n-Butanol

(CAS No. 71-36-3)

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CONTENTS

EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the toxicity and ecotoxicity data of *n*-butanol (nBA). Since the last comprehensive review of nBA by IPCS [a] in 1987, new data have become available. A hazard/risk assessment will be required under current OECD/EU schemes [b,c].

nBA is a colourless liquid that is primarily used as an intermediate in the manufacture of other chemicals, and in solvent applications. If nBA is released into the environment (airborne), a major part will be distributed to the water compartment. nBA is rapidly degraded in air and water; little accumulation in soil, biota, sediment or suspended matter is anticipated. nBA has a low order of toxicity at all trophic levels.

nBA is readily absorbed through the lungs of humans and laboratory animals and can also penetrate the skin. Following absorption, nBA is rapidly metabolised, ultimately to CO_2, with small amounts being eliminated in urine as glucuronide and sulphate conjugates.

When administered in single doses to laboratory animals by gavage, inhalation or application to the skin, nBA exhibits a low order of toxicity. Available information on the effects of nBA following repeated exposure is supplemented in this report by data on *n*-butyl acetate, an ester that hydrolyses to form nBA and acetic acid within minutes of entering systemic circulation. The typical effect of high doses of nBA following single or repeated exposure is a transient, depression (narcosis) of the central nervous system, which is commonly seen with other short chain alkyl alcohols. Specific neurotoxicity is not observed. Specific target organs and selective toxicity have not been identified. nBA is not genotoxic and there is no concern for carcinogenic potential.

nBA showed some foetotoxicity in laboratory animals at high concentrations that were toxic to the mother, but is devoid of selective developmental toxicity. Male or female fertility is not adversely affected, as shown by studies with *n*-butyl acetate.

Earlier reports describing neurotoxicity and hearing loss in workers exposed to nBA have not been substantiated. In humans, nBA is slightly to moderately irritant to the skin on prolonged contact, and moderately irritant to the eyes.

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[a] IPCS Environmental Health Criteria Documents [http://www.who.int/pcs/ra_site/ehc.html]

[b] OECD Existing Chemicals Programme [http://www1.oecd.org/ehs/hazard.htm]

[c] EU Existing Chemicals Work Area [http://ecb.ei.jrc.it/existing-chemicals/]

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced by an ECETOC Task Force as part of the Joint Assessment of Commodity Chemicals (JACC) programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals. In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

This report presents a critical evaluation of the toxicology, ecotoxicology and physico-chemical properties of *n*-butanol (nBA; CAS No. 71-36-3). This information is supplemented by toxicological data on *n*-butyl acetate, which is rapidly hydrolysed in vivo to nBA and acetic acid.

Where relevant, the Task Force has assigned a Code of Reliability (CoR) [a] to (eco)toxicological studies to reflect the degree of confidence that can be placed on the reported results. The criteria used to assess and categorise reliability are included in Appendix B.

[a] A list of special abbreaviations is given at Appendix A

1. SUMMARY AND CONCLUSIONS

n-Butanol (nBA) is a commodity chemical produced in Europe and USA in volumes exceeding 500 kilotonnes per year. A colourless, flammable liquid with an alcoholic odour, nBA is soluble in water and miscible with a large number of organic solvents. It is used primarily as an intermediate in the manufacture of other chemicals, such as butyl acetate, butyl acrylate and butyl glycol ethers; considerable quantities are used as a solvent in coating applications.

nBA enters the environment to a small extent from natural sources (biomass, fermentation), and during its production, transport, storage and use as an intermediate and a solvent. The primary route for entering the environment is release to the atmosphere when used as a solvent. Assuming equilibrium distribution, approximately 80% of nBA will partition to water and 16 - 19% to air.

nBA is readily biodegradable in water and readily decomposed in the air by photodegradation; it does not adsorb on soil. Thus, substantial environmental concentrations and biomagnification in the food chain are not anticipated. nBA has a low order of toxicity to environmental organisms at all trophic levels.

Approximately 50% of inhaled nBA is readily absorbed via the lungs of humans and laboratory animals; it can also penetrate the skin. Studies with radiolabelled material have demonstrated that, once absorbed, nBA is rapidly and completely distributed throughout the organism. The majority (approximately 80%) of the radiolabel is eliminated as CO_2, with smaller amounts eliminated in urine as glucuronide and sulphate conjugates. The half-life of nBA in plasma of rats is approximately 1 hour.

nBA exhibits a low order of toxicity when administered in single doses to laboratory animals by gavage, inhalation or application to the skin. The material is slightly to moderately irritant to the skin on prolonged contact, and moderately irritant to the eyes.

A substantial amount of information is available on the effects of repeated exposure of laboratory animals to nBA. The information is supplemented in this review by data on *n*-butyl acetate, an ester that hydrolyses to form nBA and acetic acid within minutes of entering systemic circulation. The most common effect of repeated exposure is a transient, general central nervous system (CNS) depression, often observed with other short chain alkyl alcohols. In an evaluation of neurotoxicity including schedule-controlled operand behaviour, neuropathology, motor activity and functional observational battery, no changes were observed in rats exposed to *n*-butyl acetate vapour over a 13-week period. No specific target organs have been identified from subchronic exposure to nBA, nor from systemic exposure to *n*-butyl acetate. There is no evidence in either *in vivo* or *in vitro* test systems that nBA exerts genotoxic activity.

Foetotoxicity has been observed in the offspring of laboratory rats, but only at exposure concentrations that are toxic to the mother. The lack of specific developmental toxicity is supported by studies conducted with *n*-butyl acetate in rats and rabbits.

No detectable effects on reproductive parameters were observed in studies where either male rats had been exposed to nBA and mated to non-exposed females, or in which female rats had been exposed to nBA throughout gestation. In repeated exposure studies with nBA, no treatment-related effects were observed on microscopic examination of male or female reproductive organs. In addition, supporting evidence for a lack of effect on fertility is provided by data from a subchronic study with *n*-butyl acetate.

Earlier reports of human experience in the workplace describe CNS toxicity and hearing loss related to nBA; no further cases on hearing disturbances related to nBA have been reported since. At high vapour concentrations and under poor working conditions, severe eye irritation has been reported.

Current exposures to nBA in production facilities are probably low, but insufficient detail is available for evaluation. Less data are available from other industrial settings, i.e. customer (end-user) sites. Existing regulatory exposure standards for nBA appear to be adequate to protect human health.

Overall, there seems to be no justification for the EC classification of nBA as "harmful", and it is suggested that this classification should be reviewed.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name:	*n*-Butanol (nBA)
IUPAC name:	Butan-1-ol
Synonyms:	Butanol *n*-Butan-1-ol Butyl alcohol *n*-Butyl alcohol 1-Hydroxybutane Methylolpropane Propylcarbinol
CAS name:	1-Butanol
CAS registry No:	71-36-3
UN number:	1120
Molecular mass	74.12
Formula:	$C_4H_{10}O$
Structural formula	CH_3 - CH_2 - CH_2 - CH_2 - OH

2.2 EC classification and labelling

nBA is classified and labelled in accordance with the Dangerous Substances Directive (EC, 1993).

EC (EINECS) No:	200-751-6
Index No:	603-004-00-6
Classification:	Flammable, harmful [a], irritant
Labelling, symbol:	Xn Harmful [a]

[a] The basis for the classification is unknown

R-Phrases:	R 10	Flammable
	R 22	Harmful if swallowed
	R 37/38	Irritating to respiratory system / skin
	R 41	Risk of serious damage to eyes
	R 67	Vapours may cause drowsiness and dizziness
S-Phrases:	(S 2	Keep out of reach of children) [a]
	S 7/9	Keep container tightly closed and in a well-ventilated place
	S 13	Keep away from food, drink and animal feedstuff
	S 26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
	S 37/39	Wear suitable gloves and eye/face protection
	S 46	If swallowed, seek medical advice immediately and show this container or label

2.3 Physical and chemical properties

nBA is a colourless, flammable liquid with an alcoholic odour. It is soluble in water and miscible with a large number of organic solvents. Physical and chemical properties are listed in Table 1.

[a] Only for consumer products

Table 1: Physical and chemical properties

Property	Value, unit	Reference
Melting point	-89 - -90°C	Company data sheets [a]
	-89.3°C	Hahn *et al*, 1986
	-89.5°C	Weast *et al*, 1989
	-89.9°C	Verschueren, 1986
Boiling point at 1,013 hPa	116 - 118°C	Company data sheets [a]
	117.7 °C	Hahn *et al*, 1986; Verschueren, 1986
	117.2°C	Weast *et al*, 1989
Relative density D_4^{20} (density of water at 4°C is 1,000 kg/m^3)	0.810	Company data sheets [a]
	0.8098	Hahn *et al*, 1986; Weast *et al*, 1989
Viscosity, at 20°C	2.9 mPa·s [b]	Elf Atochem, 1996; BASF, 1999; ExxonMobil, 2000
	3.0 mPa·s	Hahn *et al*, 1986; Oxeno, 2000
Refractive index nD at 20°C	1.3991	Hahn *et al*, 1986
Vapour pressure at 20°C	5.5 - 6.7 hPa [c]	Company data sheets [a]
	5.9 hPa [d]	Verschueren, 1986
Vapour density at 25°C (air = 1)	2.55 - 2.6	Company data sheets [a]
Threshold odour concentration [e]	0.6 mg/m^3 [f]	Dalton *et al*, 1997
	0.52 mg/m^3 [g]	Wysocki and Dalton, 1996
	0.36 mg/m^3	Ruth, 1986
	2.6 mg/m^3 [h]	Amoore and Hautala, 1983
Surface tension at 20°C	22.3 mN/m	Hahn *et al*, 1986
Solubility in water at 20°C	74.5 - 77 g/kg	Company data sheets [a]
	77 g/kg	Hahn *et al*, 1986; Verschueren, 1986
Solubility of water in nBA at 20°C	250 g/kg	Hahn *et al*, 1986
	200 g/kg	Elf Atochem, 1996
Miscible with alcohol, ether, acetone and benzene; ketones, esters, alcohols	Yes	Weast *et al*, 1989; Elf Atochem, 1996
Partition coefficient, log K_{ow} (octanol/water) at 20°C	0.88 [i]	Hansch and Leo, 1985 cited by Staples, 1998; Verschueren, 1986; Elf Atochem, 1996; Oxeno, 2000
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	1.86 [i]	Howard, 1990 cited by Staples, 1998
Henry's Law constant at 20 - 25°C	0.64 Pa·m^3/mol [k]	This report
	0.56 Pa·m^3/mol [l]	Howard, 1990 cited by Staples, 1998
	0.90 Pa·m^3/mol [m]	Elf Atochem, 1996
Flash point, closed cup	29 - 37°C	Company data sheets [a]
	34°C	Hahn *et al*, 1986
	28.85°C	Billig, 1992

Table 1: Physical and chemical properties (cont'd)

Property	Value, unit	Reference
Explosion limits in air at room temperature and 1,013 hPa	1.4 - 11.3% (v/v)	Company data sheets [a]; Hahn *et al*, 1986; Billig, 1992
	1.45 - 11.25% (v/v)	Lewis and Von Elbe, 1951 cited by Weast *et al*, 1989
Auto-flammability, ignition temperature	340 - 367°C	Company data sheets [a]
	342.85°C	Billig, 1992
	380°C	Hahn *et al*, 1986

[a] Shell, 1993; Elf Atochem, 1996; ExxonMobil, 2000; Union Carbide, 1998; BASF, 1999 ; Oxeno, 2000
[b] Reported as 3.60 cSt
[c] Highly dependent on small variations in temperature
[d] Reported as 4 mm (Hg)
[e] For odour detection or olfactory perception
[f] Median value, reported as 0.2 ppm (Section 2.4)
[g] Median value, reported as 0.17 ppm (Section 2.4)
[h] Reported as 0.83 ppm
[i] Measured, reported as 72
[j] Calculated
[k] Calculated: molecular mass x vapour pressure / solubility in water
[l] Presumably calculated, reported as 5.57×10^{-6} atm.m^3/mol
[m] Calculated, reported as 8.87×10^{-6} atm.m^3/mol

Typically, commercial nBA has a purity $\geq$99.8%. Common impurities are isobutanol (< 0.05% w/w), dibutyl ether (< 0.03%), butyric acid (< 0.002%) and water (< 0.1%).

2.4 Conversion factors

Conversion factors for nBA concentrations in air at standard conditions (20°C and 1,013 hPa) are:

- 1 ppm = 3.082 mg/m^3
- 1 mg/m^3 = 0.324 ppm

In this report, converted values (rounded) are given in parentheses.

2.5 Analytical methods

2.5.1 Workplace air

NIOSH (1994) developed a standard method for the detection of nBA in workplace air which involved pumping a certain volume of air (2 - 10 l) through a tube containing activated charcoal. Any adsorbed nBA (and other volatile organic compounds) was eluted with a mixture of 2-propanol and carbon disulphide, and the eluate analysed by gas chromatography (GC) using a flame ionisation detector (FID). The relatively high detection limit is sufficient for monitoring current occupational exposure limit (OEL) values of airborne nBA concentrations (Table 7).

Kawai *et al* (1997) modified the NIOSH method to achieve a lower detection limit of 0.3 ppm nBA (0.92 mg/m^3) for 8-hour exposure. The workplace air was sampled by diffusion onto carbon cloth exposed in a case holder (typically attached to the worker's chest pocket), the cloth extracted with carbon disulphide and the adsorbate analysed by GC-FID.

A further modification of the NIOSH method, in which the nBA is desorbed with hydrogen sulphide, has been standardised by BASF (2000a). The analytical sensitivity is 2.2 ng nBA and the detection limit 0.06 mg nBA/m^3 (0.02 ppm) in 25 litres of sampled air. The method is suitable for personal and area measurements. It has been certified (renewable every 3 years) by the competent German authority (Mess- und Prüfstellen der Länder, Kassel).

2.5.2 Environmental media

For the determination of nBA in ambient air, the above NIOSH method for workplace air can be used. There are no standard methods for the analysis of water, soil or sediment. No substantial concentrations of nBA in the environment are expected (Section 4.3.6 and 5.1).

2.5.3 Biological media

Urine analysis of nBA by GC-FID (detection limit 0.02 μg/ml) has been carried out following extraction with dichloromethane in the presence of acid or hydrolase, because part of the nBA was reportedly conjugated with glucuronide (Kawai *et al*, 1997).

Deisinger and English (1997) used high-pressure liquid chromatography (HPLC) to determine the amount of radiolabelled nBA in heparinised whole blood and brain homogenates. Samples were de-proteinised by adding an equal volume of 0.5 M sodium tungstate followed by an equal volume of 0.5 M cupric sulphate. Following mixing and centrifugation, injections of the clear supernatant were separated by HPLC, using a reverse-phase column and an isocratic mobile phase consisting of 25 mM sodium formate buffer (pH 4.0) with 20% acetonitrile, at 1 ml/min. The column effluent was directed to a radiochemical flow-through detector. The detection limit was determined by the specific activity of the radiolabelled material.

Deisinger and English (2001) developed an analytical method using GC with mass spectroscopy (MS) for the detection of nBA, *n*-butyl acetate, *n*-butyraldehyde, and *n*-butyric acid in heparinised whole blood (detection limit around 1 mg nBA/l of blood). The blood samples were de-proteinised by the addition of an equal volume of 0.4 M sulphuric acid containing 3-methyl-1-butanol and *n*-hexanoic acid as internal standard. The samples were extracted with a small volume of diethyl ether, and the extract treated with ethereal diazomethane to methylate the carboxylic acids. Quantitative analysis was achieved by GC using a free-fatty-acid-phase capillary column and mass-selective ion detection of the individual analyte.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

nBA is produced by the hydroformylation of propylene that has reacted with carbon monoxide and hydrogen (syngas) in the presence of a metal (generally rhodium or cobalt) catalyst. This "Oxo" process is carried out continuously at low pressure (20 atm [a] or 2,030 kPa) or high pressure (500 atm or 50,700 kPa) and yields a mixture of *n*-butyraldehyde and isobutyraldehyde. The resulting aldehydes are separated by distillation and hydrogenated to the corresponding alcohols, which are further refined by distillation (Billig, 1992). All reaction and distillation steps are carried out in closed systems.

In the USA, total production capacity of nBA in 1999 was 2,533 x 10^6 pounds (1,149 kt) [a]. The market (demand) for nBA in 1999 in the USA was 1,850 x 10^6 pounds (839 kt), including exports of 285 x 10^6 pounds (129 kt) (ChemExpo News, 1999). The 1998 US production for nBA was 1,780 x 10^6 pounds (807 kt) (CMA, 1999a). No data are available for Europe.

3.2 Storage

Storage of nBA is dictated by flammability concerns. Since the vapour density is 2.6 times that of air, any nBA that possibly accumulates in low areas may be prone to ignition (Table 1). nBA can also react with other chemicals (e.g. explosives, organic peroxides) to cause fires.

Consequently, nBA is usually stored in closed, grounded metal containers dedicated to nBA storage, with little fugitive emissions, in a well-ventilated area without exposure to heat, and away from possible ignition sources. Examples of these containers are tank cars (> 10,000 gallons [c] or 38 m^3), tank trucks (> 10,000 gallons) and chemical storage tanks in tank farms (> 25,000 gallons or 95 m^3). Conservation vents may be present. Storage in drums represents a very small percentage of the total.

3.3 Transport

Transport of nBA within production facilities is typically through dedicated transit pipes and conduits to storage tanks or transport vessels. Transport from production facilities to off-site use or processing centres is done via tank cars, tank trucks or transporting drums. Small orders are sometimes handled and shipped in drums.

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[a] 1 atm = 101.325kPa
[b] 1 pound = 1 lb = 0.4535924 kg
[c] 1 US gal = 3.785 1

3.4 Use

In the USA in 1999, most (77%) nBA was used as an intermediate in the production of other chemicals, with direct solvent use of only 8%. nBA was also used in the manufacture of adhesives, building material agents, cleaning agents, detergents, dyestuffs, fertilisers, surface treatment agents, mostly in closed systems (CMA, 1999b). A percentage breakdown is given in Table 2. No such data are available for Europe.

Table 2: Industrial use pattern in the USA (CMA, 1999b)

		USA (%)
Closed system		81
Open system		4
Export		15
	Total:	100
Chemical intermediates		
Acrylates		32
Glycol ethers		25
Butyl acetate		11
Plasticisers		4
Miscellaneous		5
Total intermediates		77
Coating solvent		8
Export from USA		15
	Total:	100

In the USA, nBA derived products and nBA as such continue to be used in many surface-coating applications. The use of the nBA-derived butyl esters in latex architectural paints is expected to increase with the continued demand for water-based paints in the housing market (ChemExpo News, 1999).

