TA100/-1535/-1537/-98/-1538	gene mutation	1- 5,000 µg/plate	-/-	Shi85
TA100/-1535/-1537/-98/-94/-92	gene mutation	up to 10,000 µg/plate	-/-	Ish84
E.coli WP2 uvrA	gene mutation	1- 5,000 µg/plate	-/-	Shi85
S.cerevisiae D61.M	mitotic aneuploidy	0.25-0.4%	-/nt	Zim85
Chinese hamster fibroblasts	chrom. abberations polyploidy	up to 2,000 µg/plate	-/nt	Ish84

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

6.2.6 *Reproduction toxicity*

The reproduction toxicity of n-butyl acetate has been evaluated in rats and rabbits (Hac83). 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 (Hac83).

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

Human data

n-Butyl acetate is only minimally irritating to the eyes and respiratory tract of volunteers exposed to 700 mg/m^3 (≈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.

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 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 ≈3,700-7,300 mg/m^3 (≈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 ≈14,520 mg/m^3 (3,000 ppm) n-butyl acetate did not induce persistent neurotoxic effects in rats. Exposure to ≈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 ≈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 tertbutyl acetate are lacking.

Chapter 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 (CEG93).

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 (Opd78, Opd79). However, according to a recent publication by FAO/WHO, no ADI has been allocated and no toxicological monograph has been prepared (FAO94). 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.

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

country	isomer	level		time	remark	reference[a]
		mg/m^3	ppm	TWA		
The Netherlands	n-	710	150	8 h	administrative	SZW99
	iso-	700	150	8 h	force	
	sec-, tert-	950	200	8 h		
Germany						
- AGS	all	950	200	8 h		Bun00
		950	200	15 min		
- DFG MAK-kom.	n-, iso-	480	100	8 h	[e]	DFG00
		960	200	15 min[b]		
	sec-	[c]				
	tert-	96	20	8 h	[e]	
		480	100	30 min[d]		
Sweden	all	500	100	8 h		Arb00
		700	150	15 min		
Denmark	all	710	150	8 h		Arb96
UK						
- HSE	n-	724	150	8 h	OES	HSE00
		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. -SCOEL		-	-			Hun97
USA						
- ACGIH	n-	-	150	8 h	TLV	ACG00
		-	200	15 min	STEL	
	iso-	-	150	8 h	TLV	
	sec-, tert-	-	200	8 h	TLV	
- OSHA	n-	710	150	8 h	PEL	ACG99b
	iso-	700	150	8 h	PEL	
	sec-, tert-	950	200	8 h	PEL	
- NIOSH	n-	710	150	10 h	REL	ACG99b
		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 compounf for which there is no reason to fear a risk of damage to the developing embryo or fetus when the OEL is observed.

ACGIH (USA)

ACGIH stated that the marked toxicity of the atomised n-butyl acetate observed in animal bioassays (i.e. an LC_{50} of ≈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 ≈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.* (NeI43) and Iregren *et al.* (Ire93) in volunteers exposed at ≈965 to 1425 mg/m^3 for 3 to 20 minutes, and a STEL of ≈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 (ACG99a).

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 ≈725 mg/m^3 (150 ppm) was recommended to minimise the potential for ocular and respiratory tract irritation (ACG91c).

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 (ACG91a; ACG91b).

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 (Gre99).

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 (Gre99).

Because of lack of data on local and systemic effects of sec-butyl acetate as weIl 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 (Gre99).

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 (Gre99).

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 ≈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 (Toy89).

Chapter **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 (Hea94).

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

* For the recommendation of a HBR-OEL only DECOS takes responsibility. The mandate of the SCG does not include recommending a HBR-OEL.

difference in methods of generating atmospheres (i.e. evaporation *vs* atomisation, or vapours *vs* aerosols; Ano92), 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; Nac94), 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 (Ber94, Hac83), 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 ≈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 (Ber96a and b). 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 (Ber96a), the committees derived a NOAEL of 2,662 mg/m^3 (550 ppm).

DECOS takes this NOAEL as a starting point in deriving a health-based recommended occupational exposure limit (HBR-OEL).

For the assessment of a HBR-OEL, in general the following considerations should be taken into account; intra- and interspecies variation, differences between experimental conditions and the exposure pattern of the worker, type of critical effect(s), dose-response curve, and the confidence of the data base. Concerning n-butyl acetate, next considerations were taken into account by the DECOS: a factor of 3 for intraspecies differences, a factor of 3 for interspecies variation, and a factor of 2 for the extrapolation of a subchronic to a chronic situation. Taken all these factors together, an overall uncertainty factor of 18 is used. Application of this overall factor and assuming that the dose inhaled by rats is equivalent to the dose inhaled by humans, a HBR-OEL of 150 mg/m^3 (≈30 ppm) for n-butyl acetate is recommended by the DECOS.

Limiting exposure of workers to levels equal or below this value is considered by DECOS to protect workers against systemic effects and irritation induced by n-butyl acetate exposure.

Isobutyl acetate, sec-butyl acetate, tert-butyl acetate

Insufficient data are available to establish a HBR-OEL for iso-, sec-, and tert-butyl acetate.

8.2 Groups at extra risk

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

8.3 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for n-butyl acetate of 150 mg/m^3 (≈30 ppm), as an eight-hour time weighted average concentration.

The committee was not able to determine a HBR-OEL for isobutyl acetate, sec-butyl acetate, and tert-butyl acetate.

8.4 Additional consideration

The committee assumes that iso- and sec-butyl acetate show comparable toxicity as n-butyl acetate. Tert-butyl acetate is, however, broken down more slowly, which may lead to higher concentrations in the body and, therefore, may result in more hazardous effects.

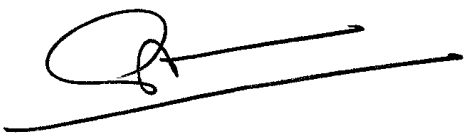
Chapter **9**

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.

The Hague, 15 November 2001,
for the committee,



dr JM Rijnkels,
scientific secretary

Prof. dr GJ Mulder,
chairman

References

ACG91a American Conference of Governmental Industrial Hygienists (ACGIH). sec-Butyl acetate. In: Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati OH, USA: ACGIH, 1991: 166.

ACG91b American Conference of Governmental Industrial Hygienists (ACGIH). tert-Butyl acetate. In: Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati OH, USA: ACGIH, 1991: 167.

ACG91c American Conference of Governmental Industrial Hygienists (ACGIH). Isobutyl acetate. In: Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati OH, USA: ACGIH, 1991: 814.

ACG99a American Conference of Governmental Industrial Hygienists (ACGIH). In:TLVs® and other occupational exposure values -1999. [CD-ROM]. Cincinnati OH, USA; ACGIH, 1999.

ACG99b American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values -1999. Cincinnati OH, USA: ACGIH, 1999: 16, 67.

ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). TLVs® and BELs®. Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati OH, USA; ACGIH, 2000: 21, 43.

Ale88 Alexandersson R, Hedenstierna G. Respiratory hazards associated with exposure to formaldehyde and solvents in acid-curing paints. Arch Environ Health 1988; 43: 222-7.

Amo83 Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol1983; 3: 272-90.

Ano92 Anonymus. Notice of intended changes - n-butyl acetate and formaldehyde. Appl Occup Environ Hyg 1992; 7: 846-51.

Ano96 Anonymus. Shell Chemical reports “surprising” results of n-butyl acetate tests. Pestic Toxic Chem News 1996; 24 (no 25; Apr 17): 16.

Ano00 Anonymus. EG-etiket, EU rectificatie 25e aanpassing. [CD-ROM]. The Hague, the Netherlands: ten Hagen & Stam, 2000.

Arb96 Arbejdstilsynet. Exposure limit value for substances and materials. Copenhagen, Denmark: Arbejd-stilsynet, 1996: 12 (Instruction no. 3.1.0.2).

Arb00 Arbetarskyddsstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: Arbetarskyddsstyrelsen, 2000: 64 (Ordinance AFS 2000:3).

BAS88a BASF AG/NOTOX C. v.. Acute inhalation toxicity study of n-butyl acetate in the rat. ‘s Hertogenbosch, the Netherlands: NOTOX C.V., 1988; ref no 0849/153 (cited from Nor97).

BAS88b BASF AG. Study on the acute inhalation toxicity LC_{50} of n-butyl acetate in rats 4-hour exposure. Ludwigshafen, FRG: BASF AG, Abteilung Toxikologie, 1988; proj no 1310001/887001 (cited from Nor97).

BAS88c BASF AG. Study on the acute inhalation toxicity LC_{50} of n-butyl acetate as a liquid aerosol in rats 4-hour exposure. Ludwigshafen, FRG: BASF AG, Abteilung Toxikologie, 1988; proj no 1310535/887063 (cited from Nor97).

BAS88d BASF AG. Study on the acute inhalation toxocity LC_{50} of n-butyl acetate as a vapor in rats 4-hour exposure. Ludwigshafen, FRG: BASF AG, Abteilung Toxikologie, 1988; proj no 1310535/887044 (cited from Nor97).

Bel82 van der Belt R, Ebens R, Hoogeveen AW, *et al.* Onderzoek naar de gezondheidsrisico’s van beroepsmatige blootstelling in de verfindustrie. Delft, The Netherlands: IMG-TNO, 1982; Deelrapport E, Omgevings-metingen, Bijlage 1.