In Europe, water-borne "acryl" paints for decorative painting in the housing market are the major outlet for materials made from nBA.

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Emissions

nBA is released to the environment from natural and human (anthropogenic) sources.

4.1.1 Natural sources

In a study conducted *in situ* on locations near Vienna, Austria, nBA was found along with 21 other volatile organic compounds (VOCs) emitted by several plants such as rape (*Brassica napus*), rye (*Secale cereale*) and grass (*Graminea* sp.), and by trees including beech (*Fagus* sp.), birch (*Betula* sp.) and hornbeam (*Carpinus* sp.) at a rate of 1.6 - 17 ng/g biomass/h (König *et al*, 1995). Other natural sources may include animal waste, microbes and insects (US EPA, 1994). Fermentation of the tundra cover was assumed to be the source of airborne nBA in Alaska (Section 5.1: Cavanagh *et al*, 1969).

Various authors (cited in US-EPA, 1994) have identified nBA as a VOC in certain foodstuffs including dried beans (0 - 7 μg/kg), split peas (150 μg/kg), lentils (120 μg/kg), apple and pear aroma, grape essence, mountain cheese, roasted filberts and fried bacon (levels not quantified)

nBA was detected in kiwi fruit (*Actinidia chinensis*) flowers, where it represented 0.01% of the total amount of 87 VOCs (Tatsuka *et al*, 1990) and in bagaceiras (Portuguese grape marc) (Silva *et al*, 1996). The levels were not quantified.

nBA concentrations of 0.391, 61.3 and 0.48 mg/kg (3 samples) were measured in poultry manure at different stages (0, 9 and 28 days, respectively) of anaerobic fermentation at 28 - 29°C (Yasuhara, 1987).

nBA was identified, but not quantified, in gas from sanitary landfills at several locations in Germany (Bruckmann and Mülder, 1982).

4.1.2 Emissions during production and use

There are few data available on man-made releases of nBA into the environment.

Emissions of nBA during production and industrial uses are probably low due to the use of closed systems (Table 2).

The US Toxics Release Inventory lists the reported releases (annual quantities emitted) from industrial facilities having 10 or more full-time employees and manufacturing or processing ≥ 25,000 lbs (11,364 kg) [a] or otherwise use ≥ 10,000 lbs (4,545 kg) of nBA. In 1997, the majority of the emissions were from its use as a solvent (Table 3).

[a] 1 lb = 1 pound = 0.4535924 kg

Table 3: Industrial emissions in the USA in 1997 (US-EPA, 1999a)

Number of facilities reporting	**1,001** (lb)	**1,001** (kg)
Total air emissions	21,456,156	9,752,798
Surface water discharges [a]	79,743	36,246
Underground injection	3,122,078	1,419,126
Off-site land releases	34,484	15,674
Total on-site releases	24,692,461	11,223,845
Transfers off-site to disposal	188,914	85,870
Total on- and off-site releases	24,881,375	11,309,715

[a] Excluding emissions from waste-water treatment plants (WWTPs)

These figures represent a worst-case estimate, as they are based on conservative assumptions and do not take into consideration any breakdown on-site by biological or physical means (such as waste-water treatment, incineration and flaring) (US-EPA, 1999b).

4.2 Environmental distribution

The primary route for nBA to enter the environment is its airborne release when used as a solvent. Using the Mackay Level 1 fugacity modelling (Paterson and Mackay, 1985), the theoretical distribution to different environmental compartments has been estimated (Table 4).

Table 4: Partitioning into the environment

Reference: **Compartment**	**Hüls, 1996a** (%)	**Staples, 1998** (%)
Air	18.7	15.8
Water	80.5	80.8
Soil	0.4	1.8
Biota	< 0.1	< 0.1
Sediment	0.4	1.7
Suspended matter	< 0.1	< 0.1

The estimates suggest that, after equilibrium distribution, approximately 80% of nBA will be found in water and 16 - 19% in air. Small amounts of nBA are expected to partition to soil and sediment (< 2%); the amounts in biota and suspended soil are negligible. These results reflect the relatively high water solubility of nBA, and its modest vapour pressure and Henry's Law constant (Table 1).

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate

In the atmosphere, photochemically produced hydroxyl radicals (· OH) or similar oxidants will cause nBA to degrade rapidly with a short half-life of 0.43 to 2.4 days (Staples, 1998) or 2.2 days (US-EPA, 1994). The Atmospheric Oxydation Program (version 1.87) SRC, 2000) calculated half-lives of 2.33 days (&OH-timeframe of 12 h/d) and 4.66 days (· OH-timeframe of 24 h/d) using an · OH rate constant of 6.89 x 10^{-12} cm^3/molecule/s. Campbell *et al* (1976) measured · OH rate constants of 4.1 x 10^{-12} cm^3/molecule/s and predicted a half-life of 5 hours for nBA in urban air. Physical removal of nBA from the atmosphere by wet deposition is another possible removal mechanism (US EPA, 1994).

When emitted to the atmosphere, nBA may contribute to the formation of tropospheric ozone through oxidation of atmospheric NO to NO_2, by the oxidation of intermediates produced during its degradation and further photolysis of NO_2 to NO and atomic oxygen. The experimental half-life for photodecomposition of nBA (initial concentration 5 ppm, 15 mg/m^3) in the presence of NO was 6.5 hours (Dilling *et al*, 1976). Derwent *et al* (1998) calculated the photochemical ozone creation potential (POCP) of nBA to be 61.2, moderate when compared to ethylene (100), which serves as a reference.

4.3.2 Aquatic fate

Indirect photolysis in water and hydrolysis are not significant degradation mechanisms for nBA (Staples, 1998; US-EPA, 1994). Biodegradation is the most important process (Section 4.3.4).

4.3.3 Terrestrial fate

The partitioning coefficient log K_{oc} value of 1.86 (Table 1) indicates that nBA will not be bound to soil. Because it is readily soluble in water, nBA is expected to be fairly mobile in soil and may leach into groundwater. Biodegradation of nBA would be expected to reduce the amount available (US-EPA, 1994).

4.3.4 Biodegradation

Aerobic

In a closed bottle test, 88% nBA was degraded within 30 days (Hüls, 1996b; CoR 1a). In an OECD-screening test, 98% of the added nBA (initial concentration 20 mg nBA/l) was eliminated within 14 days (Hüls, 1996c; CoR 1a). Based on these results nBA is classified as readily biodegradable (> 60% degradation reached within a 10-d window). The same conclusion was reached in a review by Staples (1998; CoR 4b).

A Zahn-Wellens test with 450 mg nBA/l showed 100% degradation in 5 days (Hüls, 1996d; CoR 1a). In a Coupled Units test, which runs constantly, 98.5% nBA were degraded (Hüls, n.d. CoR 1a). Therefore nBA is expected to degrade in wastewater treatment plants (WWTPs).

In addition to the above standard biodegradation tests, several earlier studies showed rapid biodegradation within a few days (McKinney and Jerris, 1955; CoR 2e; Hatfield, 1957; CoR 2e; Pitter, 1976; CoR 2e; Bridié *et al*, 1979a; CoR 2e).

Anaerobic

The anaerobic biodegradation potential of nBA was determined in a submerged up-flow filter with a retention time of 2 - 10 days. After 52 days (earlier measurements not stated), 95% of both chemical oxygen demand (COD) and total organic carbon (TOC) had been removed. In acetate-enriched (to enhance co-metabolism) methanogenic cultures, 100% degradation (based on gas production) of nBA was achieved within 4 days (Lin Chou *et al*, 1979; CoR 2e).

4.3.5 Bioaccumulation

No measured bioconcentration factor (BCF) is available.

From the partition coefficient, a BCF of approximately 3 was calculated (SRC, 1988 cited by Staples 1998; CoR 4b). This and the partition coefficient itself suggest that nBA has low bioaccumulation potential. The US EPA (1995) has stated that nBA is not a "bioaccumulative chemical of concern". Biomagnification of nBA in the aquatic and terrestrial food chains is therefore unlikely.

4.3.6 Summary and evaluation

nBA enters the environment from natural sources (biomass, fermentation) and to a small extent during its production, transport, storage and use, as an intermediate and a solvent. The primary route for entering the environment is the release to the atmosphere when used as a solvent. Assuming equilibrium distribution, approximately 80% of nBA will partition to water and 16 - 19% to air.

nBA is readily degradable in water and readily decomposed in the air by photodegradation; it does adsorb on soil. Thus, substantial environmental concentrations and biomagnification in the food chain are not anticipated.

Based on the data available and the above discussion, no further tests are considered to be necessary.

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[a] Appendix B

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

Few data are available on concentrations of nBA in air and water.

5.1.1 Air

The available data on background concentrations of nBA in air are presented in Table 5.

Table 5: Concentrations in air

Location, year	Concentration ($\mu g/m^3$)	(ppb)	Reference
Hawaii USA (summer 1967)	-	0	Cavanagh *et al*, 1969
Point Barrows, Alaska USA (summer 1967)	-	34 - 445 190[a]	Cavanagh *et al*, 1969
Tucson, Arizona USA (February - September 1982)	-	0.12	Snider and Dawson, 1985 -
Santa Rita and Mt. Lemmon, Arizona USA (August - September 1982)	-	0.06	Snider and Dawson, 1985
Above estuary, Southampton UK,	< 0.1 - 6.4	(0.03 - 2.1) [b]	Bianchi and Varney, 1992
(summer 1991 and winter 1990 - 1991	0.4 - 10.2	(0.13 - 3.3) [b]	
Vicinity of solvent reclamation plant, Maryland, USA	3,030 - 30,300	(980 - 9,800) [b]	US-EPA, 1994
Indoor air in homes in Italy	20	6 [b]	US-EPA, 1994

[a] Mean

[b] Converted following Section 2.3

nBA has been detected, but not quantified, in Black Forest air and in suburban air of the city of Tübingen in Germany (Jüttner, 1986).

5.1.2 Water

No data on natural background concentrations are available.

nBA concentrations of 87 - 318 μg/l and < 1 μg/l were reported in the Hayashida River, Japan, and the Lee River, UK. nBA has also been detected (concentration not specified) in Lake Ontario (US EPA, 1994).

In 1980, a concentration of 318 μg nBA/l was measured in surface water receiving waste from the leather industry in Tasuno City (Japan) (Yasuhara *et al*, 1981).

5.2 Human exposure levels and hygiene standards

5.2.1 Non-occupational exposure

Pellizari *et al* (1982) detected nBA in 7 of 8 samples of human milk from mothers living in the urban areas of Bridgeville (PA), Bayonne (NJ) and Baton Rouge (LA) in the USA. Actual concentrations levels were not reported. The source was not identified.

nBA was identified by GC MS along with 149 other VOCs emitted from furniture coatings (Salthammer, 1997).

5.2.2 Occupational exposure

Because of its production in closed systems, no substantial workplace concentrations of nBA are anticipated. Workplace concentrations during production (distillation) and use as an intermediate for the production of butyl acetate, were measured by Hüls (1995, 1997). The average workplace concentrations in all production steps were much less than 1 mg nBA/m^3 (0.32 ppm), well below the occupational exposure standard (Section 5.2.3).

From 1979 to 1999, extensive workplace exposure measurements were undertaken within a chemical company at all sites involved in the production and use of nBA. The measurement method was comparable to NIOSH, detailed in Section 2.5.1. The strategy was based on personal air sampling. The frequency of measurement (10/site on average) could be kept low due to compliance with hygiene standards (Section 5.2.3). The results are summarised in Table 6. However, the general representativeness of these results, for all down-stream scenarios, cannot be evaluated (see also Section 10).

Table 6: Workplace (8-h TWA) concentrations [a] (BASF, 2000b)

Concentration	ppm [b]	mg/m^3
Range	0.03 - 160	0.09 - 493
Mean	0.54	1.66
95%	≤ 1.1	≤ 3.4
90%	≤ 0.48	≤ 1.48
50% (median)	≤ 0.04	≤ 0.12

[a] 3,678 personal samples at 323 sites

[b] Reported values, converted following Section 2.3

nBA has been identified in the workplace air of Belgian printing shops (31% of samples obtained from 24 shops), and industrial painting operations (22% of samples from 21 sites from 1983 to 1985) (Veulemans *et al*, 1987). In addition, nBA was detected in 63% of samples of workplace air from 19 plants involved in various other industrial operations (including production and distribution of chemicals, metal manufacturing, food industries, production and sterilisation of medical equipment and cleaning companies).

Median air concentrations of 5.7, 1.5, 5.4 and > 300 mg/m^3 (1.85, 0.5, 1.75 and > 97 ppm) were reported in a wood and metal working industry sites with ventilation, two wood and metal working sites without ventilation and a spray painting operation in booths with ventilation, respectively (Vincent *et al*, 1994). These values appear to be area samples rather than personal samples.

Measured air concentrations of nBA during spray painting of commercial aircraft ranged from approximately 25 to 70 mg/m^3 (8 - 23 ppm) (Triebig *et al*, 1992).

Eleven male printers, working in two small shops, were exposed to mixed solvent vapours. The geometric mean nBA concentration at the workplace was 1.4 ppm nBA (4.3 mg/m^3). The measurement methods are described in Section 2.5.1 (Kawai *et al*, 1997) (Section 7.1.1).

US-EPA (1994) has reported concentrations of 3.6 mg/m^3 (1.17 ppm) in the breathable air of workers using nBA as a solvent.

The NIOSH Hazard Evaluation and Technical Assistance (HETA) branch reported on hygiene surveys made from 1978 to 1985 at different US companies. During the production of butylglycidyl ether, exposure of workers was confounded by low concentrations (not quantified) of butanol (isomer not specified) and epichlorohydrin (NIOSH, 1979). No butanol (isomer not specified) was detected in personal and area samples of workplace air in a label manufacturing plant (NIOSH, 1983). Fourteen workers at a soft drinks company, during can-lining (using a waterborne epoxy spray containing 8% nBA and 8% butylcellosolve), were exposed to 8-hour TWA concentrations of 0.757 - 3.44 ppm nBA (2.33 - 10.6 mg/m^3) (NIOSH, 1984).

During cleaning of wing parts at an aircraft manufacturing plant, personal air samples from the breathing zone of seven workers exposed to vapours from a degreasing solvent (containing 5% nBA mixed with 35% perchloroethylene, 30% methylene chloride, 25% aromatic petroleum solvents, and 5% diacetone alcohol) contained up to 0.5 ppm nBA (1.5 mg/m^3) (NIOSH, 1986a).

One worker of a graphite fishing rod manufacture was exposed to various solvents evaporating from coating materials (including nBA, methyl ethyl ketone, 2-ethoxyethyl acetate and 2-ethoxyethanol). The personal nBA concentration measured was less than the detection limit of 0.7 ppm nBA (2.2 mg/m^3) (NIOSH, 1986b). In another workshop manufacturing graphite and fibreglass fishing rods, two workers, a coater and a blank washer, were exposed to a mixture of nBA, acetone, toluene and xylene evaporated from the coating solvent used. nBA concentrations (8 h TWA) were 1.4 - 8.0 ppm (4.3 - 25 mg/m^3) in the coating area, 2.8 - 3.3 ppm (8.6 - 10.2 mg/m^3) in the breathing zone of the coater and 0.6 - 0.9 ppm (1.8 - 2.8 mg/m^3) in the breathing zone of the blank washer (NIOSH, 1986c).

5.2.3 Hygiene standards

Several industrialised countries have adopted an OEL value for nBA; examples are given in Table 7. Almost all the OELs include a skin notation (for which no further documentation is available).

Table 7: Examples of occupational exposure limit values

	TWA		Ceiling Limit		STEL		Notation	Reference
Country	(ppm)	(mg/m^3) [a]	(ppm)	(mg/m^3) [a]	(ppm)	(mg/m^3) [a]		
Austria	100	310	-	-	200 [ab]	620 [ab]	-	DFG, 1999
Belgium	20	61	-	-	-	-	-	ACGIH, 2002
Denmark	-	-	50	150	-	-	Skin	Arbejdstilsynet, 2000
France	-	-	-	-	50	150		INRS, 1999
Finland	20	61	-	-	-	-	-	ACGIH, 2002
Germany	100	310	-	-	200 [ab]	620 [ab]	-	DFG, 1999
Italy	20	61	-	-	-	-	-	ACGIH, 2002
Japan	-	-	50	150	-	-	Skin	JSOH, 1999
Netherlands	-	-	-		15	45	Skin	Sdu, 1999
Norway	-	-	25	75	-	-	-	Arbeidstilsynet, 1997
Sweden	15	45	30	90	-	-	Skin	AFS, 1996
Switzerland	20	61	-	-	-	-	-	ACGIH, 2002
UK	-	-	-	-	50	154	Skin	HSE, 2000
USA	20	61	-	-	-	-	-	ACGIH, 2002 [c]
	-	-	50	150	-	-	Skin	NIOSH, 2000
	100	300	-	-	-	-	-	OSHA cited by NIOSH, 2000

TWA Time-weighted average concentration (8-h working period)

STEL Short-term exposure limit (15 min, unless specified otherwise)

[a] Official values; some countries use different conversion factors and/or other ambient temperature

[b] 5 min, max. 8 x/shift

[c] OELs in other countries are also directly linked to the value published by ACGIH, including Australia, Bulgaria, Colombia, Jordan, Korea, New Zealand, Singapore and Vietnam

No environmental or public health standards are available for nBA in indoor air, drinking water or food residues.

5.2.4 Other standards

In the USA, an Immediately Dangerous to Life or Health (IDLH) concentration of 1,400 ppm (4,300 mg/m^3) was established, based on acute inhalation toxicity data. This value is considered protective and includes conservative assumptions (NIOSH, 1996). The Reference Dose (RfD) for chronic oral exposure is 0.1 mg nBA/kg/d (US-EPA, 2001).

5.2.5 Summary

Background exposure to nBA from various, mostly unknown, environmental sources appears to be common (IPCS, 1987 p. 20). Various concentrations were reported from working areas depending on working hygiene, degree of ventilation and incident situation. Exposure as high as 300 mg/m³ was reported for certain working sites with spray operations, with the additional risks of acute or chronic respiratory irritation due to the aerosol nature of the material.

Occupational exposure limit values of 50 or 100 ppm (155 and 310 mg/m³) have been established.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Micro-organisms

nBA has been tested for its toxicity to bacteria and protozoa (Table 8).