Ben97 Bennick JE. Acute inhalation toxicity study in rats. Sugar land TX, USA: Stillmeadow, Inc, 1997; Stillmeadow, Inc study no: 3639-97 (available from the National Technical Information Service, Springfield VA, USA; order no: OTSO0573684-1).

Ber93 Berdowski JJM, Jonker WJ. Industriële emissies in Nederland. Bedrijfsgroepen, individuele stoffen en verdeling over regio’s. Vijfde inventarisatieronde - 1990. The Hague, The Netherlands: Ministry of Housing, Physical Planning and Environment, 1993: 106, 118 (Publikatiereeks Emissieregistratie nr 14).

Ber94 Bernard LG, David RM. n-Butyl acetate. An acute inhalation toxicity study in the rat. HAEL No. 93-0305, KAN 900710 CAS, No 000123-86-4. Final Report. Rochester NY, USA: Eastman Kodak Company, Corporate Health and Environmental Laboratories, Toxicologal Sciences Laboratories, 1994 (lab proj id 93-030512) (by courtesy of the Manager of the Oxo Process Panel of the Chemical Manufacturers Association, Washington DC, USA).

Ber95 Bernard LG, David RM. n-Butyl acetate. A two-week inhalation probe study. HAEL No. 94-0305, KAN 900710, Cas No. 000123-86-4. Final Report. Rochester NY, USA: Eastman Kodak Company, Corporate Health and Environmental Laboratories, Toxicologal Sciences Laboratories, 1995 (lab proj id: 94030513) (available from the National Technical Information Service, Springfield VA, USA; order no: OTSO0558851).

Ber96a Bernard LG, David RM. n-Butyl acetate. A thirteen-week subchronic inhalation toxicity study in the rat. HAEL No. 94-0305, KAN 900710, Cas No. 000123-86-4. Final Report. Rochester NY, USA: Eastman Kodak Company, Corporate Health and Environmental Laboratories, Toxicologal Sciences Laboratories, 1996 (lab proj id: 94030517) (available from the National Technical Information Service, Springfield VA, USA; order no: OTS00558876).

Ber96b Bernard LG, David RM, Hosenfeld RS. n-Butyl acetate. A thirteen-week subchronic inhalation neurotoxicity study in the rat. HAEL No. 93-0305 and 94-0306, KAN 900710, CAS No 000123-86-4. Final Report. Rochester NY, USA: Eastman Kodak Company, Corporate Health and Environmental Laboratories, Toxicologal Sciences Laboratories, 1996 (lab proj id 93-030515).

Bis94 Bisesi MS. Esters. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. 4th ed. New York: J. Wiley & Sons, 1994: 2967-3118 (Toxicology; Vol IID).

Bos92 Bos PMJ, Zwart A, Reuzel PGJ. Evaluation of the sensory irritation test for the assessment of occupational health risk. CRC Crit Rev Toxicol 1992; 21: 423-50.

BRR87 Bushy Run Research Center (BRRC). n-Butyl acetate: acute vapor inhalation toxicity test in rats. Export PA, USA: BRRC, 1987; proj rep 50-116 (by courtesy of the Manager of the CMA Oxo Process Panel Washington DC, USA).

Bun00 Bundesministerium für Arbeit und Sozialordnung. Grenzwerte in derluft am Arbeitsplatz; Technische Regeln für Gefahrstoffe;TRGS900. FRG: Verlag W. Kolharnmer, 2000; Bundesarbeitsblatt 2/2000.

CEG93 Commissie van de Europese Gemeenschappen (CEG). In: Bijlage bij Richtlijn 93/72/EEG van de Commissie van 1 september tot negentiende aanpassing aan de vooruitgang van de techniek van Richtlijn 67/543/EEG van de Raad betreffende de aanpassing van de wettelijke en bestuursrechtelijke bepalingen inzake de indeling, de verpakking en het kenmerken van gevaarlijke stoffen (vervolg). Maastricht, The Netherlands: Ellis Publications, 1993: 843-4 (Publicatieblad van de Europese Gemeenschappen L258A, deel II).

Dah87 Dahl AR, Miller SC, Petridou-Fischer J. Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. Toxicol Lett 1987; 36: 129-36.

Dav98 David RM, Tyler TR, Ouellette R, *et. al.* Evaluation of subchronic neurotoxicity of n-butyl acetate vapor. Neurotoxicology 1998; 19: 809-22.

Deb86 Debets FMH. Evaluation of the acute inhalation toxicity study of T-3916 in the rat. 's Hertogenbosch, The Netherlands: NOTOX C.V., 1986 (by courtesy of REN Bradfield, 3M, Bracknell (Berkshire) England).