Table 8: Toxicity to micro-organisms

Organism	Biological	Method endpoint / Parameter	Time	Concentration	Reference (mg/l)	CoR [a]
Bacteria	**Growth inhibition**					
Pseudomonas putida	EC_{10}	Bringmann-Kühn	16 h	2,250	Hüls, 2001	1d
Pseudomonas putida	EC_3	Bringmann-Kühn	16 h	650	Bringmann and Kühn, 1977a	1d
Photobacterium phosphoreum	EC_{50}	Microtox	5 min	2,041	Blum and Speece 1991	1d
Aerobic heterotrophic bacteria	EC_{50}	Microtox	24 h	3,980	Blum and Speece, 1991	1d
Methanogenic bacteria	EC_{50}	Microtox	24 h	10,714	Blum and Speece, 1991	1d
Microcystis aeruginosa	EC_3	Bringmann-Kühn	8 d	≥100 [b]	Bringmann and Kühn, 1978a,b	1d
Protozoa	**Growth inhibition**					
Entosiphon sulcatum	Toxicity threshold [c]	Bringmann-Kühn	16 h	55	Bringmann and Kühn, 1978c, 1980a	1d
Uronema parduczi	Toxicity threshold [c]	Bringmann-Kühn	20 h	8	Bringmann and Kühn, 1980b	1d

[a] Code of reliability (Appendix B)

[b] Also, erroneously, listed as ≥ 312 mg/l

[c] Screening test showing the onset of adverse effects (3 - 5% growth inhibition)

The results show that nBA has a low order of toxicity to bacteria and protozoa. As the protozoa tests are screening tests showing the onset of adverse effects, the toxicity thresholds are much lower than the EC50 values for bacteria.

6.2 Aquatic organisms

nBA has been tested for its toxicity to invertebrates and fish (Table 9).

Table 9: Toxicity to invertebrates and fish

Organism	Biological	Method	Time	Concentration	Reference	CoR [a]
Invertebrates	**Lethality**					
Artemia salina	Tolerance limit	Static	24	2,950	Price *et al*, 1974	2c
	Immobility					
Daphnia magna	EC_0	Static	24	1,677	Kühn *et al*, 1989	2c
	EC_{50}			2,337		
	EC_{100}			5,700		
Daphnia magna	EC_0	Static	48	1,26015	Kühn *et al*, 1989	2c
	EC_{50}			1,983		
	EC_{100}			2,455		
Daphnia magna	EC_0	Static	24	300	Bringmann and	2c
	EC_{50}			1,855	Kühn, 1977b	
	EC_{100}			5,000		
Daphnia magna	EC_0	Static	24	1,411	Bringmann and	2c
	EC_{50}			1,880	Kühn, 1982	
	EC_{100}			2,500		
Harpaticoid *Nitocra spinipes*	EC_{50}	Static	96	2,100	Bengtsson *et al*, 1984[b]	1b
Fish	**Lethality**					
Pimephales promelas	LC_{50}	Flow-through	96	1,730	Brooke *et al*, 1984	1b
Pimephales promelas	LC_{50}	Flow-through	96	1,740	Veith *et al*, 1983a,b	4b
Alburnus alburnus	LC_{50}	Static	96	2,300	Bengtsson *et al*, 1984 [b]	1b
Carassius auratus	LC_{50}	Static	24	1,900	Bridié *et al*, 1979b	1c
Carassius auratus	Tolerance threshold	Static		7,412	Hill *et al*, 1981	2c
Leuciscus idus	LC_{50}	Static	48	1,200 - 1,770	Juhnke and Lüdemann, 1978	1c
Pimephales promelas	LC_{50}	Static	96	1,910	Mattson *et al*, 1976	1d
Semolitus atromaculatus	Critical range	Static	24	1,000 - 1,400	Gillette *et al*, 1952	3a

[a] Code of reliability (Appendix B)

[b] Methodology described by Lindén *et al*, 1979

The available data show that nBA is practically non-toxic to invertebrates and fish. All LC_{50} and EC_{50} values are well above 1,000 mg/l. No chronic data are available.

Furthermore, tadpoles of the frog *Rana pipiens* became immobilised at 38 mmol nBA/l (2,820 mg/l) (Munch, 1972; CoR 1d).

Table 10 shows that nBA has a low order of acute and chronic toxicity to algae.

Table 10: Toxicity to algae

Organism	Biological endpoint / Parameter	Method	Time	Concentration (mg/l)	Reference	CoR[a]
	Growth inhibition					
Scenedesmus subspicatus	EC_{50}	DIN 38412 Part 9	96 h	>500	BASF, 1990	1c
Scenedesmus quadricauda	EC_3	Bringmann -Kühn	8 d	≥875 [b]	Bringmann and Kühn, 1977a, 1978a,b, 1980a	1d

[a] Code of reliability (Appendix B)

[b] Also, erroneously, listed as ≥ 95 mg/l in Bringmann and Kühn, 1977a, 1978a,b

6.3 Terrestrial organisms

The acute toxicity of nBA to starlings (*Sturnus vulgaris*) was low (LD_{50} 2,500 mg/kgbw) (Schafer *et al*, 1983; CoR 1d).

Hoffman and Eastin (1981; CoR 4e) incubated fertile eggs of the mallard duck (*Anas platyrhynchos*) for 3 or 8 days and immersed them in butanol (isomer not specified) dissolved in water. By 18 days, there were no measurable effects at 10% (100 mg butanol/l), but higher concentrations were embryotoxic.

For larvae of the clawed toad Xenopus laevis an LC50 of 1,200 mg nBA/l was reported (De Zwart and Sloof, 1987; CoR 1d).

6.4 Summary and evaluation

nBA has a low order of toxicity at all trophic levels. The acute EC_{50}/LC_{50} values were generally well above 1,000 mg nBA/l. Algae were more sensitive, with EC_{50} values ranging upwards from 500 mg/l. These values are several orders of magnitude above environmental levels.

nBA is readily biodegradable in water and does not bioaccumulate (Section 4.3). Measured concentrations are low and long-term adverse effects to the aquatic organisms are not expected. No accumulation of nBA in the atmosphere is expected, due to its rapid photodegradation.

7. KINETICS AND METABOLISM

7.1 Absorption and excretion

7.1.1 Humans

Dermal

The uptake of nBA through human skin has been estimated using *in vitro* methodologies.

The absorption rate of nBA across isolated human epidermis was 0.048 mg/cm^2/h compared to 0.57 mg/cm^2/h for ethanol (Scheuplein and Blank, 1971 cited by Dugard *et al*, 1984 and Boman and Maibach, 1996; CoR 4b).

Boman and Maibach (1996; CoR 2e) determined an *in vitro* absorption rate of 2.30 ± 0.52 mg/cm^2/h and a permeability constant of 2.84 ± 0.65 x 10^{-3} cm/h for pure nBA through normal split-thickness human thigh skin. The authors observed increased skin absorption of nBA following concurrent administration of nBA with various surfactants and co-solvents, or with injured or delipidised skin.

Scheuplein and Blank (1973; CoR 2e) studied the *in vitro* permeability of nBA on human abdominal epidermal sheets and full-thickness dermis, obtained at autopsy, with diffusion cells at 25°C for 24 hours. The receiver half of the diffusion cell was filled with distilled water and 0.1 M aqueous nBA (7.4 g/l) or pure nBA, radiolabelled in some trials, was placed in the donor half-cell in contact with the stratum corneum or external side of the tissue. The permeability constants upon contact with aqueous nBA solution were 2.5 x 10^{-3} cm/h and 30 x 10^{-3} cm/h, for epidermis and dermis, respectively. The respective permeability constants for pure nBA were 0.060 x 10^{-3} cm/h and 1.0 x 10^{-3} cm/h. Pure nBA did not cause any structural alterations of the epidermis as judged by histopathological examination. In comparison to the stratum corneum, the dermis was an inferior permeability barrier to nBA.

Inhalation

Two groups of 6 healthy male volunteers (21 - 34 years of age) were exposed intermittently, through a breathing valve and mouthpiece, to concentrations of 100 or 200 ppm nBA (300 or 600 mg/m^3). Initial exposure (30 min at rest) was followed by a pause of 20 minutes. Three subsequent exposures (3 x 30 min) were combined with physical exercises of 50, 100 and 150 W (light, moderate and heavy) in the low exposure (100 ppm) group, and 50 W each in the high exposure (200 ppm) group. No significant EGG changes were recorded in any subject from either group, either at rest or during the exercises.

In the 100 ppm group, the uptake of nBA during initial exposure at rest was 43 mg of nBA, which corresponded to 48% of the dose applied. During the 3 subsequent exercises of 50, 100 and 150 W the uptake was 80, 130 and 135 mg nBA, i.e. 37, 40 and 41% of the dose. Arterial blood concentrations in the 100 ppm group increased from 0.3 mg nBA/l at rest to 0.6, 0.9, and 1.3 mg/l during the respective exercises. Following initial exposure to 200 ppm, about 80 mg of nBA (47% of the dose applied) was taken up. The uptake during the 3 subsequent exposures to 200 ppm with light exercise was 145 - 160 mg nBA, corresponding to 36 - 39% of the dose. In the 200 ppm group, arterial blood concentrations rose from 0.5 mg nBA /l at rest, to a plateau of 1.1 mg/l (Åstrand *et al*, 1976; CoR 2e).

A mean blood level of 0.45 mg nBA/l (maximum 1.288 mg/l) was reported, at the end of the work shift, in 9 healthy parquet workers (25 - 58 years of age) occupationally exposed to mixtures of organic solvent vapours containing nBA. The average measured concentration was 66.7 mg nBA/m^3 (21.6 ppm), with peaks up to 1,200 mg/m^3 (400 ppm) (Denkhaus *et al*, 1986; CoR 2e).

Urine samples were collected from 11 male printers, working in two small shops, exposed to mixed solvent vapours. The geometric mean of workplace concentrations were 1.4 ppm nBA (4.3 mg/m^3), 3.3 ppm ethyl acetate (12.1 mg/m^3), 10.9 ppm toluene (41.8 mg/m^3), 1.2 ppm ethyl benzene (5.3 mg/m^3) and 1.5 ppm xylene (6.6 mg/m^3); a control group was not exposed to solvent. The measurement methods are described in Section 2.5.1 and 2.5.3. Urine samples were analysed after hydrolysis with hydrochloric acid. At the end of the 8-hour work shift, there was a significant increase in total nBA concentration (228 ± 62 ng/mg creatinine) in the urine of exposed workers when compared to controls (12 ± 9 ng nBA/mg creatinine) (Kawai *et al*, 1997; CoR 2e).

7.1.2 Animals

Oral

nBA is generally considered to be readily oxidised via aldehyde dehydrogenase to butyric acid. To some extent the aldehyde also appears to be bound to glutathione (GSH) since a decrease of GSH in rat liver could be observed 6 hours after treatment with nBA (560 mg/kgbw) (Videla *et al*, 1982; CoR 2e).

Sprague-Dawley rats (male, 200 - 250 gbw) were administered single doses of *n*-[1-^{14}C]butanol mixed with corn oil (4.5, 45 or 450 mg nBA/kgbw) by gavage. Within 24 hours, approximately 80% of the radioactivity was eliminated as $^{14}CO_2$ in expired air and up to 13% excreted in urine and faeces (Table 11) (DiVincenzo and Hamilton, 1979; CoR 2e).

Table 11: Distribution (%) of radioactivity in rats dosed with n-[1-^{14}C]butanol

(adapted from DiVincenzo and Hamilton, 1979)

Dose	Expired air nBA (unchanged)	$^{14}CO_2$	Urine	Carcass	Faeces	Overall recovery
4.5 [a]	0.56, 0.40	79.1, 75.6	2.6, 4.6	15.2, 16.3	0.75, 1.1	98.2, 98.0
45 [a]	0.27, 0.20	78.3, 84.8	5.1, 5.0	12.8, 12.1	1.03, 0.69	97.5, 102.8
450 [b]	0.34 ± 0.15	83.3 ± 1.6	4.4 ± 1.1	12.3 ± 0.47	0.6 ± 0.08	101.0 ± 2.2

[a] Individual values for 2 rats

[b] Mean ± standard deviation for 4 rats

In a similar experiment, *n*-[1-^{14}C]butanol (dose level not specified) was administered orally to rats (strain not stated). Within 72 hours, 95% of the radioactivity had been eliminated, while 2.8% was found in urine and faeces (Rumyanstev *et al*, 1975 cited by CIR Expert Panel, 1987 and IPCS, 1987; CoR 4d).

After administration of a single oral dose of 2,000 mg nBA/kgbw (20% unlabelled nBA dissolved in water) to fasted Wistar rats, only 0.03 ± 0.004% of the dose was excreted unchanged in the urine (Gaillard and Derache, 1965; CoR 2e).

Dermal

DiVincenzo and Hamilton (1979; CoR 2e) quantified the percutaneous absorption rate of nBA in dogs by attaching an absorption cell to the clipped thorax of 2 anaesthetised male beagle dogs. A 55.6 cm² area of the skin was exposed for 1 hour to 20 µCi of *n*-[1-^{14}C]butanol mixed with 15 ml of an unknown carrier (probably unlabelled nBA). Expired air and urine were collected for 8 hours and the radioactivity was determined. The results were compared with the excretion of radioactivity from 3 dogs injected intravenously with *n*-[1-^{14}C]butanol (1 mg/kgbw) dissolved in physiological saline (Tables 12 and 13).

Table 12: Elimination of radioactivity by dogs dermally exposed to n-[1-^{14}C]butanol

(adapted from DiVincenzo and Hamilton, 1979)

Dog No.	Radioactivity excreted (dpm [a])		nBA absorbed through skin (mg)	Skin absorption rate (µg/min/cm²)
	Expired air	Urine		
1	13,500	4,600	29.08	8.7
2	16,770	1,470	29.38	8.8

[a] Disintegrations per minute

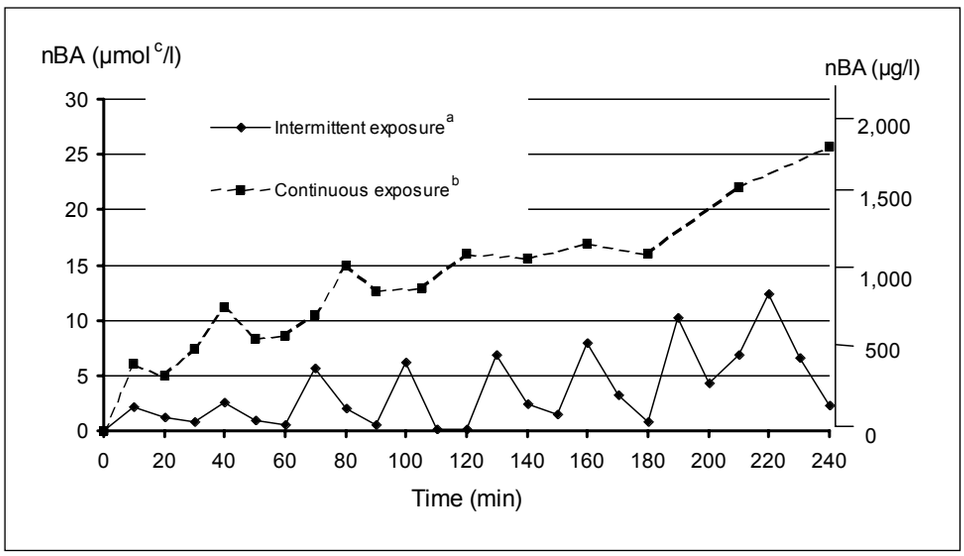
Table 13: Elimination of radioactivity by dogs following intravenous injection of n-[1-^{14}C]butanol (adapted from DiVincenzo and Hamilton, 1979)

Dog No.	Expired air		Urine	8-h recovery
	nBA (unchanged) (%)	$^{14}CO_2$ (%)	(%)	(%)
1	0	15.4	2.86	18.3
2	0	16.1	2.91	19.0
3	0	11.9	2.22	14.12

The dogs given nBA intravenously eliminated on average 15% of the administered radioactivity as $^{14}CO_2$ in expired air and 2.7% in the urine, of which 75% was accounted for as nBA-sulphate and O-glucuronide. No unchanged nBA was detected in expired air. It was assumed that the metabolic fate and disposition of nBA were the same after intravenous or dermal administration. The authors calculated that 29 mg of nBA was absorbed through the skin of the dogs at a rate of 8.8 µg/min/cm^2 (DiVincenzo and Hamilton, 1979; CoR 2e). The absorption rate is equivalent to 0.528 mg/cm^2/h and approximately 5 fold lower than the absorption rate determined for human skin *in vitro* (Section 7.1.1).

Skin absorption of an infinite amount (not quantified) of nBA in guinea pigs under intermittent exposure conditions (8 x 1 min at 30-min intervals for 4 h), was compared to the absorption under continuous exposure over 4 hours. Skin absorption of nBA was assessed by following the concentration of nBA in the blood of the animals (Figure 1). There was a normal build-up of concentration during continuous exposure. During intermittent exposure a considerable amount of nBA was absorbed while the blood concentration fluctuated with a steady increase in amplitude during the consecutive exposures. All coinciding samples from intermittently exposed animals revealed significantly lower concentrations of nBA (except at 70 and 80 min) than those from continuously exposed animals. The absorption of nBA was highest at the end of the exposure period (Boman *et al*, 1995; CoR 2e).

Figure 1: Concentration of nBA in blood of guinea pigs following dermal exposure to nBA (adapted from Boman et al, 1995)



[a] Mean of 5 animals

[b] Mean of 16 animals

[c] 1 µmol = 74.12 µg/l

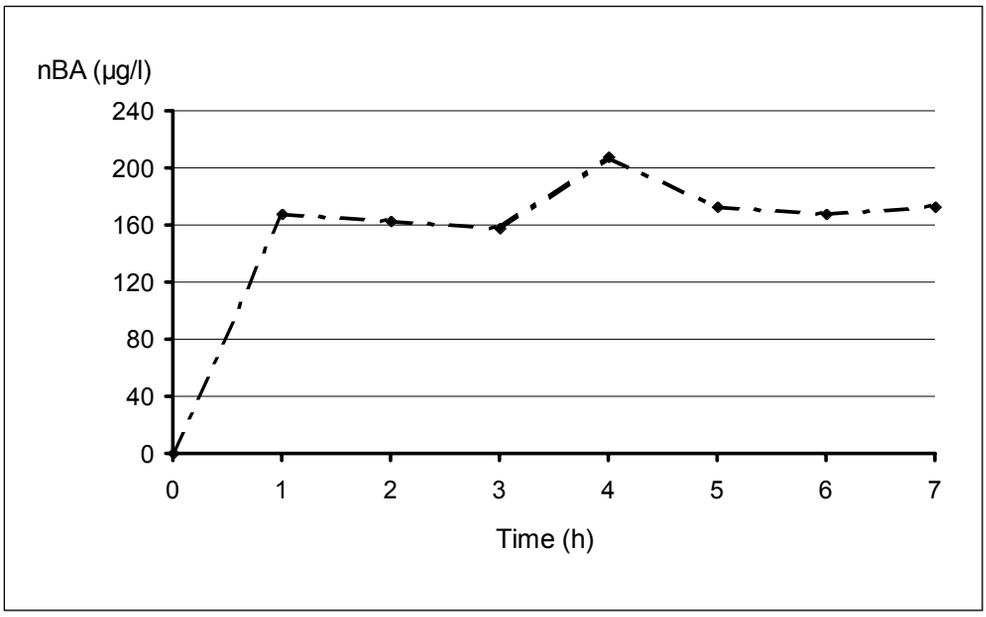
Skin absorption of nBA, as reflected by the blood concentration in guinea pigs, was enhanced by acute (e.g. stripping, sandpaper or needle abrasion and defattening) and subacute injuries (e.g. irritation and allergic contact dermatitis). The subacute injuries had a less pronounced effect. Induced contact dermatitis had no effect on nBA absorption (Boman and Wahlberg, 1989; CoR 2e).

From the physico-chemical properties of nBA, Fiserova-Bergova *et al* (1990) predicted a high transdermal penetration rate (flux) and potential toxicity of nBA, and proposed a basis for skin notation, taking into account the current OEL value.

Inhalation

Wistar rats were exposed (whole-body) by inhalation to nBA vapour concentrations of 94 ± 9 ppm (290 ± 28 mg/m^3) for 7 hours. The level of nBA in the blood of the animals reached a steady state within the first hour, with a mean value of 173 ± 16 µg/l (Figure 2) (Swiercz *et al*, 1995).

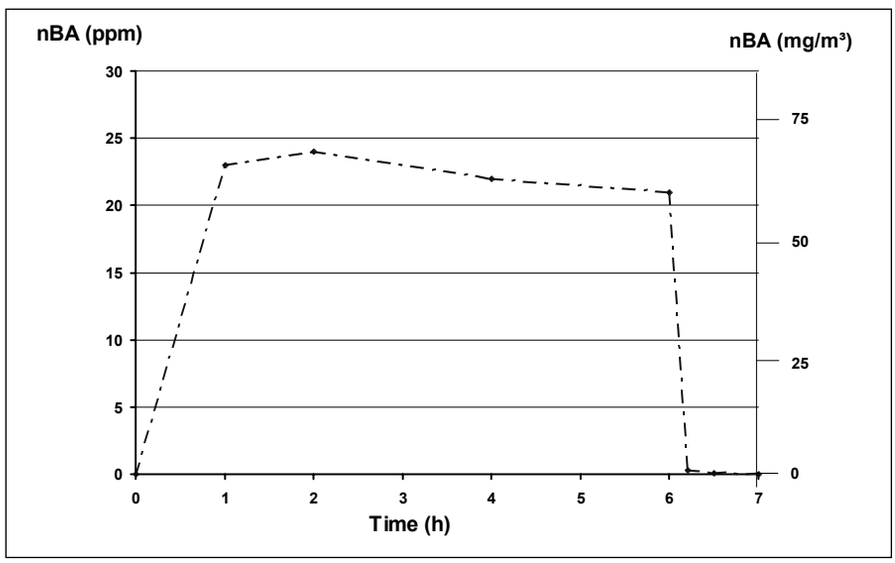
Figure 2: Concentration of nBA in blood of rats [a] during inhalation (whole-body) of 94 ppm nBA (adapted from Swiercz *et al*, 1995)



[a] Mean of 4 rats

Serial concentrations of nBA were measured in male beagle dogs exposed (whole-body) by inhalation to 50 ppm (150 mg/m^3) of unlabelled nBA vapour for 6 hours. Venous blood samples were collected periodically during and after the exposure. About 55% of the inhaled nBA was absorbed through the lungs. Expired air samples were taken by means of a latex mask during sample collection and through a 50-ml syringe in the late phase of exhalation. Expired air contained about 22 ppm nBA (68 mg/m^3) throughout the exposure period; the concentration rapidly decreased when the exposure was terminated (Figure 3). The concentration of nBA in the blood was below the limit of detection, both during and after exposure (DiVincenzo and Hamilton, 1979; CoR 2e).

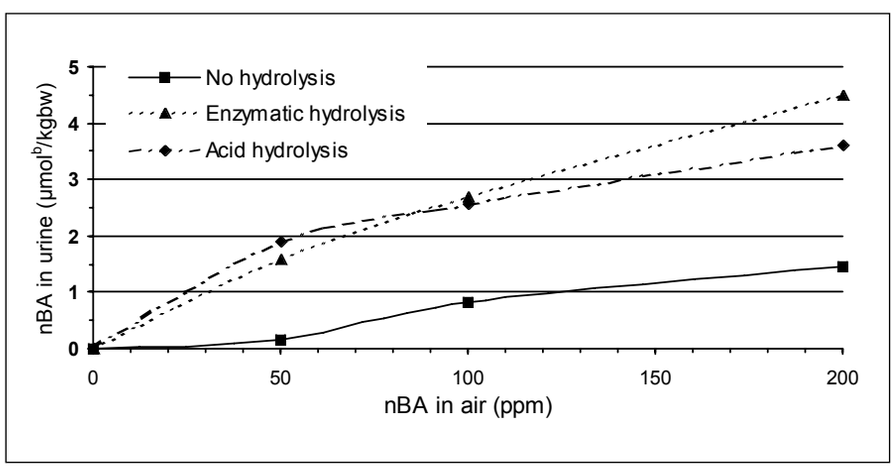
Figure 3: Concentration of nBA in expired air of dogs [a] exposed to 50 ppm nBA by inhalation (adapted from DiVincenzo and Hamilton, 1979)



[a] Mean of 4 dogs

Wistar rats were exposed by inhalation to 50, 100 and 200 ppm nBA (150, 300 and 600 mg/m^3) for 8 hours. Urine samples were collected 16 hours after exposure and analysed as such, or after treatment with hydrochloric acid or hydrolase preparation (Section 2.5.3). The results are displayed in Figure 4. The proportion of the amount of free to total (free plus conjugated) nBA in urine after exposure to 100 or 200 ppm was 35 - 40%, i.e. higher than after exposure to 50 ppm, when it was approximately 8%. This indicated saturation of the conjugation process at high concentrations (Kawai *et al*, 1997; CoR 2e).

Figure 4: Concentration [a] of nBA in urine of rats after inhalation of 50, 100 and 200 ppm of nBA (adapted from Kawai *et al*, 1997)



[a] Mean of 5 measurements

[b] 1 µmol = 74.12 µg

7.2 Distribution and metabolism

7.2.1 *In vivo* data

Oral route

The tissue distribution of radioactivity was measured in Sprague-Dawley rats, dosed by gavage, with *n*-[1-^{14}C]butanol (450 mg/kgbw) mixed with corn oil. The highest concentrations of radioactivity (% of dose) were found in the liver and blood 8 hours after nBA administration; the overall distribution of radioactivity to other tissues was relatively low (Table 14). The plasma concentration of the parent substance nBA reached a maximum of 70.9 μg/ml at 1 hour after dosing. At 4 hours the plasma concentration was below the limit of detection, which shows that nBA was rapidly metabolised. At 24 hours, 4.4 % of the nBA dose was excreted in the urine, as judged by the detected radioactivity, of which 44.4% was conjugated as O-sulphate and 30.7% as O-glucuronide; urea accounted for the remainder of the excreted radioactivity (DiVincenzo and Hamilton, 1979).

Table 14: Distribution of radioactivity in rats dosed with h- [1-^{14}C]butanol (450 mg/kgbw) by gavage (adapted from DiVincenzo and Hamilton, 1979)

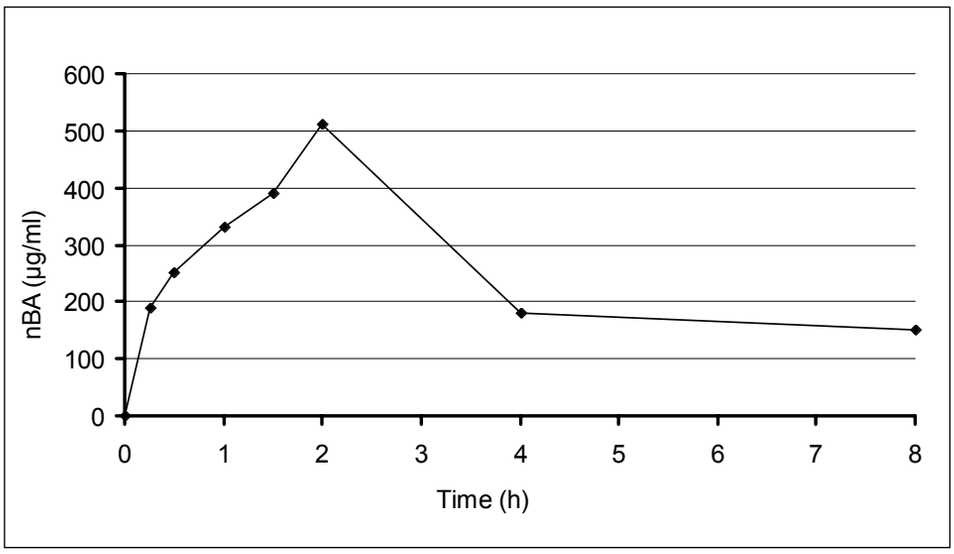
Tissue	Radioactivity (% of dose)		
	4 h	8 h	24 h
Liver	2.64 ± 0.34	3.88 ± 0.40	2.65 ± 0.2
Blood	0.51 ± 0.05	0.74 ± 0.11	0.38 ± 0.04
Kidney	0.24 ± 0.01	0.18 ± 0.01	0.11 ± 0.01
Lung	0.11 ± 0.008	0.12 ± 0.004	0.07 ± 0.009
Fat	0.05 ± 0.02	0.09 ± 0.01	0.06 ± 0.008
Brain	0.03 ± 0.004	0.04 ± 0.001	0.04
Heart	0.05 ± 0.004	0.02 ± 0.002	0.02 ± 0.004
Adrenal glands	0.006 ± 0.002	0 009 ± 0.002	0.009 ± 0.001

[a] Mean ± standard deviation for 4 rats

The time course for the concentration of nBA in the blood of fasted Wistar rats was determined following a single oral administration of 2,000 mg nBA/kgbw (20% unlabelled nBA dissolved in water). The highest concentration of nBA (510 μg/ml) was reached at the 2-hour sampling. nBA disappeared rapidly from the plasma but 150 μg/ml was still present 8 hours after dosing (Figure 5). The alcohol-oxidation coefficient of 165 ± 13 mg/kgbw/h for nBA, compared to 162 ± 14 mg/kgbw/h for ethanol, indicated a high substrate affinity of nBA for alcohol dehydrogenase (ADH) (Gaillard and Derache, 1965; CoR 2e).

Figure 5: Concentration [a] of nBA in blood of rats dosed orally with 2,000 mg nBA//kgbw

(adapted from Gaillard and Derache, 1965)



[a] Mean from 6 rats

The administration of 16 mmol of nBA (approximately 400 mg/kgbw) by gavage to 3 chinchilla rabbits resulted in a 1.8% increase in total glucuronic acid excretion in urine collected within 24 hours, indicating a low rate of conjugation of nBA (Kamil *et al*, 1953; CoR 2e).

One hour after oral administration of *n*-[1-^{14}C]butanol (dose level not specified) to rats (strain not stated), radioactivity was found in the liver, kidneys, small intestine and lungs. Four hours post-treatment, radioactivity had substantially decreased (Rumyanstev *et al*, 1975cited by CIR Expert Panel, 1987 and IPCS, 1987; CoR 4b).

Parenteral route

A poorly reported study indicated that after intraperitoneal injection of 840 mg nBA/kgbw to rats, the plasma half-life of nBA was 25 minutes and the distribution volume of nBA was determined as 95% of the body weight, indicating little affinity to structures or compartments other than body water (Rietbrock and Abshagen, 1971; CoR 3a).

7.2.2 *In vitro* data

Following absorption, nBA is expected to be uniformly distributed throughout the body, as indicated by the tissue-blood partition coefficients of around 1 for brain, kidney and liver in rats; for adipose and muscle tissues, the coefficients were slightly lower (0.78) (Kaneko *et al*, 1994).

In the first metabolic step, nBA is oxidised to n-butanal (*n*-butyric aldehyde), mainly by ADH(s) (Merritt and Tomkins, 1959; Von Wartburg *et al*, 1964). Several isoenzymes exist that differ in their intracellular topochemistry and substrate specificity. Thus, nBA was metabolised *in vitro* by Class I and II ADHs isolated from human liver, whereas Class III ADH showed no activity up to 100 μmol/l (7,400 μg/l). The concentrations corresponded to those seen in blood after ingestion of alcoholic drinks (10 - 100 μmol/l; 740 - 7,400 μg/l). Ethanol (2.5 - 10 μmol/l; 115 - 740 μg/l) caused a concentration-dependent inhibition of the ADH activities towards nBA (Ehrig *et al*, 1988).

In liver slices obtained from Wistar rats, nBA was converted to CO_2, primarily via ADH(s), with approximately 60% of the metabolism inhibited at 25 μl nBA/200 mg liver/2 ml incubate. Production of CO_2 was depressed in favour of lactate with a 10-fold increase in the lactate-pyruvate ratio (Forsander, 1967). This may indicate that under certain conditions, non-oxidative pathways may be employed after the rate-limiting step.

Microsomes, obtained from the liver of Sprague-Dawley rats, oxidised nBA to *n*-butanal in the presence of a nicotine-amide adenine dinucleotide phosphate hydrogenase (NADPH) generating system, without involvement of catalase. Oral administration of ethanol to female rats for 6 to 8 weeks resulted in a striking enhancement of microsomal activity from 4.4 ± 0.3 nmol *n*-butanal/min/mg microsomal protein in the controls to 7.4 ± 0.7 nmol/min/mg in ethanol-treated rats (Teschke *et al*, 1974). The involvement of cytochrome P450 was implicated by inhibition of the metabolism with carbon monoxide. In addition, the ability of the microsomal fraction to oxidise nBA by means of hydrogen peroxide was demonstrated directly by the addition of H_2O_2, and indirectly by inhibiting the catalase-dependent decomposition of hydrogen peroxide with azide (Cederbaum *et al*, 1978, 1979). The finding that hepatic microsomes are capable of oxidising nBA to *n*-butanal shows that, at least in rodents, there may be non-dehydrogenase mediated metabolism of nBA *in vivo*. The apparent Km value 4.9 mM for nBA (363 mg/l) (Teschke *et al*, 1975; CoR 2e), if applicable *in vivo*, indicates that the hepatic microsomal system could be near to its maximum activity.

Auty and Branch (1976) observed that elimination of nBA in isolated perfused livers from female Wistar rats was a saturable process. The initial concentration of 2.0 mM nBA (148 mg/l) decreased by more than 50% at a rate of 3.3 mmol/min (245 mg nBA/min) after an initial zero-order phase until, after 9.1 minutes, a concentration of 0.8 mM (59 mg/l) was reached; the decline followed first-order kinetics below this concentration. The apparent Km was 0.86 mM (64 mg/l) and the Vmax was 0.077 mmol/min (57 mg/min). Handler and Thurman (1988) perfused livers from nBA-fed and fasted rats, and found that catalase-H_2O_2 was the predominant pathway of nBA oxidation in the fasted state in the presence of fatty acids. Thus, under the conditions of the perfused rat liver model, diet and nutritional state may play important roles in the relative contribution of ADH and catalase pathways to nBA oxidation. However, this is not regarded as particularly relevant for the human situation.

In addition to its conversion via oxidative pathways, *in vitro* and *in vivo* investigations have shown that nBA may be a substrate of enzymes esterifying fatty acids. Carlson (1994a,b) observed the formation of *n*-butyl esters of palmitic, stearic and oleic acid in rats after intraperitoneal bolus injection of 1 ml nBA/kgbw. Since it may be expected that specific and non-specific esterases will hydrolyse these esters quite readily, this esterification step is regarded as transient, and probably occurs at high concentrations only. Carlson and Olson (1995) investigated the relative kinetic properties of liver and lung ADHs in their propensity to oxidise nBA (as well as 1-pentanol and 1 propanol). Pulmonary Km values were higher than those in the liver. Furthermore, the pH optimum of the pulmonary enzyme was in the alkaline range. The experiments support the assumption that the liver serves as the major source of metabolic clearance of nBA.

7.3 Evaluation

Inhalation studies with nBA in human volunteers and dogs show that a significant amount of nBA is absorbed through the lung (40% in humans and 55% in dogs, respectively). Although the data obtained from humans do not provide blood half-life values, the plasma levels of nBA were proportionally exposure-related, suggesting rapid elimination.

In vitro studies indicate that nBA can permeate human skin (epidermis and dermis). A skin absorption rate of 8.8 μg/cm^2/min was determined in dogs.

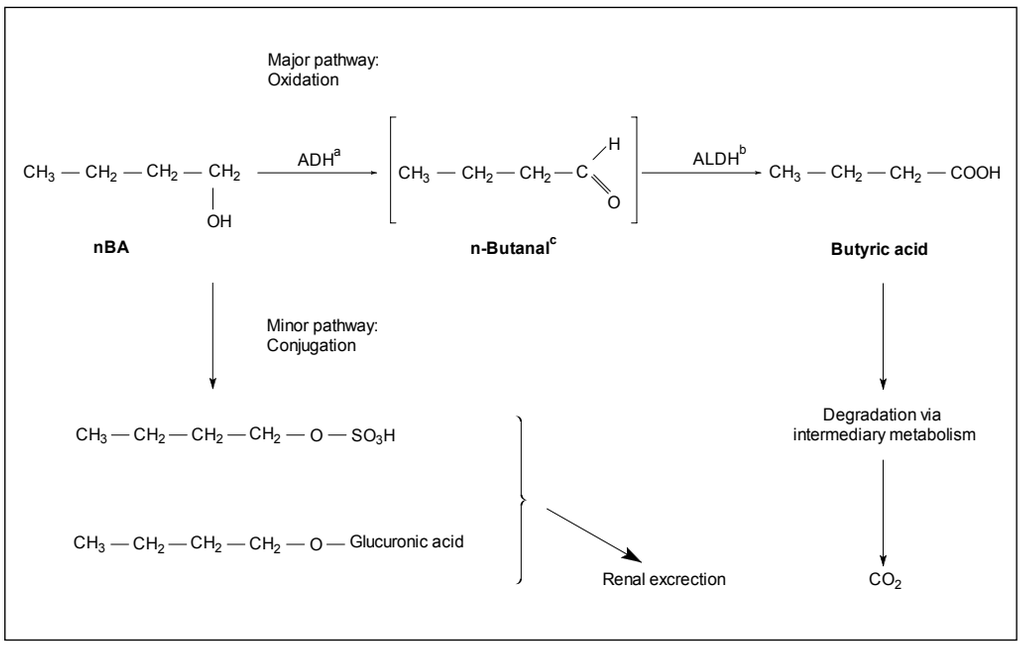
The pattern of excretion and overall recovery observed in different experimental animals demonstrate complete absorption of nBA by the oral route.