DeB87 De Bortoli M, Mølhave L, Ullrich D. European interlaboratory comparison of passive samplers for organic vapour monitoring in indoor air. In: Commission of the European Communities, ed. Diffusive sampling: an alternative approach to workplace air monitoring. Luxemburg: Office for official publications of the European Communities, 1987: 238-41 (pub no EUR 10555).

DeG97a DeGeorge G. Primary dermal irritation in rabbits. Spinnerstown PA, USA; MB Research Laboratories, Inc, 1997; MB res proj no: MB 97-6119.03 (available from the National Technical Information Service, Springfield VA, USA; order no; OTSO0573684-1).

DeG97b DeGeorge G. Primary eye irritation/corrosion in rabbits. Spinnerstown PA, USA: MB Research Laboratories, Inc, 1997; MB res proj no: MB 97-6119.04 (available from the National Technical Information Service, Springfield VA, USA; order no: OTS00573684-1).

DeG97c DeGeorge G. Acute dermal toxicity in rabbits/LD_{50} in rabbits. Spinnerstown PA, USA: MB Research Laboratories, Inc, 1997; MB res proj no: MB 97-6119.02 (available from the National Technical Information Service, Springfield VA, USA; order no: OTSO0573684-1).

DeG97d DeGeorge G. Single dose oral toxicity in rats/LD_{50} in rats. Spinnerstown PA, USA: MB Research Laboratories, Inc, 1997; MB res proj no: MB 97-6119.01 (available from the National Technical Information Service, Springfield VA, USA; order no: OTSO0573684-1).

Dei97 Deisinger PJ, English JC. The in vivo pharmacokinetics of n-butyl acetate in rats after intravenous administration. HAEL No 94-0306, CAS No 00123-86-4, KAN 900710. Final report. Rochester NY, USA: Eastman Kodak Company, Corporate Health and Environmental Laboratories, Toxicologal Sciences Laboratories, 1997; lab proj id 94-0306BT01 (only abstract available from Documents Express, Washington DC, USA; see also Pestic Toxic Chem News 1997; 25 (no 15; Feb 5): 6).

DeM88 De Medinilla J, Espigares M. Contamination by organic solvents in auto paint shops. Ann Occup Hyg 1988; 32: 509-13.

Dev90 Devos M, Patte F, Rouault J, *et al.* Standardized human olfactory thresholds. Zeist, the Netherlands; TNO Nutrition and Food Research, 1990; TNO rep no; 2639-A.

DFG00 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 2000. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: Wiley-VCH, 2000; 33-4 (Mitteilung 36).

DiV74 DiVincenzo GD, Karsavage WJ. Serum ornithine carbamyl transferase as a liver response test to organic solvents. Am Ind Hyg Ass J 1974; 35: 21-9.

Doo86 Doorgeest T, Meijer PB, De Mik G. Chronische effecten tengevolge van blootstelling aan organische oplosmiddelen. Voorburg, The Netherlands: Directorate General of Labour, Ministery of Social Affairs and Employment, 1986; rep no S 29-1.

Düb89 Düblin T, Thöne HJ. Quantitative analyses of organic multicomponent mixtures of gases and vapors in industrial air emissions by IR-spectroscopy. Fresenius Z Anal Chem 1989; 335: 279-85.

ECE92 European Chemical Industry Ecology & Toxicology Centre (ECETOC). Eye irritation: reference chemicals databank. Brussels, Belgium: ECETOC, 1992: A9-10 (Technical Report no 48).

Ell84 Eller PM, ed. NIOSH manual of analytical methods. 3rd ed. Cincinnati OH, USA: DHHS/ NIOSH, 1984; pub no 84-100 (Vol 2).

Ess89 Essig KM, Groth G, Freundt KJ. Different elimination of n-butyl acetate and t-butyl acetate. Arch Pharmacol 1989; suppl 340: R33 (abstr no 87).

FAO94 Food and Agriculture Organization/World Health Organization (FAO/WHO): Joint FAO/WHO Expert Committee on Food Additives (JECFA). Buthyl acetate. In: Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1956-1993 (first through forty-first meetings). USA: ILSI Press, 1994: B-12.

Fra88 Franke JP, Wijsbeek J, De Zeeuw RA, *et al.* Systematic analysis of solvents and other volatile substances by gas chromatography. J Anal Toxicol 1988; 12: 20-4.

Gad86 ad SC, Dunn BJ, Dobbs DW, *et al.* Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol Appl Pharmacol 1986; 84, 93-114.

Gen87 entry SJ, Walsh PT. Eight-hour TWA personal monitoring using a diffusive sampler and short-term stain tube. Am Ind Hyg Assoc J 1987; 43: 287-92.

Gre99 Greim H, ed. 1-Butylacetat. iso-Butylacetat. 2-Butylacetat. tert-Butylacetat. In: Gesundheitsschädliche Arbeitsstoffe. Toxikologisch- arbeitsmedizische Begründungen von MAK-Werten (Maximale Arbeitsplatzkonzentrationen). Ist- 29th ed. Weinhem, FRG: Wiley-VCH, 1999.

Gro91 Groth G, Freundt KJ. Blutalkohol unter Anwesenheit von n-Butylacetat. Blutalkohol. 1991; 28: 166-73.

Gro94 Groth G, Freundt KJ. Inhaled tert-butyl acetate and its metabolite tert-butyl alcohol accumulate in the blood during exposure. Hum Exp Toxicol 1994; 13: 478-80.

Hac83 Hackett PL, Brown MG, Buschbom RL, *et al.* Teratogenic study of ethylene and propylene oxide and n-butyl acetate. Springfield VA, USA: National Technical Information Service/US Dept of Commerce, 1983; rep no PB83-258038.

Hea94 Health Council: Dutch Expert Committee on Occupational Standards (DECOS). 1-, 2- and t-Butanol. Health-based Recommended Occupational Exposure Limit. The Hague: Health Council of The Netherlands, 1994; pub no 1994/10.

Hii87 Hiipakka D, Samimi B. Exposure of acrylic fingernail sculptors to organic vapors and methacrylate dusts. Am Ind Hyg Assoc J 1987; 48: 230-7.

Hof97 Hoff T. Delayed contact dermal sensitization test -Buehler method. Spinnerstown PA, USA: MB Research Laboratories, Inc, 1997; MB res proj no: MB 97-6119.06 (available from the National Technical Information Service, Springfield VA, USA; order no: OTSO0573684-1).

HSE00 Health and Safety Executive (HSE). EH40/2000. Occupational Exposure Limits 2000. Sudbury (Suffolk), England: HSE Books, 2000: 13, 20.

Hun97 Hunter WI, Aresini G, Haigh R, *et al.* Occupational exposure limits for chemicals in the European Union. Occup Environ Med 1997; 54: 217-22.

Ire93 Iregren A, Loef A, Toomingas A, *et al.* Irritation effects from experimental exposure to n-butyl acetate. Am J Ind Med 1993; 24: 727-742.

Ish84 Ishidate MJ, Sofuni T, Yoshikawa K, et al. Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 1984; 22: 623-36.

Iva78 Ivanetich KM, Lucas S, Marsh JA, *et al.* Organic compounds. Their interaction with and degradation of hepatic microsomal drug-metabolizing enzymes in vitro. Drug Metab Dispos 1978; 6: 218-25.

Kan94 Kaneko T, Wang PY, Sato A. Partition coefficients of some acetate esters and alcohols in water, blood, olive oil, and rat tissues. Occup Environ Med 1994; 51: 68-72.

Kay53 Kay IH. Report to the Texas Company. Toxicity studies on TFA-168. Northbrook IL, USA: Industrial 810- TEST Laboratories, Inc, 1953 (available from the National Technical Information Service, Springfield VA, USA; order no: OTS00556824).

Ken89 Kennah HE II, Hignet S, Laux PE, *et al.* An objective procedure for quantitating eye irriration based upon changes of corneal thickness. Fundam Appl Toxicol 1989; 12: 258-68.

Kor94 Korsak Z, Rydzynski K. Effects of acute combined inhalation exposure to n-butyl alcohol and n-butyl acetate in experimental animals. Int J Occup Med Environ Health 1994; 7: 273-80.

Kri87 Kristensson J, Beving H. A study of painters occupationally exposed to water and solvent based paints. In: Commission of the European Communities, ed. Diffusive sampling: an alternative approach to workplace air monitoring. Luxemburg: Office for official publications of the European Communities, 1987: 71-4 (pub no EUR 10555).

Kro79 Kronevi T, Wahlberg J, Holmberg B. Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs. Environ Res 1979; 19: 56-69.

Kru88 Kruize I. Bepaling van de geurdrempelwaarde van een zestal oplosmiddelen. Apeldoorn, the Netherlands: TNO Environment, Energy and Process Innovation, 1988; TNO rep no: MT 88-339.

Kur82 Kurppa K, Husman K. Car painter's exposure to a mixture of organic solvents. Serum activities of liver enzymes. Scand J Work Environ Health 1982; 8: 137-40.

Lon77 Longland RC, Shilling WH, Gangolli SD. The hydrolysis of flavouring esters by artificial gastrointestinal juices and rat tissue preparations. Toxicology 1977; 8: 197-204.