Once absorbed, nBA is distributed throughout the organism, with highest concentrations found typically in the liver, kidneys and lungs. After oral administration to rats, a peak blood level was reached after 1 to 2 hours; nBA then disappeared rapidly from the blood with an estimated half-life of 1 hour.

nBA is metabolised, primarily via alcohol and aldehyde dehydrogenases in the liver. This pathway involves oxidation to butyric acid and further degradation to shorter acids and ketones, ultimately to CO_2. A minor pathway involves conjugation, mainly as nBA-O-glucuronide or nBA-O-sulphate and excretion in urine. Some nBA may be excreted in urine or expired unchanged.

Thus, the metabolic pathways can be illustrated in the following manner (Figure 6).

Figure 6: Metabolism of nBA



[a] ADH = alcohol dehydrogenase

[b] ALDH = aldehyde dehydrogenase

[c] *n*-Butanal = butyric aldehyde

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 Acute toxicity

Several studies on the acute toxicity of nBA by the oral, dermal and inhalation routes have been reported, mostly in summarised form. These earlier investigations do not comply with current GLP requirements (CoR 1), because the purity of test substance, administered concentrations, strain and, number of animals and dose groups are often not specified (CoR 2).

8.1.1 Oral

Findings of acute lethality following oral administration of nBA to rats and rabbits are detailed in Table 15. The signs of intoxication were mainly associated with sedative effects on the CNS.

Table 15: Acute oral toxicity

Species, strain, number, sex	LD^{50} (mg/kgbw), 95% confidence limits	Observation period (d)	Effect	Remark	Reference	CoR
Rat						
Carworth-Wistar, NS	4,360 (3,980 - 4,780)	14	NS [a]		Smyth *et al*, 1951	2g
Osborne-Mendel, 5 M +5 F	2,510 (2,220 - 2,840)	14	Depression, comma, death after 4 - 18 h	Fasted animals	Jenner *et al*, 1964	2g
NS, 4 M 4 F	2,020 (1,180 - 3,280) 790 (280 - 2,240)	10	Death after 2 - 6 h, liver and kidney toxicity		Purchase, 1969	2e
Wistar, 10 M 10 F	3,829 (3,014 - 4,862) 3,831 (3,219 - 4,559)	7	Agitation, lateral	nBA solution 70% in water decubitus, dyspnoea	Ciugudeanu *et al*, 1985	2e
Rabbit						
NS	3,484 [a] (NS)	1	NS	ND_{50} [b] 815 mg/kgbw [c]	Munch, 1972	3a

[a] Reported as 47 mmol/kgbw

[b] Dose inducing narcosis in 50% of the animals

[c] Reported as 11 mmol/kgbw

NS Not stated

In the study of Purchase (1969), there was a large variability of lethality in the lower dose ranges (LD_{50} confidence limits for males and females overlapped). The author reported liver and kidney toxicity that was not observed in the other studies of Table 15. The Task Force considers that this might have been caused by possible impurities in the test substance.

8.1.2 Dermal

LD_{50} values following dermal administration of nBA to rabbits are presented in Table 16. In these studies, no data on exposure conditions or clinical signs were recorded.

Table 16: Acute dermal toxicity in rabbits

LD_{50} (mg/kgbw)	Reference	CoR
7,600 [a]	Treon, 1967	4b
5,300	Rowe and McCollister, 1982	4b,d
4,200	Rowe and McCollister, 1982	4b

[a] Reported as $LD_{67/24h}$ of 9.4 ml/kgbw

8.1.3 Inhalation

Results (LC_{50} values) and details of acute inhalation studies with nBA are presented in Table 17. Additional observations are reported below.

Table 17: Acute inhalation toxicity

Species, strain,	Time (h)	LC_{50} (ppm)	(mg/m3)	Effect	Reference	CoR
Rat						
Albino, 6 M	8	> 7,800	> 24,000 [a]	NS [b]	Smyth *et al*, 1951	2e
Sprague-Dawley, 10 M, 10 F	4	> 5,76	> 17,760 [c]	Slight decrease in body weight gain	Klimisch and Zeller, 1979	2c
Mouse						
NS	7	6,600 [d]	20,300	Giddiness after 1 h, prostration after 1.5 - 2h deep narcosis with loss of reflexes after 3 h and death of some animals	Rowe and McCollister, 1982	2g

[a] Reported as 24 mg/l, saturated vapour

[b] Range-finding, 14 d observation

[c] Reported as 17.76 ± 6.58 mg/l

[d] Reported value

NS Not stated

Rats survived inhalation exposure to saturated nBA vapour for 8 hours (Smyth *et al*, 1951). In mice, signs of intoxication were mainly associated with effects on the CNS (Rowe and McCollister, 1982).

When 0.2 ml (162 mg) nBA liquid was placed in the mouth of anaesthetised Sprague-Dawley rats and aspiration induced, 9 of 10 rats died instantly of respiratory and cardiac arrest due to the high concentration of nBA in the blood stream. Small areas of focal pulmonary haemorrhage and oedema were observed, but most of the pulmonary tissue appeared normal (Gerarde and Ahlstrom, 1966; CoR 3c).

RTECS (2000; CoR 4c) reported an LC_{50} value of 28,400 mg/m^3. No other details are available.

8.1.4 Other routes

LD_{50} values obtained after intraperitoneal injection of nBA in mice (> 2,000 mg/kgbw) (Maickel and Nash, 1985) and intravenous injection in dogs (1,260 mg/kgbw) (McGregor *et al*, 1964) do not indicate unusual differences in terms of species and administration routes. CNS depression, including hypothermia and decreased rotarod performance, are typical signs of nBA intoxication in mice and rats at dose levels of 1,000 - 2,000 mg/kgbw (Maickel and Nash, 1985; Mohler and Gordon, 1991).

8.1.5 Summary

The LD_{50} and LC_{50} values are mostly derived from old and/or poorly documented acute toxicity studies. However, they appear to show plausible values and a consistent pattern, which is not contradictory to what is known about other alcohols of similar chain length. The weight of evidence suggests that nBA is of low acute toxicity via the oral ($LD_{50} \geq$ 2,500 mg/kgbw), dermal ($LD_{50} \geq$ 4,200 mg/kgbw) and inhalation (LC50 > 20,000 mg/m^3) routes of exposure. At high dose levels or concentrations, nBA induces depressor effects on the CNS.

Although the studies on acute dermal toxicity are poorly reported, no serious or unexpected systemic toxicity was seen by any other route tested. The data do not support the current EC classification as harmful (Xn) (Section 2.2).

8.2 Skin, respiratory tract and eye irritation, sensitisation

8.2.1 Skin irritation

The skin irritation of undiluted nBA has been assessed in rabbits, using different methodologies. One test also included diluted nBA (Table 18).

Table 18: Skin irritation in rabbits

Method	Time (h)	Effect	Reference	CoR
Draize, occlusive	2	Irritant [a], superficial necrosis	Schreiber, 1979	2e
Draize, occlusive	1	Irritant	Schreiber, 1979	2e
Modified OECD, occlusive [b]	4	Irritant [c]	Jacobs *et al*, 1987	2a
NS, probably uncovered	9	Not irritant	McOmie and Anderson, 1949	2e
NS, probably uncovered	12 x 5 [d]	Slightly irritant, drying of skin	McOmie and Anderson, 1949	2e
Modified Draize, occlusive	24	Variable [e]	Weil and Scala, 1971	2e

[a] When extrapolated to EC/OECD method

[b] Teflon chamber

[c] Undiluted and diluted 50% (probably in water)

[d] For 21 d

[e] Results from 22 laboratories

There are two other reports of non-irritant or moderately irritant effects using an uncovered belly vesicant system. Details of the test method are not available (Union Carbide, 1951; CoR 4c; cited by RTECS, 1990; CoR 3a).

Whereas the study of Schreiber (1979) mentions superficial necrosis on occlusive application of nBA, the data of McOmie and Anderson (1949) show only minor irritation. The latter authors did not state whether the skin was exposed under cover. If not, the results could be explained by evaporation. There is no skin irritation test under semi-occlusive conditions (OECD 404).

In an interlaboratory study, Weil and Scala (1971) reported on a wide range of skin irritation reactions for nBA (including erythema, oedema and necrosis), with primary irritation scores ranging from 0.2 to 11.2 on a scale of 0 to 30. The results are difficult to evaluate as the exposure duration (24 h) extended beyond that of the OECD standard method (4 h).

On balance, nBA is irritant to the skin under occlusive conditions and slightly or not irritant under conditions allowing evaporation.

8.2.2 Eye irritation

The irritancy of undiluted and diluted nBA to the rabbit eye was assessed, following standard Draize or OECD 405 protocols. Some authors used a different scoring system (Table 19).

Table 19: Eye irritation in rabbits

Method	Dilution of nBA (%)	Time	Effect	Score [a]	Reference	CoR
Draize [b]	Undiluted	24 h	Irritant: some conjunctivitis, corneal oedema	18	McOmie and Anderson, 1949	2e
		72 h	Largely reversible	8		
		7 d	Reversible	Not stated		
Draize [c]	40	24 h only	Irritant: corneal effects	> 5.0 [d]	Carpenter and Smyth, 1946	2g
	15	24 h only	Irritant: corneal effects	≤ 5.0 [d]		
Draize	Undiluted	24 h	Moderately irritant	21.2 [e]	Weil and Scala, 1971	2e
		72 h	Moderately irritant	9.8 [e]		
		7 d	Largely reversible	2.0 [e]		
Draize	Undiluted	24 - 72 h	Moderately irritant	27.5	BASF, 1979	2e
		7 d	Reversible	0		
Draize	Undiluted	24 h	Largely reversible	19.5	Sugai *et al*, 1990	3a
Draize	Undiluted	24 h	Severely irritant	61 [f]	Kennah *et al*, 1989	2e
	30	24 h	Moderately irritant	45 [f]		
	25	24 h	Moderately irritant	34 [f]		
	15	24 h	Slightly irritant	4 [f]		
	10	24 h	Slightly irritant	3 [f]		
OECD 405	Undiluted	24, 48, 72 h	Irritant	60.8 [g,h]	Bagley *et al*, 1999	1a
		7, 10, 14, 21 d	Reversible	0	ECETOC, 1998	

[a] Maximum 110, according to the Draize scale (unless stated otherwise)

[b] Instilled not stated

[c] Instilled volume 50 µl

[d] Out of a maximum of 20; 10 was employed as maximum for nBA; > 5 considered as severe

[e] Mean of median Draize scores from 25 laboratories

[f] Draize score and correlation with corneal thickness

[g] Modified maximum average score, maximum 110

[h] Individual data according to EC classification are available (ECETOC, 1998)

In a data compilation to rank various chemicals for eye irritancy, nBA showed moderate corneal opacity, iritis and conjunctivitis, which were reversible within 7 days (ECETOC, 1998; Bagley *et al*, 1999; CoR 1a). In most of the other studies the irritant effects of nBA also proved to be reversible over 7 days.

The large data set from individual animals and laboratories reported by Weil and Scala (1971) showed a wide variability in susceptibility/sensitivity towards this test material.

Jacobs and Martens (1988, 1989; CoR 2e) presented *in vitro* data from an enucleated eye test. Scores for corneal opacity and for epithelial damage were presented that indicated a slight to moderate irritant potential. The test system has not been fully validated (Gettings *et al*, 1996), but appears to be able to recognise potent irritants.

In conclusion, undiluted nBA is moderately to strongly irritant to the rabbit eye, but the effects are reversible. Lower concentrations are moderately or slightly irritant.

8.2.3 Respiratory tract irritation

nBA is used as a positive control in studies investigating sensory irritation and effects on olfaction. RD_{50} values for respiratory rate depression in the mouse are presented in Table 20.

Table 20: Respiratory rate depression in the mouse

Exposure time (min)	RD_{50} (ppm)	(mg/m^3) [a]	Reference	CoR
5	1,268	3,910	De Ceaurriz *et al*, 1981; Schaper, 1993	2e
1	3,080	9,490	Korsak *et al*, 1993	2e
10	4,784	14,740	Kane *et al*, 1980	2e
1	11,696	35,050	Kristiansen *et al*, 1988	2e

[a] Converted values

8.2.4 Sensitisation

No sensitisation studies in experimental animals are available for nBA.

The structurally-related primary alcohol n-propanol showed no allergenic properties in a mouse ear swelling test, in a guinea pig maximisation test or in occluded patch tests (Gad *et al*, 1986).

Human experience with nBA does not indicate that there should be concern regarding sensitisation (Section 10.2).

8.2.5 Evaluation

The results of the available skin and eye irritation studies appear consistent when the differences in methodology are taken into account. On balance, undiluted nBA is slightly to moderately irritant to the skin, and shows acute eye irritation to a moderate to strong degree with complete reversibility within 7 to 21 days. The data do not support an EC classification of R41, risk of serious damage to eyes (Section 2.2).

nBA is not expected to be a sensitiser, taking into consideration the animal data with structurally-analogous alcohols (and also the human experience).

8.3 Repeated dose toxicity

8.3.1 Oral

Four groups of male and female CD rats (30/sex/group) were administered daily (not further specified; 5 or 7 d/wk) by gavage 0, 30, 125 or 500 mg nBA/kgbw/d for either 6 or 13 weeks. Body weight and food consumption were recorded weekly. Any signs of mortality and overt toxicity were noted twice a day. Ophthalmic examination was conducted prior to treatment and during week 13 before final necropsy. Clinical pathology of urine and blood was investigated, prior to study initiation, in a separate group of 10 male and 10 female rats, during week 6 in all surviving rats scheduled for interim kill and during week 13 in the first 10 male and 10 female rats scheduled for final necropsy. Ten male and ten female rats from each group were necropsied on study days 43 to 44 and the remaining animals on study days 92 to 93. Gross pathology of all animals was assessed and organs from animals necropsied on study days 92 to 93 were weighed. A complete histopathological investigation was made of all animals of the control and high-dose groups. In the low and mid-dose groups, histopathology included the liver, kidney, and heart from all animals and all gross lesions. All animals found dead or killed *in extremis* were also microscopically examined. No dose-related differences were observed between treatment or control rats in body or organ weight changes, food consumption or mortality, gross pathology, and histopathological and ophthalmic evaluations. Ataxia and hypoactivity (lasting less than 1 h) were observed 2 to 3 minutes after dosing in both sexes of the high-dose group (500/mg/kgbw/d) during the final 6 weeks of dosing. Such ataxia and hypoactivity are typically seen following high oral doses of alcohols. The rapid induction/remission of these effects and the reported increased incidence after the interim kill may be due to the fact that personnel were able to collect post-dose observations more quickly since fewer animals required dosing. nBA was not expected to persist or accumulate over time. No treatment-related signs were observed in the 30 or 125 mg/kgbw/d treatment groups, the latter value being the no-observed adverse effect level (NOAEL) (US-EPA, 1986; CoR 2e).

Thirty Wistar rats (4 wk) received 6.9% nBA (equivalent to 3,500 - 7,000 mg/kgbw) in drinking water containing 25% sucrose for up to 3 months; 30 male rats served as control. The authors did not report clinical, macroscopical and classical histological effects, but only described ultrastructural changes, namely elongated mitochondria (megamitochondria), without stating the frequency. The ultrastructural changes were not accompanied by functional changes; the coupling efficiency was preserved (Wakabayashi *et al*, 1984; CoR 3a).

8.3.2 Dermal

When nBA was applied under occlusion to rabbit skin (12 x 5 h) for 21 days, drying of the skin was reported and on continuous exposure, cracking, furrowing and exfoliation of the epidermis (McOmie and Anderson, 1949; CoR 2e).

8.3.3 Inhalation

In rodents, other oxidative enzymes such as catalase or cytochrome P450 may also play a significant role in the oxidation of nBA (Lieber *et al*, 1978). Inhalation of 2,000 ppm nBA (6,200 mg/m^3) over 3 days by male Sprague-Dawley rats was associated with a 30% increase of cytochrome P450 activity in the liver, but not in lung or kidney (Aarstad *et al*, 1985).

Male Sprague-Dawley rats (5/group) inhaling (6 h/d) 50 ppm nBA (150 mg/m^3) for 1 week, initially showed a decrease in the concentration of circulating testosterone and an increase in corticosterone. The concentration of luteinising hormone remained constant. Levels of testosterone and corticosterone returned to normal within 7 days of exposure (Cameron *et al*, 1985; CoR 1d).

Male Wistar rats (12/group) were exposed (6 h/d, 5 d/wk) to 50 or 100 ppm nBA vapour (150 or 310 mg/m^3) for 3 months. A group of 24 male rats was sham exposed and served as controls. The concentration of nBA was analysed by GC at 30-min intervals. Haematology of tail vein blood was evaluated prior to exposure and one week before study termination. Clinical biochemistry was investigated 24 hours after the final exposure. Liver microsomal mixed function oxidase levels were determined using cytochrome P450 as an indicator and liver peroxidation was measured by malon-dialdehyde formation. Neurological effects were assessed by means of the animals' performance on a rotarod, prior to and at monthly intervals during the study. Measurement of the level of analgesia was determined by hot plate avoidance behaviour at the end of the 3 months exposure period. No histological examinations were made. During the study, there were no deaths, or evidence of clinical signs of toxicity, at either exposure concentration. There were no effects on body weight or on absolute or relative (to body weight) organ weights of 7 organs examined. There was a slight but statistically significant decrease in haemoglobin concentration at both exposure concentrations (this did not appear to be dose-related) and a decrease in red blood cell count in the 100-ppm group. There were no statistically significant changes in serum enzymes or in mixed function oxidase activity, however, lipid peroxidation activity was increased at both exposure concentrations (this did not appear to be treatment-related). The authors reported a decreased performance on the rotarod at both concentrations, which increased as the study progressed. The decrease appeared to be dose-related (Task Force comment:

the data were only reported in graphical form and no tabular data for rotarod performance were presented). There were no apparent changes in sensitivity of thermal response at either concentration. Thus, the lowest-observed-effect level (LOEL) was 50 ppm (Korsak *et al*, 1994; CoR 3a). The description of the study shows no methodological deficiencies, but it lacks elements of a standard study for repeated exposure, including histopathological evaluation of tissues. No data were given on the nBA blood levels.