Lun85 Lundberg I, Hakansson M. Normal serum activities of liver enzymes in Swedish paint industry workers with heavy exposure to organic solvents. Br J Ind Med 1985; 42: 596-600.

Maa89 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).

Mul84 Muller J, Greff G. Recherche de relations entre toxicité de molécules d'interêt industriel et propiétés physico-chimiques: test d'irritation des voies aériennes supérieures appliqué à quatre familles chimiques. Food Chem Toxicol 1984; 22: 661-4.

Mun72 Munch JC. Aliphatic alcohols and alkyl esters: Narcotic and lethal potential to tadpoles and to rabbits. Int J Med Surg 1972; 41: 31-33.

Mye92 Myers RC, Tyler TR. Acute toxicologic evaluation of n-butyl acetate. Acute Toxic Data 1992; 1: 196.

Nac87 Nachreiner DJ, Dodd DE. n-Butyl acetate: acute vapor inhalation toxicity test in rats. Export PA, USA: Bushy Run Research Center, 1987; proj rep 50-135 (by courtesy of the Manager of the CMA Oxo Pocess Panel, Washington DC, USA).

Nac93 Nachreiner DJ. n-Butyl acetate (old production process material): acute inhalation toxicity study. Export PA, USA: Bushy Run Research Center, 1993 (lab proj id 91U0111) (by courtesy of the Manager of the Oxo Process Panel of the Chemical Manufacturers Association, Washington DC, USA).

Nac94 Nachreiner DJ. n-Butyl acetate, urethane grade (current production material): acute inhalation toxicity study. Export PA, USA: Bushy Run Research Center, 1994 (lab proj id 92U1102) (by courtesy of the Manager of the Oxo Process Panel of the Chemical Manufacturers Association, Washington DC, USA).

Nel43 Nelson KW, Ege JF, Ross M, *et al.* Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 1943; 25: 282-285.

NIO00 US National Institute of Occupational Safety and Health (NIOSH). In: Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM], issue July 2000. SilverPlatter International, 2000 (last update separate butyl acetate files: July 2000).

NLM00 US National Library of Medicine (NLM). In: Hazardous Substances Data Bank (HSDB) [CD-ROM], issue August 2000. SilverPlatter International, 2000 (last update separate butyl acetate files: February 2000).

Nor95 Norbäck D, Wieslander G, Edling C. occupational exposure to volatile organic compounds (VOCs), and other air polutants from the indoor application of water-based paints. Ann Occup Hyg 1995; 39: 783-94.

Nor97 Norris IC, Nachreiner DI, Tyler TR, *et al.* Acute inhalation toxicity studies of n-butyl acetate. Inhal Toxicol1997; 7: 623-46.

Opd78 Opdyke DLJ. Monographs on fragrance raw materials. Isobutyl acetate. Food Cosmet Toxicol 1978; 16: 795-6.

Opd79 Opdyke DLJ. Monographs on fragrance raw materials. Butyl acetate. Food Cosmet Toxicol 1979; 17: 515-9.

Ørb98 Ørbræk P, Österberg K, Äkesson B, *et al.* Suprathreshold intensity and annoyance reactions in experimental challenge to toluene and n-butyl acetate among subjects with long-term solvent exposure. Scand I Work Environ Health 1998; 24: 432-8.

Öst00 Österberg K, Ørbræk P, Karlson B, *et al.* Psychological test performance during experimental challenge to toluene and n-butyl acetate in cases of solvent-induced toxic encephalopathy. Scand I Work Environ Health 2000; 26: 219-26.

Pel82 Pellizzari ED. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. Environ Sci Technol 1982; 16: 781-5.

Pen95 Peng HM, Raner GM, Vaz ADN, *et al.* Oxidative cleavage of esters and amides to carbonyl products by cytochrome P450. Arch Biochem Biophys 1995; 318: 333-9.

Pet87 Petren S, Vesterberg O. Studies of transferrin in serum of workers exposed to organic solvents. Br J Ind Med 1987; 44: 566-8.

Roe80 Roed-Petersen J. Allergic contact dermatitis from butyl acetate. Contact Dermatitis, 1980; 6: 55.

Rot92 Rothweiler H, Waeger PA, Schlatter C. Volatile organic compounds and some very volatile organic compounds in new and recently renovated buildings in Switzerland. Atmos Environ (Part A) 1992; 26A: 2219-25.

Rou70 Roudabush RL. Toxicity and health hazard summary of sec-butyl acetate. Rochester NY, USA: Eastman Kodak Company, Laboratory of Industrial Medicine, 1970 (available from the National Technical Information Service, Springfield VA, USA; order no: OTS00556683).

Sal87 Sala C. Passive sampling with liquid or solid substrate. In: Commission of the European Communities, ed. Luxemburg: Office for official publications of the European Communities, 1987: 262-5 (pub no EUR 10555).

Sam82 Samimi B. Exposure to isophorone and other organic solvents in a screen printing plant. Am Ind Hyg Assoc J 1982; 43: 43-8.

Say36 Sayers RR, Schrenk HH, Patty FA. Acute response of guinea pigs to vapors of some new commercial organic solvents. n-Butyl acetate. Pub Health Rep 1936; 51: 1229-39.

Sch85 Scheffers TML, Jongeneelen FJ, Bragt PC. Development of effect-specific limit values (ESLVs) for solvent mixtures in painting. Ann occup hyg 1985; 29: 191-9.

Sei89 Seifert B, Mailahn W, Schulz C, *et al.* Seasonal variation of concentrations of volatile organic compounds in selected German homes. Environ Int 1989; 15: 397-408.

Shi85 Shimizu H, Suzuki Y, Takemura N, *et a*l. The results of microbial mutation test for forty-three industrial chemical. Jpn J Ind Health 1985; 27: 400-19.

Shu96 Shulman RN. letter and attachment (dd March 13) to the Document Processing Center of the Office of Toxic Substances of USEPA, Washington DC, USA. Houston TX, USA: Shell Chemical Company, Health, Safety and Environment, 1996 (available from Documents Express, Washington DC, USA; see also Ano96).

Smy54 Smyth HF, Carpenter CP, Weil CS, *et al.* Range finding toxicity tests. List V. Arch Ind Hyg Occup Med 1954; 10: 61-8.

Smy62 Smyth HF, Carpenter CP, Weil CS, *et a*l. Range-finding toxicity data. List VI. Arch Ind Hyg Occup Med 1962; 23: 95-107.

Spi82 Spingarn NE, Northington DJ, Pressely T. Analysis of volatile hazardous substances by GC/MS. J Chromatogr Sci 1982; 20: 286-8.

Stu97 Studiegroep Chemiekaarten, eds. In: Chemiekaarten: gegevens voor het veilig werken met chemicaliën. 11 th ed. Alphen a/d Rijn, the Netherlands: Samson HD Tjeenk Willink bv, 1997: 176, 177, 607.

Str92 Streete PJ, Ruprah M, Ramsey JD, *et al.* Detection and identification of volatile substances by headspace capillary gas chromatography to aid the diagnosis of acute poisoning. Analyst (London) 1992; 117: 1111-27.

Syr79 Syracuse Research Corp: Center for Chemical Hazard Assessment. Information profiles on potential occupational hazards. Volume 1. Single chemicals. n-Butyl acetate. Springfield VA, USA: National Technical Information Service/US Dept of Commerce, 1979; rep no PB81-147993.

SZW99 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). De nationale MAC-Iijst 1999. The Hague, The Netherlands: Servicecentrum Sdu Uitgevers, 1999: 19, 30.

Toy89 Toy NJ. Final report on the safety assessment of ethyl acetate and butyl acetate. J Am Coll Toxicol 1989; 8: 681-705.

Tri91 Triebig G, Schaller KH. Arbeitsmedizinische Untersuchungen zur Gefahrstoffbelastung von Malern und Lackierern. Staub - Reinhalt Luft 1991; 51: 1-4.

Ueh87 Uehori R, Nagata T, Kimura K, et al. Screening of volatile compounds present in human blood using retention indexes in gas-chromatography. J Chromatogr 411: 251-7.

Wal84 van der Wal JF, van de Belt R. Expositie van werknemers in een lijmfabriek aan luchtverontreininging. Delft, the Netherlands: IMG-TNO, 1984; rep no F2171.

Wan93 Wang, JD, Chen JD. Acute and chronic neurological symptoms among paint workers exposed to mixtures of organic solvents. Environ Res 1993; 61: 107-16.

Wel89 Weller JP; Wolf M. Mass spectroscopy and headspace-GC. Beitr Gerichtl Med 1989; 47: 525-32.

WHO87 World Health Organization (WHO): International Programme on Chemical Safety (IPCS). Butanols - four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. Geneva, Switzerland: WHO, 1987; Environmental Health Criteria 65.

Wil95 Williams CH. Exposure assessment study for n-butyl acetate in paint spray aerosols. Volume 1 Report. Austin TX, USA: Radian Corporation, 1995 (by courtesy of the Manager of the Oxo Process Panel of the Chemical Manufacturers Association, Washington DC, USA).

Win92 Winder C, Turner PJ. Solvent exposure and related work practices amongst apprentice spray painters in automotive body repair workshops. Ann Occup Hyg 1992; 36: 385-94.