The above results indicate a moderately disturbed co-ordination performance, which is a frequent sequel of an unspecific solvent impact on the CNS (and not of neurotoxicity as such). (The same authors previously observed a similar effect in an acute exposure regimen at nBA concentrations of 500 ppm and higher [Korsak *et al*, 1993]). They do not indicate a neurotoxicity in the sense of irreversible effects on the CNS or peripheral nervous system. Further information corroborating this assessment may be taken from in-depth studies with *n*-butyl acetate (the latter is rapidly hydrolysed into nBA and acetate), (Section 9.4 and 9.2).

8.3.4 Summary and evaluation

The effects of repeated exposure to nBA have been investigated in rats in two studies, by the oral (gavage) and inhalation routes of exposure.

The most sensitive indicator of oral toxicity was ataxia and hypoactivity at 500 mg nBA/kgbw/d, the highest dose tested; this is typical of alcohol CNS depression. There was no clear evidence of other systemic toxicity. Slight effects on haematological parameters were noted in female rats at 500 mg/kgbw/d after 6 weeks, but not after 13 weeks of dosing. The NOAEL was 125 mg nBA/kgbw.

Neurological effects typical of alcohol CNS depression (as judged by measuring rotarod performance) were the endpoint of nBA exposure by inhalation at 50 and 100 ppm (150 and 310 mg/m^3). In addition, increased lipid peroxidation was noted at both exposure concentrations. The relevance of the latter observation is not clear. Slight and non-treatment-related decreases in red blood cell count at 50 ppm and in haemoglobin concentration at 50 and 100 ppm are consistent with some haematological findings of borderline significance in the gavage study. However, their biological relevance is questionable in view of the magnitude of the changes and the lack of a dose-response relationship. Thus, the LOAEL was 50 ppm.

The above oral and inhalation study results are not consistent with more recent, well-performed acute and repeat-dose neurotoxicity and behavioural studies with *n*-butyl acetate (which, following absorption, is rapidly cleaved into nBA), where NOAELs of 1,500 and 500 ppm, respectively, were identified (Section 9.4 and 9.2)).

8.4 Genotoxicity

8.4.1 *In vitro*

Gene mutation

nBA was tested in a number of gene mutation assays on different *Salmonella typhimurium* strains using a standard plate incorporation protocol in the presence and the absence of metabolic activation (Table 21). No signs of toxicity were reported. All tests demonstrated reproducibly that nBA is not genotoxic.

Aneuploidy induction was observed during early germination of *Aspergillus nidulans* at concentrations up to 1.0% nBA (v/v), the highest, cytotoxic concentration tested (Table 21).

Table 21: Gene mutation assays in bacteria and yeast

Species, strain	Concentration	Endpoint Metabolic activation [b]	Result [c]	Reference	CoR
Salmonella typhimurium	(µg/plate [a])	**Histidine reversion**			
TA98, TA100, UTH8413, UTH8414	≤ 2,000	Yes/No	-ve	Connor *et al*, 1985	2e
TA98 and TA100	NS	Yes/No	-ve	Khudoley *et al*, 1987	2e
TA100, TA1535, TA1537, TA98	NS	Yes/No	-ve	McCann *et al*, 1975	3a
TA102	≤ 5,000	Yes/No	-ve	Jung *et al*, 1992; Müller *et al*, 1993	1b1b
Aspergillus nidulans	(µg/ml)	**Mitotic chromosome segregation**			
Diploid strain P1	5,670 - 8,100 [d]	No	+ve	Crebelli *et al*, 1989	3b

[a] Plate incorporation assay

[b] Aroclor 1254-induced rat liver S9-mix

[c] -ve, negative: not mutagenic; +ve, positive: mutagenic

[d] Reported as 0.7 - 1.0% (v/v)

Chromosomal damage

nBA did not increase the frequency of micronuclei in male Chinese hamster lung fibroblast cells, nor the rate of sister chromatid exchanges in Chinese hamster ovary cells. No increase, above negative control, in DNA repair was seen in the *umu* test, with and without metabolic activation. No cytotoxicity was reported in those three tests (Table 22).

Table 22: Chromosome damage assays

Test system	Concentration) (µg/ml)	Metabolic activation	Endpoint	Result [a]	Reference	CoR
Male Chinese hamster lung (CHL) fibroblast V79 cells, micronucleus assay	810 - 40,500 [b]	No	Chromosome aberrations	-ve	Lasne *et al*, 1984	2a
Chinese hamster ovary (CHO) cells, 7 days	810 [c]	No	Sister chromatid exchanges	-ve	Obe and Ristow, 1977	1d
Salmonella typhimurium strain TA1535/pSK1002, *umu* test	≤ 27,000	Yes [d]/No	DNA repair	-ve	Nakamura *et al*, 1987	2a

[a] -ve, negative: not mutagenic

[b] Reported as 0.1 - 5% (v/v)

[c] Reported as 0.1% (v/v)

[d] Phenobarbital and 5,6-benzoflavone induced rat liver S9-mix

Chen *et al* (1984; CoR 3a) demonstrated that nBA inhibited the metabolic co-operation between 6 thioguanine sensitive and resistant Chinese hamster lung fibroblast (V79) cells.

8.4.2 *In vivo*

In a micronucleus assay, male and female NMRI mice (5 - 8 wk) received single oral doses of 0, 500, 1,000 and 2,000 mg nBA/kgbw (99.9% pure), in olive oil. Clinical signs of toxicity were evident at 2,000 mg/kgbw. Twenty-four hours after administration the animals were killed and the bone marrow examined for micronuclei in 2,000 polychromatic and normochromatic erythrocytes, and the ratio of polychromatic to normochromatic erythrocytes determined; a positive control group was also included. In addition, another 2,000 mg/kgbw group was evaluated 48 hour post-exposure for the same endpoints. No increase was noted in the number of normochromatic and polychromatic erythrocytes containing either small or large micronuclei and no inhibition of erythropoiesis or aneuploidy was detected (Engelhardt and Hoffmann, 1998; CoR 1a).

Up to 10 µl of a 15% solution of nBA in water (1,215 µg nBA) did not induce sister chromatid exchanges or chromosomal aberrations after 3 to 4 days in the Cornell K-strain chicken embryo *in ovo* cytogenetic assay. No signs of toxicity were reported (Bloom, 1981; CoR 2a).

8.4.3 Evaluation

There is no evidence of *in vitro* genotoxicity of nBA from bacterial mutagenicity, sister chromatid exchanges, and primary DNA damage assays. nBA induced aneuploidy in *Aspergillus nidulans*. No micronucleus induction was detected *in vitro* in V79 cells and *in vivo* in the bone marrow of mice after oral administration of nBA. Since micronuclei can reflect clastogenicity and aneuploidy, the latter result suggests that the *in vitro* aneuploidy results in *Aspergillus nidulans* are not significant to mammalian cells *in vivo*. nBA did not induce sister chromatid exchanges or chromosomal aberrations in chicken embryos.

In conclusion, the available data do not demonstrate that nBA has a genotoxic potential.

8.5 Chronic toxicity and carcinogenicity

No chronic toxicity studies have been carried out with nBA.

The US National Cancer Institute (cited in IPCS, 1987; CoR 4b) recorded two older Japanese long-term studies on rats, recorded by the US National Cancer Institute, without further documentation or reference. According to IPCS "Both of these studies were inadequate, by present standards, for the assessment of the carcinogenicity of the substance. No adequate data on carcinogenicity are available".

Due to the lack of mutagenicity and specific target/organ-directed repeat-dose toxicity, there is at present no evidence for carcinogenic effects of nBA.

8.6 Reproductive toxicity

8.6.1 Developmental toxicity

Pregnant Sprague-Dawley rats (15 - 18/group) were exposed (whole-body, 7 h/d) by inhalation to 0, 3,500, 6,000 or 8,000 ppm of nBA (0, 10,800, 18,500 or 24,700 mg/m^3) on day 1 to 19 of gestation. Dams were killed on day 20 and foetuses weighed and examined for malformations. Maternal toxicity and decreased food consumption were noted in the 6,000 and 8,000 ppm groups. Two of the 18 dams at 8,000 ppm died during the exposure period. At 8,000 ppm narcosis occurred in approximately half of the dams on gestation day 20. At 3,500 ppm no effects were seen in the dams. Foetal weights were slightly decreased at 6,000 and 8,000 ppm, but unaffected at 3,500 ppm. No effects were observed on the number of corpora lutea, resorptions, mean number of live foetuses or mean sex ratio. No external foetal malformations were observed and there were no differences in skeletal or visceral malformation rates, or in rates of commonly observed variations.

There was a slight increase in the percent of foetuses with rudimentary cervical ribs only in the 8,000-ppm group. Considering the pronounced maternal toxicity at 8,000 ppm, the developmental toxicity of nBA appeared to be low and did not indicate selective foetal effects. The NOAEL for maternal and foetal toxicity was 3,500 ppm. For foetuses, the LOAEL based on a slight decrease in foetal weight was 6,000 ppm (Nelson *et al*, 1989a; CoR 1d).

In a behavioural teratology study, male Sprague-Dawley rats (18/group) were exposed (7 h/d) to concentrations of 0, 3,000 or 6,000 ppm nBA (0, 9,200 or 18,500 mg/m^3) for 6 weeks. The males were then mated to non-exposed females. Separate groups of 15 pregnant females were exposed (7 h/d) to the same concentrations from day 1 to 20 of gestation, and were allowed to deliver. The offspring from those two groups were observed during postnatal days 10 to 90 for signs of developmental neurotoxic effects by measuring ascent on a wire mesh screen, rotarod and running wheel performance, open-field and photoelectrically-monitored activity, avoidance conditioning and operand conditioning. In addition, the neurochemical levels of acetylcholine, dopamine, norepinephrine, serotonin, met-encephalin, β-endorphin, and substance P neurotransmitter, were measured in the cerebrum, cerebellum, brainstem, and midbrain. No general toxicity to maternal and paternal animals was reported. No detectable effect on pregnancy rate was found after either maternal or paternal exposure. In the 6,000 ppm group, 5% (4/78) of behavioural and 6% (4/64) of neurochemical measures differed from those of controls. There were no discernible patterns of effects. The authors concluded that "In view of this, it is highly unlikely that administration of nBA at the current Permissible Exposure Limit (PEL) of 100 ppm would produce structural or behavioural teratogenicity in rats using the test employed here." The NOAEL for maternal and paternal animals, and their offspring was 6,000 ppm (Nelson *et al*, 1989b; CoR 1d).

Female rats (undefined strain, breeding colony Nofer Institute of Occupational Medicine, Lodz, Poland) (11 - 17/group) were given drinking water containing 0, 0.24, 0.8 and 4% [a] of nBA (probably nominal concentrations, equivalent to doses of 0, 300, 1,000 and 5,000 mg nBA/kgbw/d) for 8 weeks, during which time oestrus cyclicity was evaluated. After the 8 week exposure period the females were mated with untreated males for 3 weeks. Dosing of the females continued until the animals were killed on day 20 of gestation, when foetuses were collected and examined for skeletal and visceral malformations. Weight gain, food and water consumption, and general behaviour were recorded during pre-mating (8 wk), mating (3 wk) and gestation (20 d). The unit of statistical analysis in this study was the individual foetus, not the litter. General appearance, food consumption, body weight, rate of weight gain, oestrus cycle length and number, absolute and relative organ weight (not specified), haemoglobin concentration, haematocrit values, foetal body weights, intra-uterine mortality, corpora lutea, total implants, and placental weight were unaffected by nBA exposure.

[a] The 4% solution was described as delivering total daily doses twice as high as the acute oral LD_{50} (~ 2.1 g/kg/d by gavage). This may correspond to the rapid metabolism, but, in addition, may also reflect a reduced water intake.

At 4% the crown-rump length was decreased (mean of 4.0 to 3.8 cm for the control and treated group, respectively). Developmental effects were reported in all 3 dose groups. Skeletal effects were limited to an extra 14th rib in 1 foetus in the low dose group and 2 foetuses in the high dose group, and wavy ribs in 1 foetus in the low dose group. CNS defects included dilation of either the subarachnoid space or lateral and/or third ventricles of the brain, or external or internal hydrocephalus. Dilated renal pelves were also observed. Of the 65 control foetuses examined for skeletal effects, none had an extra fourteenth or wavy rib(s) or any other skeletal malformation or variation. Two of the 61 control foetuses examined for visceral anomalies had dilatation of the lateral and/or third ventricles of the brain, while none had dilatation of the subarachnoid space or external or internal hydrocephalus. Although the authors considered all 3 dose levels as related to increased foetal effects when compared to controls, there was no dose-dependent increase. The NOAEL for maternal toxicity was 5,000 mg nBA/kgbw/d; a NOAEL was not reported for offspring (Sitarek *et al*, 1994; CoR 3b). However, since no foetus of the middle dose group was affected, and only 2 in the low dose, it appears probable that the observations in the low dose group were not treatment related.

The authors considered the recorded developmental effects (dilatation of the brain ventricles/spaces or renal pelvis, internal hydrocephalus, wavy or extra ribs) as being related to nBA and assessed these findings as variations or delayed development commonly seen in large historical control databases. Of significance, the incidence of all but one of the reported developmental effects in the actual control population was 0%. In the MARTA-MTA 1995 database, using Crl:CD BR rat, the incidence of "cerebral ventricle, enlargement" was 2%/foetus or 4.4%/litter, and the incidence of "renal pelvis, dilated" 0.95%/foetus or 5.2%/litter (Wise and Petrere, 1996). The "malformations" reported that were assessed as "variations" in other databases should be classified based on the incidence within the rat strain. The incidence of variations within the rat strain used in this study is unknown, since the authors used a rat strain common only to their laboratory in Poland. The laboratory diet was also unique. Since the strain of rat and type and quality of diet can have profound effects on rates of variations and malformations, and since there is no historical database available for the strain tested, the term "variation" has to be assigned with reservation. However, the term may still be appropriate since the variations reported are also common in several rat strains frequently used in the USA. In fact, Nelson *et al* (1989a) described some of these variations following inhalation exposure to nBA. It should not be surprising that high oral doses of nBA that alter normal maternal physiology would also cause an increase in common variations in laboratory rodents. Thus, the developmental effects seen by Sitarek *et al* (1994) cannot be regarded as a selective foetal effect.

8.6.2 Fertility and effects on reproductive organs

In a behavioural teratology study, male Sprague-Dawley rats (18/group) were exposed (whole-body, 7 h/d) to concentrations of 0, 3,000 or 6,000 ppm nBA (0, 9,200 or 18,500 mg/m^3) for 6 weeks. The males were then mated with non-exposed female rats. Separate groups of 15 pregnant female rats were exposed (7 h/d) to the same concentrations from day 1 to 20 of gestation, and were allowed to deliver. The offspring from those two groups were observed for signs of developmental neurotoxicity (Section 8.6.1). No general maternal or paternal toxicity was reported. Paternal exposure had no detectable effect on pregnancy rate in non-exposed females; maternal exposure was also without detectable effect on pregnancy rate. Although the study was designed to provide animals for postnatal assessment of developmental neurotoxicity, the lack of effect on pregnancy rate following either maternal or paternal exposure suggested that nBA had no effect on fertility up to 6,000 ppm (Nelson *et al*, 1989b; CoR 1d).

Female rats (undefined strain, breeding colony Nofer Institute of Occupational Medicine, Lodz, Poland) (11 - 17/group) were given drinking water containing 0, 0.24, 0.8 and 4% [a] of nBA (probably nominal concentrations, equivalent to doses of 0, 300, 1,000 and 5,000 mg nBA/kgbw/d) for 8 weeks, during which time oestrus cyclicity was evaluated. After the 8 week exposure period the females were mated with untreated males for 3 weeks. Dosing of the females continued until the animals were killed on day 20 of gestation, when foetuses were collected and examined for skeletal and visceral malformations (Section 8.6.1). No effects were noted on the number and length of the oestrous cycles, while foetal body weight, intrauterine mortality, corpora lutea, total implants, and placental weights were unaffected (Sitarek and Berlinska, 1996; CoR 3b). These results confirm the finding of Nelson *et al* (1989a) that nBA has a low propensity for affecting the reproductive ability of rats at relatively high exposures.

8.6.3 Summary and evaluation

Treatment of rats with up to 8,000 ppm nBA by inhalation for 6 weeks prior to mating did not affect male fertility when bred to non-exposed females.

Additional supportive evidence for this conclusion comes from a 13-week inhalation study with *n*-butyl acetate, which is rapidly cleaved into nBA (Section 9.1.1), that showed no effects up to 3,000 ppm on homogenisation-resistant spermatid head counts from both the testes and the epididymides and on reproductive organ histopathology (Section 9.3.2).

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[a] The 4% solution was described as delivering total daily doses twice as high as the acute oral LD_{50} (~ 2.1 g/kg/d by gavage). This may correspond to the rapid metabolism, but, in addition, may also reflect a reduced water intake.

Female rats dosed up to 5,000 mg nBA/kgbw/d via drinking water did not produce altered oestrous cycles, fertility rates, or reduced number of offspring. In several developmental toxicity studies, exposure to nBA, either by inhalation or via the drinking water, did not affect the ability of female animals to successfully maintain pregnancies and produce viable litters.

Exposure of pregnant animals to high levels of nBA by inhalation caused significant toxicity to the dams and slight developmental toxicity in the offspring. Tests for developmental neurotoxicity at similar exposure concentrations did not reveal any pattern of effects suggestive of structural or behavioural teratogenicity. Interpretation of a developmental toxicity study conducted via drinking water is problematic as common variations were termed malformations and the control animals had an unusually low incidence (0% in most cases) of variations and/or malformations.

The weight of evidence suggests that nBA is not a selective developmental toxicant and induces developmental toxicity only at high doses that also cause significant toxicity to the dam.

In conclusion, nBA does not present a hazard for male or female reproductive function in experimental animals.

8.7 Neurotoxicity

Experimental investigations into the neurotoxic potential of nBA have been carried out in the frame of subacute and subchronic toxicity studies with nBA (Section 8.3). nBA caused a concentration-dependent reduced performance in the rotarod test at 50 and 100 ppm (150 and 310 mg/m^3) during the course of a 3-month inhalation study. This observation was indicative of CNS depression; it is frequently recorded with most organic solvents at high(er) levels. The sensitivity in the thermal response assay was not influenced (Korsak *et al*, 1994; CoR 3a) (Section 8.3.3).