Zal92 Zaleski J. Butyl acetates. In: Thurman RG, Kaufman FC, eds. Ethel Browning's toxicity and metabolism of industrial solvents. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers BV, 1992: 247-55 (Alcohols and ethers; Vol 3).

Zei92 Zeiger E, Anderson B, Haworth S, *et al.* Salmonella Mutagenicity tests: 5. Results form the testing of 311 chemicals. Environ Mol Mutagen, 1992; 19 (suppl 21): 2-141.

Zim85 Zimmerman FK, Mayer VW, Scheel I and Resnick MA. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are stong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat Res, 1985; 149: 339-351.

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the

case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committees

Members of the DECOS

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research, Zeist
- DJJ Heederik
  epidemiologist; IRAS University Utrecht, Utrecht
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- TM Pal
  occupational physician; Nederlands Centrum voor Beroepsziekten, Amsterdam.

- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

Members of the SCG (as of June 1997)

- Johan Högberg, *chairman*
  Toxicologist; Swedish Natl Inst for Working Life, Solna
- Gunnar Johanson, *v. chairman*
  Toxicologist; Swedish Natl Inst for Working Life, Solna
- Olav Axelson
  Occupational physician, epidemiologist; University Hospital, Linköping
- Sven Bergström
  Union representative; Swedish Trade Union Confederation
- Christer Edling
  Occupational physician, epidemiologist; University Hospital, Uppsala
- Lars Erik Folkesson
  Union representative; Swedish Metal Workers' Union
- Francesco Gamberale
  Behavioural neurotoxicologist; Swedish National Institute for Working Life, Solna
- Stig Holmquist
  Union representative; Swedish Confederation of Professional Associations
- Bengt Järvholm
  Occupational physician, epidemiologist; University Hospital, Umeå

- Ulf Lavenius
  Union representative; Swedish Factory Worker's Union
- Bengt Olof Persson, *observer*
  Physician, organic chemist; Sw Natl Board of Occup Safety and Health, Solna
- Bengt Sjögren
  Occupational physician; Swedish Natl Inst for Working Life, Solna
- Jan Wahlberg
  Dermatologist; Swedish Natl Inst for Working Life, Solna
- Kerstin Wahlberg, *observer*
  Chemical engineer; Swedish Natl Board of Occupational Safety and Health, Solna
- Arne Wennberg
  Neurotoxicologist; Swedish Natl Inst for Working Life, Solna
- Olof Vesterberg
  Physician, biochemist; Swedish Natl Inst for Working Life, Solna
- Per Lundberg, *scientific secretary*
  Toxicologist; Swedish Natl Inst for Working Life, Solna

The first draft of the present advisory report was prepared by W Bogaerts, PhD, and H Stouten, MSc from TNO, Department of Occupational Toxicology, Zeist.

Secretarial assistance: T van der Klugt.
Lay-out: J van Kan.

Annex **C**

Comments on the public review draft

A draft of this report was released in 1997 for public review. The following persons or organisations commented on the draft document:

- T Fischer
  Swedish Criterea Group, Solna, Sweden
- Mw C Davies
  Health and Safety Executive, Merseyside, United Kingdom
- P Teheux
  Oxygenated Solvents Producers Association, Brussel, Belgium

Annex **D**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at wAbbreviationshich inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion $(v/v)10^{-9}$
ppm	parts per million $(v/v)10^{-6}$
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit

STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration

MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

RD_{50}	concentration associated with 50% decrease in respiratory rate
ND_{50}	the quality that produced stupor and loss of voluntary movement on half of the animals
TSCA	Toxic Substances Control Act
SCOB	Scheduled-Controlled Operant Behaviour
FOB	Functional Observational Battery

Annex **E**

DECOS-documents

DECOS has produced documents on the following substances.
To be ordered from the Health Council of the Netherlands:

Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chromium and its inorganic compounds	1998/01WGD
Cresols	1998/15WGD
Copper sulphate	1999/01OSH
1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dibromoethane	1999/07OSH
1,2-Dichloroethane	1997/01WGD
Diethylsulphate	1999/08/OSH

Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
Endotoxins	1998/03WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene thiourea	1999/03OSH
Formamide and dimethylformamide	1995/08WGD
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Isopropyl acetate	1997/04WGD
Man made mineral fibers	1995/02WGD
2-Meathylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD
Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH
1- and 2-Propanol	1994/24
Propylene oxide	1997/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Quartz	1998/02WGD
1,1,1-Thrichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD
Urethane (ethyl carbamate)	200012OSH
Vinylbromide	1999/15OSH
Wood dust	1998/13WGD