Additional data from well designed neurotoxicity studies with *n*-butyl acetate (that is rapidly cleaved into nBA; Section 9.1.1) do not indicate selective neuro- or CNS-related toxicity. Transient signs of reduced general activity levels at airborne exposure concentrations of 1,500 and 3,000 ppm were observed (David *et al*, 1998; CoR 1a) (Section 9.3).

In a well-designed developmental study following prenatal exposure of rats to nBA, no behavioural effects on offspring were found (Nelson *et al*, 1989b) (Section 8.6.1).

Overall, nBA does not show selective or cumulative neurotoxicity in experimental animals.

9. OTHER CONSIDERATIONS AND SUPPORTIVE DATA ON *n*-BUTYL ACETATE

nBA is the product of the rapid hydrolysis of *n*-butyl acetate [a] *in vivo*. The enzymes responsible are predominantly located in the liver and therefore, systemic exposure to nBA requires a lag time of a few seconds after the onset of *n*-butyl acetate exposure.

9.1 Metabolism

9.1.1 Formation of nBA

When *n*-[1-^{14}C]butyl acetate was injected into the tail vein of 32 male Sprague-Dawley rats at a mean dose of 30.2 mg/kgbw (16.8 μCi/rat), rapid systemic distribution of radioactivity occurred, followed by rapid elimination from the tissues, as measured by liquid scintillation analysis of whole blood and brain tissue samples. HPLC with radiochemical detection was used to separate and quantitate *n*-butyl acetate, its hydrolysis product nBA, and products of the subsequent oxidative and conjugate metabolism of nBA (Figure 6, Section 7.3). The analyses indicated that *n*-butyl acetate was rapidly eliminated from the blood ($t_{1/2}$ = 0.41 min), and was detected in brain tissue only at low concentrations (mean maximum of 3.8 μg equivalents [b]/g at 1.9 min) in the first 2.5 minutes following dosing. The higher concentrations of nBA, found in both blood (C_{max} = 52 μg equivalents/g at t_{max} [c] 2.6 min) and brain (C_{max} = 79 μg equivalents/g at t_{max} 2.5 min), were also rapidly eliminated ($t_{1/2}$ = 1.0 - 1.2 min) and were undetectable 20 minutes post dosing. *n*-Butyric acid was present at low concentrations in blood (mean maximum of 5.7 μg equivalents/g at 7.4 min) that declined slowly following dosing; it was largely undetected in brain tissue. Early eluted polar metabolites (presumably Krebs cycle intermediates of [^{14}C]nBA and glucuronide and sulphate conjugates of [^{14}C]nBA) were detected in whole blood (mean maximum of 12.2 μg equivalents/g at 4.2 min); trace amounts were seen in brain tissue. The hydrolysis of *n*-butyl acetate in blood and brain was estimated to be 99% complete within 2.7 min at this dose level (Deisinger and English, 1997; CoR 2e).

Data on *n*-butyl acetate should not be used indiscriminately as representative of nBA. The enzyme capacity for the hydrolytic cleavage of nBA to *n*-butyl acetate may become saturated at excessive concentrations, and particularly the local and acute effects of both materials may not be identical. Furthermore, it is known that the acetate moiety has some propensity to exert cellular metabolic acidosis, e.g. at the olfactory epithelium.

No data are available on the hydrolysis rate in humans. It is, however, generally known that unspecific esterases are widespread in all mammalian tissues and that esters of primary alcohols are accessible to those enzymes.

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[a] CAS No. 123-86-4, formula: $CH_3CO_2(CH_2)_3CH_3$; molecular mass 116

[b] Since only the radioactivity is counted, the μg/g tissue may represent *n*-butyl acetate, nBA or further sequel products

[c] Time of maximum nBA concentration

Due to the rapid cleavage in rats, several studies on the systemic toxicity of *n*-butyl acetate may be of relevance to corroborate the data base on nBA in rats. These studies are detailed below.

9.2 Repeated dose toxicity

Bernard and David (1996; CoR 1a) exposed (whole-body, 6 h/d, 5 d/wk) male and female Sprague-Dawley rats (15/sex/group) to concentrations of 0, 500, 1,500 or 3,000 ppm of *n*-butyl acetate (0, 2,400, 7,200 or 14,500 mg/m^3) [a] for 13 weeks. The time-weighted average analytical concentrations were within 10% of the target concentrations. No spontaneous mortality occurred during the study. Animals were observed for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to 1 hour after exposure. There was minor reduction in physical activity levels during exposure of rats to 3,000 ppm. Signs of sialorrhea and red discoloration on the chin hair were also observed. The physical activity of rats exposed to 1,500 ppm was also reduced during exposure, though generally with minimal severity. Control and 500 ppm animals appeared normal during exposure. After exposure, animals in all groups had porphyrin nasal discharges and dried porphyrin stains around the nose. These clinical signs were also seen occasionally during the morning examination before exposure. Mean body weights of the 3,000 ppm group were significantly lower than the control group for males and females. Overall weight gains at 3,000 ppm were 62% and 78% of weight gains for the controls (males and females, respectively). Mean food consumption of the 3,000 ppm group was significantly lower than the control values throughout the study for male rats and at all intervals except days 84 and 91 for female rats. Mean weekly food consumption at 3,000 ppm was 14 - 25% lower than that of the controls for male rats and 6 - 16% for female rats. Mean body weights of the males and females at 1,500 ppm were significantly lower than the controls. However, overall weight gains for males and females were 90 and 107% of the control group, respectively. Mean food consumption of the 1,500 ppm group was significantly lower and mean weekly food consumption lower than those of the controls, both in male and female rats. Mean body weights at 500 ppm were comparable to the control group throughout the study, and no statistically significant differences were noted. However, mean food consumption at 500 ppm was significantly lower than controls for male and female rats at several time points during the study. Mean weekly food consumption at 500 ppm was 3 - 12% lower than controls for male rats and 2% higher to 7% lower for female rats.

Blood was collected from 5 animals per group after 30 days of exposure, and from 10 animals per group at termination. No significant differences in haematological parameters were seen after 30 days of exposure. Slightly higher erythrocyte counts, haematocrit levels, and haemoglobin concentrations were observed for the 3,000 ppm male and female rats after 90 days; none of the differences was considered to be biologically significant.

[a] 1 ppm = 4.829mg/m^3

Evaluation of blood cell morphology did not suggest any compound-related effects. After 30 days of exposure, slight but significantly lower mean sodium concentrations were observed in males and females at 3,000 ppm compared with controls, and significantly lower mean chloride concentrations for the 1,500 ppm males. No other differences in serum chemistry were seen. After 90 days exposure, minor but statistically significant changes were observed in mean albumin (lower) and total protein concentrations (lower) for the 3,000 ppm females, and mean sorbitol dehydrogenase activity (higher) for the 1,500 ppm males. These changes were not considered to be toxicologically relevant.

No treatment-related ophthalmologic changes were observed. Mean terminal body weights were significantly lower in the 1,500 and 3,000 ppm males and females than in the controls. Mean absolute liver, kidney and spleen weights were significantly lower, but relative organ weights (to body weight) were not significantly different with one exception, i.e. the mean spleen-to-body weight ratio for the 3,000 ppm males was significantly lower than for the controls. In addition, mean testes-to-body weights for the 1,500 and 3,000 ppm males and the mean relative lung weight for the 3,000 ppm males were significantly higher than for the controls. Mean adrenal gland-to-body weight ratios for the 1,500 ppm female and 3,000 ppm male and female groups were significantly higher than for the respective controls.

Signs of irritation of the glandular stomach and necrosis in the non-glandular stomach were observed in two 3,000 ppm female rats. Focal necrosis of the olfactory epithelium was seen in the nasal passages of some rats exposed to 1,500 and all rats at 3,000 ppm. The severity of the olfactory lesion was mild to moderate at 3,000 ppm and minimal to mild at 1,500 ppm. No lesions were observed in the nasal passages at 500 ppm. Inflammation of the stomach mucosa (glandular or forestomach) was also observed microscopically in a few 3,000 ppm female rats; this lesion may be due to stress. Other lesions that were observed microscopically were not considered to be compound-related. There was no effect on either epididymal or testicular sperm counts.

In conclusion, exposure of rats to *n*-butyl acetate vapour resulted in acute, transient signs of reduced physical activity levels during exposure to 1,500 and 3,000 ppm. Decreased body weight and food consumption were noted at 1,500 and 3,000 ppm, but there was no systemic, organ-specific toxicity. Signs of upper respiratory tract irritation were seen in the nasal passages of 1,500 and 3,000 ppm animals. The NOAEL for this study is considered to be 500 ppm *n*-butyl acetate (2,400 mg/m^3). This would be equivalent to 500 ppm nBA (1,500 mg/m^3).

9.3 Reproductive toxicity

9.3.1 Developmental toxicity

Pregnant Sprague-Dawley rats (4 x 37 - 43 females) were exposed (whole body, 7 h/d) to *n*-butyl acetate concentrations in air of 0 or 1,500 ppm (0 or 7,200 mg/m^3) for 3 weeks. Group 1 was not exposed to test material throughout the study and served as control. Group 2 was continuously exposed to 1,500 ppm *n* butyl acetate from day 7 to 16 of gestation and group 3 from day 1 to 16 of gestation. Group 4 was exposed (5 d/wk) for 3 weeks prior to gestation and then continuously from day 1 to 16 of gestation. All exposures were discontinued from gestation day 17 until study termination. On gestation day 21 (sperm positive = day 1), the foetuses were collected and examined for both skeletal and visceral malformations. Food consumption was decreased in each test group in the week following initiation of *n*-butyl acetate exposure. The decrease in food consumption was accompanied by decreases in body weight in Group 3 and 4. Relative kidney and lung weights were increased in animals exposed to *n*-butyl acetate, with the greatest increase occurring in animals receiving the longest exposure. There were no changes in histopathology that could be attributed to *n*-butyl acetate exposure. Mating and reproductive performance and intrauterine mortality were unaffected. Foetal growth measurements (foetal body weights and crown-rump length) and placental weights were lower in Groups 2, 3, and 4. However, the duration of exposure and period of gestation during which exposure occurred did not affect foetal growth indices. Sex ratios were unaffected. There was no increase in the incidence of "major malformations" in any of the *n*-butyl acetate exposed groups. There was an increase in the incidence of skeletal anomalies ("total rib dysmorphology") and skeletal variation ("reduced ossification of the pelvis") in Groups 2 and 3, but not in Group 4. The incidence of rib dysmorphology in the control population was zero. Group 4 had an increased incidence in "hydroureter" when compared to the control group (Group 1); Groups 2 and 3 were unaffected. Because none of the observed foetal anomalies were seen in all treatment groups, each of which included exposure to the same dose (1,500 ppm) of *n*-butyl acetate over the period of organogenesis (gestation days 7-16) the authors did not consider these effects to be evidence of teratogenicity of *n*-butyl acetate (Hackett *et al*, 1982; CoR 2e).

Pregnant New Zealand white rabbits (3 x 21 - 25 females) were exposed (whole-body, 7 h/d) to *n*-butyl acetate concentrations in air of either 0 (control) or 1,500 ppm (0 or 7,200 mg/m^3) for 19 days. Rabbits in all groups were housed outside of the exposure chambers between exposure periods. Group 1 received sham exposures to filtered air throughout the study and served as controls; Group 2 was exposed to 1,500 ppm *n*-butyl acetate from day 7 to 19 of gestation and Group 3 was exposed to test material from gestation day 1 to 19. All test material exposures were discontinued from gestation day 20 through study termination on gestation day 30, when the foetuses were collected and examined for both skeletal and visceral malformations. Food consumption was decreased in Group 2 and 3 in the week following initiation of *n*-butyl acetate exposure, but also in controls. The body weight in Groups 2 and 3 were consistently higher than in controls;

organ weights and histopathology appeared normal in the *n*-butyl acetate exposed animals. Mating and reproductive performance and intrauterine mortality were unaffected by *n*-butyl acetate exposure. Foetal growth measures (foetal body weights and crown-rump length), placental weights, and sex ratios were not affected by *n*-butyl acetate exposures. There was no increase in the incidence of "major malformations" in any of the *n*-butyl acetate exposed groups. In terms of "minor anomalies", there was an increase in the incidence of "misaligned sternbrae" and "retinal folds" in Group 3; Group 2 was not affected. The only increased incidence in "morphologic variations" was an increase in "clear gallbladder"; and that only in Group 3. The authors concluded that rabbit foetuses were unaffected by *n*-butyl acetate exposure as none of the effects occurred in both exposure groups (Hackett *et al*, 1982; CoR 2e).

Evaluation

Exposure of pregnant animals to high concentrations of *n*-butyl acetate by inhalation caused slight maternal toxicity in all studies conducted to date. Some developmental toxicity was also observed at those high exposure concentrations, although those findings are not consistent across the treatment groups of the studies, with one reporting a slight increase and another reporting no effect. The lack of continuity and similarity for these findings suggests that they are incidental and unrelated to *n*-butyl acetate exposure. This is also the conclusion of the study authors.

9.3.2 Fertility and effects on reproductive organs

Sprague-Dawley rats (10/sex/group) were exposed by inhalation (whole-body, 6 h/d, 5 d/wk) to concentrations of 0, 500, 1,500, or 3,000 ppm of *n*-butyl acetate (0, 2,400, 7,200 or 14,500 mg/m^3) for 13 weeks. The study was conducted according to the US-EPA Toxic Substances Control Act Health Effects Testing Guidelines, with the exception that the histology of tissues from the central and peripheral nervous systems was not examined. (Those tissues were evaluated in a companion neurotoxicity study, reported in Section 9.4, using animals exposed concurrently with the animals from the study). Exposures to *n*-butyl acetate vapour resulted in acute, transient signs of reduced activity levels during exposure to 1,500 and 3,000 ppm. There was decreased body weight and food consumption at 1,500 and 3,000 ppm, but no systemic, organ-specific toxicity. Signs of irritation were seen in the nasal passages of 1,500 and 3,000 ppm animals. The left testis and left epididymis of each male rat were frozen at -25°C for evaluation of homogenisation-resistant sperm counts. The right testis and right epididymis of each male rat were processed for histopathological examination. No exposure-related effects on epididymal or testicular sperm count or histopathology was observed (Bernard and David, 1996; CoR 1d). Since *n*-butyl acetate is rapidly hydrolysed on entering systemic circulation, any effects would be likely to be caused by nBA. Since no changes were noted, it is not anticipated by the Task Force that equivalent doses of nBA would have adverse effects on the male reproductive tract.

Four groups of 37 - 43 female Sprague-Dawley rats were exposed (7 h/d) to *n*-butyl acetate air concentrations of 0 or 1,500 ppm (0 or 7,200 mg/m^3). The rats were maintained in the exposure chambers throughout the study for 3 weeks before gestation until gestation on day 21. Group 1 was not exposed to test material throughout the study and served as the control. Group 2 was continuously exposed to 1,500 ppm *n*-butyl acetate from day 7 to 16 of gestation and group 3 from day 1 to 16 of gestation. Group 4 was exposed (5 d/wk) for 3 weeks prior to gestation and then continuously from day 1 to 16 of gestation. All test material exposures were discontinued from gestation day 17 until study termination. On gestation day 21 (sperm positive = day 1), the foetuses were collected and examined for both skeletal and visceral malformations (Section 9.3.1). Mating and reproductive performance and intrauterine mortality were unaffected by *n*-butyl acetate exposure. Although the study was designed to provide animals for assessment of developmental toxicity, the lack of effect on pregnancy rate following maternal exposure (pre-mating and during exposure) to 1,500 ppm indicated that *n*-butyl acetate and therefore, its metabolite nBA, had little or no potential to affect fertility in female rats (Hackett *et al*, 1982; CoR 2e).

Evaluation

There was no effect of up to 3,000 ppm of *n*-butyl acetate for 13 consecutive weeks on homogenisation-resistant spermatid head counts from both the testes and the epididymides or on reproductive organ histopathology. Female rats exposed via inhalation to 1,500 ppm *n*-butyl acetate for 3 weeks prior to mating and up to day 16 of gestation did not have altered fertility rates or reduced number of offspring. Female rats exposed for different times during gestation were able to successfully maintain pregnancies and produce viable litters. Though there are no data from conventional studies designed specifically to investigate effects on fertility and reproductive function, the findings of these studies provide a strong indication that *n*-butyl acetate does not present a reproductive hazard to both male and female animals. This conclusion is given further support by data from the sub-chronic and developmental toxicity studies that showed no evidence for effects on the male and female reproductive organs, even at the highest dose levels, for both *n*-butyl acetate and its major metabolite, nBA.

9.4 Neurotoxicity

Bernard and David (1994; CoR 1d) exposed (whole-body) male and female Sprague-Dawley rats (10/sex/group) by inhalation to 0, 1,500, 3,000 or 6,000 ppm of *n*-butyl acetate (99% pure) (0, 2,400, 7,200, 14,500 or 29,000 mg/m^3) for a single 6-hour period. The study was conducted according to the US-EPA Toxic Substances Control Act Health Effects Testing Guidelines and included post-exposure motor activity (MA) measurement and a functional observational battery (FOB). Animals near the chamber windows were observed every 30 minutes during exposure. Beginning immediately after onset and

continuing until the end of the exposure, there was minimally reduced activity (hypoactivity) and minimally reduced responses to extra-chamber stimulation (tapping on the outside wall of the inhalation chamber). At 6,000 ppm, the severity of hypoactivity was minor to moderate. At 3,000 ppm, the severity of hypoactivity in female rats was minor, while male rats were characterised as having minimal hypoactivity. Only minimal hypoactivity was observed at 1,500 ppm. Sialorrhea was observed in exposed male rats, but only occasionally in exposed female rats. Tearing was also noted occasionally in treated female rats. There were no deaths during exposure and no clinical signs were noted at any time post-exposure. Mean total MA and total ambulations on day 0 (post-exposure) by the 3,000 and 6,000 ppm male and female groups were significantly lower than those of the controls, but no differences were noted on days 1, 7 or 14. The FOB was performed on all animals 6 days prior to the exposure and again after MA determination on day 0, and on days 7 and 14. On day 0, the hair coat scores of the 6,000 ppm male and female groups were significantly higher than the controls, indicating that the hair coat appeared slightly unkempt. In addition, forelimb grip strength for the females at 3,000 ppm was significantly higher on day 0 than for the control group. No differences were noted on days 7 and 14. Individual animal body weights were measured on day 0, prior to exposure, and on days 7 and 14 prior to FOB examinations. The male 6,000 ppm rats had significantly lower mean body weights on days 7 and 14 than the controls. Male 1,500 ppm rats also had significantly lower mean body weights on day 7. The differences in mean body weight between treated and control groups were less than 10%. No differences were noted among female rats or between male 3,000 ppm rats and the control group. No treatment-related gross lesions were noted at necropsy. These results indicated that *n*-butyl acetate, at concentrations up to 6,000 ppm, reduced activity and response to stimulus during exposure. Thus, no NOAEL could be established. Immediately after exposure, transient decreases in MA occurred in groups exposed to 3,000 and 6,000 ppm. These changes were not observed during the FOB examination after MA on day 0 or on the day after exposure, indicating a transient effect. The authors considered 1,500 ppm to be the NOAEL for changes that occurred after the animals were removed from the vapour.

Bernard and David (1996; CoR 1d) conducted a 13-week inhalation neurotoxicity study according to the US-EPA Toxic Substances Control Act Health Effects Testing Guidelines. The study consisted of two sets of Sprague-Dawley rats: (i) male and female ad *libitum*-fed animals for FOB, MA and neuropathology (NP) endpoints, and (ii) male rats restricted to 12 - 14 g food/d for schedule-controlled operand behaviour (SCOB). Both sets were exposed (6 h/d, at least 65 exposures) to concentrations of 0, 500, 1,500 or 3,000 ppm of *n*-butyl acetate (0, 2,400, 7,200 or 14,500 mg/m^3) for 14 weeks. The time-weighted average analytical determinations of the test substance vapour concentrations were within 10% of the target concentrations. Nominal concentrations were generally 13 - 70% higher than the concentrations measured analytically. Animals were observed daily for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to 1 hour after exposure. No mortality occurred during the study.

Neurotoxicity was evaluated in *ad libitum*-fed animals using FOB and quantitative measurement of MA during weeks 1, 4, 8, and 13, and NP at termination. SCOB testing was conducted daily in food-restricted male rats. Prior to *n*-butyl acetate exposure, rats were trained to obtain food rewards by pressing a lever 20 times (Fixed Ratio 20, FR_{20}) and after a 120 seconds interval (Fixed Interval 120, FI_{120}). The animals were then tested on a schedule of 4 x FR_{20} and 2 x FI_{120} in 47-min sessions (1 x/d, 5 d/wk) during weeks 1 - 13 of exposure and weeks 14 and 15 following cessation of exposure.

Animals exposed to 1,500 ppm and higher had minor reduction in activity levels. There was no evidence of a cumulative effect on the severity of the reduced activity. Control and 500 ppm animals appeared normal during exposure. There were no other apparent differences in the clinical condition of FOB/MA/NP and SCOB animals. Mean body weights and body weight gains of the 3,000 ppm male and female ad *libitum*-fed rats were significantly lower than in controls. At 1,500 ppm, there was still some decreased body weight gain among *ad libitum*-fed females. Mean body weight gains for the 500 ppm *ad libitum*-fed groups were comparable to controls throughout the study. No differences in body weight were noted among the male SCOB rats. There was no evidence of neurotoxicity during FOB examinations. Mean total MA at 3,000 ppm was significantly higher in males than controls during week 4. Mean total MA counts for all male groups were closer to baseline values during weeks 8 and 13 and no significant differences were observed among groups. No time-treatment interactions were observed in total ambulations for male groups, and no significant MA differences were present in female rats. No significant differences were seen in SCOB at any air concentration. No treatment related changes were detected during gross necropsy examinations of male or female FOB/MA/NP rats exposed to the test substance. Microscopic evaluations of sections from the brain, spinal cord (cervical and lumbar regions), dorsal and ventral spinal roots, dorsal root ganglia, sciatic nerve, and tibial nerve of animals in the control and 3,000 ppm groups did not reveal any treatment-related effects.

In conclusion, repeated exposure to *n*-butyl acetate vapour at 1,500 and 3,000 ppm resulted in acute, transient signs of reduced activity during exposure. There was no evidence of a cumulative effect on activity during the 13-week exposure period. In addition, there was no evidence of neurotoxicity based on FOB, MA, NP, and SCOB endpoints. Therefore, the NOAEL for subchronic neurotoxicity to *n*-butyl acetate for this study was 3,000 ppm.

Since the *n*-butyl acetate is rapidly hydrolysed to nBA and acetic acid on entry into systemic circulation, it is not anticipated by the Task Force that nBA would have effects other than transient CNS depression.

10. EFFECTS ON HUMANS

10.1 Acute and subchronic toxicity

10.1.1 Acute toxicity

Oral, intramuscular, or intravenous administration of 5 to 10 ml of a saturated nBA solution in saline or water (presumably 7%; 0.35 - 0.70 g nBA) given to 344 patients with profuse haemorrhage successfully controlled bleeding and did not elicit any signs of adverse effects (Revici and Ravich, 1953).

Welt (1950) reported another study by Ravich and Revici where patients tolerated intravenous infusion of 500 ml nBA solution (7%; 35 g nBA) and 10 daily oral doses of up to 1,500 ml nBA solution (7%; 10 x 105 g nBA) with no negative effects. Based on these observations and a further study including 938 patients, nBA was found to be an effective means of pain control.

10.1.2 Short- and long-term exposure

During controlled experiments on the kinetics and metabolism of nBA, human volunteers tolerated exposure inhalation to levels of up to 200 ppm (620 mg/m^3) for 2 hours without signs of discomfort (Åstrand *et al*, 1976) (Section 7.1.1).

The physical condition of approximately 100 male workers exposed to nBA during the coating and drying of photographic paper was followed for 10 years. At the beginning of the study, when the average concentration of nBA in the workplace was 200 ppm (620 mg/m^3), the mean erythrocyte count was slightly decreased. When the average concentration was reduced to 100 ppm (310 mg/m^3), no systemic effects were observed, and there were no changes in clinical chemistry or chest X-ray parameters that could be associated with occupational nBA exposure (Sterner *et al*, 1949).

In a soft drinks company, 14 workers using a waterborne epoxy spray containing 8% nBA and 8% butylcellosolve during can-lining were exposed to 8-hour TWA concentrations in air of 0.757 to 3.44 ppm nBA (2.33 - 10.6 mg/m^3). The authors concluded that the expoxy ingredient was responsible for the transient respiratory irritation seen in nearly all 14 workers and for one case of lung sensitisation (NIOSH, 1984).

During cleaning of wing parts at an aircraft manufacture, personal air samples from the breathing zone of 7 workers exposed to vapours from a degreasing solvent, containing 5% nBA (mixed with 35% perchloroethylene, 30% methylene chloride, 25% aromatic petroleum solvents, and 5% diacetone alcohol), were found to contain up to 0.5 ppm nBA (1.5 mg/m^3). The same workers sometimes used another heavy-degreasing solvent

containing 1,1,1-trichloroethylene (98%) and dioxane (2%). The 7 solvent-exposed workers scored lower on neurobehavioural tests measuring attention and alertness than did 13 non-exposed controls. Apart from the small number of participants in the study, the different scores might be attributable to the fact that the selected control subjects were probably more attentive and alert since their jobs involved reading and writing (NIOSH, 1986a).

There have been several reports relating to effects in workers of poorly-defined mixed solvent exposures including nBA from which no conclusions can be drawn regarding nBA.

One worker engaged in graphite fishing rod manufacture was exposed to various solvents, including nBA, methyl ethyl ketone, 2-ethoxyethyl acetate and 2-ethoxyethanol, evaporating from coating materials. The personal nBA concentration was less than the detection limit of 0.7 ppm nBA (2.2 mg/m^3). Potential adverse health effects (on male and female reproduction) were associated with 2-ethoxyethyl acetate and 2-ethoxyethanol (NIOSH, 1986b). In another workshop manufacturing graphite and fibreglass fishing rods, a coater and a blank washer were exposed to a solvent mixture of nBA, acetone, toluene and xylene. nBA concentrations (8 h TWA) were 1.4 to 8.0 ppm (4.3 - 25 mg/m^3) in the coating area, and 2.8 to 3.3 ppm (8.6 - 10.2mg/m^3) in the breathing zone of the coater and 0.6 to 0.9 ppm (1.8 - 2.8 mg/m^3) in the breathing zone of the blank washer (NIOSH, 1986c). In both studies, the subjects complained of headache, light-headedness and dizziness.

Chronic bronchitis was found in all 11 male workers (age not specified) exposed to nBA during the manufacture of cellulose acetate ribbon. Subsequently, the workplace concentration was found to be 246.2 mg nBA/m^3 (80 ppm); this might not have been representative of the original exposure concentration. Of the 11 workers, 4 had dyspnoea and cough, 5 showed signs of moderate anaemia, 3 had abnormal liver function and 2 experienced hand tremor, while 5 were classified as asymptomatic (Velazquez *et al*, 1969). The findings were not matched to an unaffected control group or considered in the context of possible confounding factors such as smoking or alcohol, or exposure to other materials including dust.

Velazquez *et al* (1969) examined the hearing of the same 11 men who had been exposed to nBA during the manufacture of cellulose acetate ribbon and who were without the benefit of personal protective equipment from noise. Nine of the men experienced hearing loss (hypo-acusia) in direct relation to exposure duration when compared with 23 individuals of a control group and 47 workers exposed to 90 to 100 dB of industrial noise alone. The average hearing loss of the nBA-exposed group in the central frequencies (500 - 3,000 Hz) was not large, 21.94 dB (range 11.59 - 32.39 dB), with a mean widening of the break between 3,000 and 4,000 Hz of 42.22 dB. The average hearing loss tended to decrease as the frequencies moved away from the central zone.

Royster (1993) concluded that the audiologic procedures and industrial hygiene methods used by Velazquez *et al* (1969) were possibly not adequate and that care should be taken in drawing firm conclusions from the report. Royster pounted out that horizontal and vertical axes were mislabelled on various charts and that the audiograms were misinterpreted. Furthermore, calibration problems had existed and subjects were not screened correctly. In summary, the audiologic impairment observed by Velazquez *et al* may possibly only have been an age- or equipment-related effect.

Three case histories from 1965 to 1971 concerned workers who had handled nBA under intense light and heat without any precautions in a non-ventilated photographic laboratory. Exposure levels were not quantified but must have been excessive; the exposure duration ranged from 1 months to 2 years. Obvious signs of transient vertigo with nausea, vomiting, and headache were observed in 1 worker; this was interpreted as a Ménière-like disease. The 2 other workers did not show any signs or symptoms (Seitz, 1972). Because of incomplete reporting of the cases and the levels of exposure, no firm conclusions can be drawn. The single case of vertigo may have been due to an extremely high or otherwise incidental exposure level, or to a spontaneous outbreak of Ménière-like disease.

10.1.3 Evaluation

No adverse effects were reported following the acute oral, intramuscular or intravenous administration of massive doses of nBA for therapeutic purposes.

In an occupational setting, long term exposure of workers to high concentrations of nBA vapour was associated with bronchitis, slight anaemia and CNS effects. Another study reported hearing losses in workers exposed to nBA vapours for several years. However, the results must be interpreted with caution because of deficiencies in documentation and methodology. Thus, no definitive conclusion can be drawn at present. More information is needed, especially on possible over-exposure on user's sites.

10.2 Eye and respiratory irritation

10.2.1 Epidemiological studies

In a raincoat manufacturing plant, a mixture of nBA with various amounts of diacetone alcohol and denatured alcohol was used for the "cementing" process. nBA concentrations ranged from 15 to 100 ppm (46 - 310 mg/m^3). Of the 35 employees, 28 had between 10 to 1,000 vacuoles in the corneal epithelium. The affected workers showed signs of epiphora and complained of itching and burning of the eyes; swelling of the eyelids and occasional redness of the eyes were also reported. The symptoms were more severe on wakening in the morning than during the day. When the patients were away from work, the corneal vacuoles decreased and resolved completely in 10 days. The authors presumed that the symptoms were caused by nBA, without giving a basis for this assumption, but added that other compounds might also have been responsible. No information on dust exposure was given (Cogan and Grant, 1945).

Similar cases were described in 6 plants producing waterproof clothing such as ponchos and raincoats. nBA was used alone or together with other solvents including methylethy lketone, ethanol and naphtha (concentrations not stated). No complaints of ocular irritation were received from 30 workers when nBA concentrations in workplace air ranged from 5 to 14 ppm (15 - 43 mg/m^3). When concentrations were between 20 and 65 ppm (62 - 200 mg/m^3), 5 of the 30 workers suffered from eye irritation, "sickening odour", headache, and dizziness. These symptoms were common at exposures between 60 and 115 ppm (185 - 354 mg/m^3) (Tabershaw *et al*, 1994).

Corneal inflammation was occasionally observed in workers of a photographic paper production plant exposed to concentrations of nBA of 200 ppm (620 mg/m^3) or more. The symptoms included a burning sensation (that sometimes continued for several days after cessation of exposure), blurred vision, lachrymation, and photophobia. These symptoms began in the middle of the working week and became more severe towards the end of the week. When the average concentration was reduced to 100 ppm (310 mg/m^3) complaints of eye irritation or unpleasant odour were rare. The authors also noted that there were numerous instances of plant employees working without complaint at concentrations which were irritating and objectionable to the casual visitor or to office workers, suggesting that those working with nBA had become acclimated upon repeated exposure (Sterner *et al*, 1949). This does not necessarily preclude detrimental effects to eyes and respiratory tract from chronic exposure. Moreover, it demonstrates that the irritant properties of a material do not necessarily protect against potential systemic over-exposure.

Employees at a paper processing plant complained of burning eyes, accompanied with lachrymation. Clinical examination revealed oedema of the conjunctiva and the corneal epithelium and, in some cases, corneal epithelial defects. The causative agent was believed to be a printing ink containing a considerable amount of nBA. No exposure levels of nBA or other materials were reported (Peters, 1958).

10.2.2 Studies with volunteers / controlled clinical studies

Controlled chamber studies with 10 male and female volunteers, exposed to nBA for 3 to 5 minutes experienced objectionable nose and throat irritation at 25 ppm (77 mg/m^3) and in addition ocular irritation at 50 ppm (154 mg/m^3) (Nelson *et al*, 1943). This result is in contrast to more recent experience (see below) and may possibly be due to limited means of exposure or exposure assessment.

No discomfort was reported by human volunteers exposed to 200 ppm (620 mg/m^3) for 2 hours ((Åstrand *et al*, 1976) (Section 7.1.1).

Cometto-Muñiz and Cain (1993) established an odour detection threshold of 54 ppm nBA (166 mg/m^3) in 4 normosmic subjects and a nasal sensory irritation (pungency) threshold of 1,100 ppm (3,400 mg/m^3) in 4 anosmic subjects, lacking olfaction.

The thresholds for olfactory perception and for sensory irritation towards nBA (purity 99.8%) were determined in 64 individuals (32 acetone-exposed workers and 32 naïve subjects), and also in 142 individuals ranging in age from 20 to 89 years to evaluate the effect of age. The lateralisation technique used allowed objective determination and ability to distinguish between odour perception and sensory irritation threshold, the latter being defined as the concentration that produced trigeminal nerve stimulation. The median threshold for olfactory perception was 0.17 ppm nBA (0.52 mg/m^3), which is considerably lower than the data reported by Cornetto-Muñiz and Cain (1993), and for irritation 2,402 ppm (7,403 mg/m^3). The lowest irritation threshold in any test subject was 289 ppm (891 mg/m^3). With increasing age there was a reduction in olfactory perception (Wysocki and Dalton, 1996), which appears to be a common observation.

Subsequent to the Wysocki and Dalton studies, Cometto-Muñiz and Cain (1998) repeated their study using similar lateralisation techniques to determine the odour and irritation thresholds of a series of *n*-alcohols, including nBA, in 4 normosmic and 5 anosmic subjects. Little, if any, difference was noted between the responses of normosmic and anosmic subjects. The thresholds of nBA for odour detection (28.8 ppm or 89 mg/m^3) and nasal irritation (4,163 ppm or 12,830 mg/m^3), as extrapolated from a graphical representation of the data, were similar to, but greater than, the values reported by Wysocki and Dalton. The results of this study support those of Wysocki and Dalton, providing further evidence that the sensory irritation threshold lies substantially above the odour threshold.

It should be noted that both Cometto-Muñiz and Cain (1993, 1998) studies used few subjects and also there is a significant discrepancy between the anosmic results of the two studies. Specifically the 1993 study observed nasal pungency at 1,100 ppm (3,400 mg/m^3), whereas, in the second study, the value was above 4,000 ppm (12,300 mg/m^3). This discrepancy questions the reliability of the experimental design (small sample size) and verification of the exposure concentration in those studies.

10.2.3 Evaluation

nBA is irritant to the skin on repeated or prolonged exposure. Ocular and respiratory irritation, including damage of the cornea, has been reported under occupational and controlled exposure conditions at concentrations higher than 50 ppm (154 mg/m^3). According to two controlled studies, odour perception and nasal irritation thresholds were 0.17 or 28.8 ppm (0.52 or 89 mg/m^3) and 2,402 or 4,163 ppm (7,403 or 12,830 mg/m^3). A more accurate quantitation of the threshold of irritation, if feasible, would be informative.

11. HAZARD ASSESSMENT

nBA is a commodity chemical produced in Europe and USA in volumes exceeding 500 kt/y. The material is a colourless liquid with a vapour pressure of 5.5 to 6.7 hPa, allowing for saturated vapour concentrations of approximately 29,000 mg/m^3 (~ 9,400 ppm). nBA is manufactured in closed systems, transported in bulk containers (tank cars or tank trucks) or in smaller quantities (drums and pails). nBA is primarily used as an intermediate in the manufacture of other chemicals such as butyl acetate, butylacrylate and butylglycolethers; considerable quantities are used in applications involving coating solvents (Table 2). Although released to air and water during production and use (Table 3), the majority of nBA released to the environment is expected to partition to water with little accumulation in soil, biota, sediment or suspended matter (Table 4). nBA is readily biodegradable in water, 98.5 to 100% being degraded within 14 days in OECD guideline studies (Section 4.3.4). Estimates of half-life in air range from 0.4 to 2.4 days, based on calculated photo-reactivity with hydroxyl radicals or other volatile oxidants.

The production of nBA and its use in the manufacture of other chemicals are carried out in closed systems; the potential for exposure is therefore low. In applications where nBA is used as a solvent, exposure could result from vapour inhalation or absorption through skin. In general, measured values of nBA vapour in an industrial setting fall well below current regulatory standards (Table 5).

nBA has a low order of toxicity to bacteria and protozoa (Table 8). In aquatic invertebrates (*Daphnia magna*), 48-hour EC_{50} values based on immobility were ~2,000 mg nBA/l (Table 9). In studies with fish, 96 hour LC_{50} values ranged from 1,700 to 2,300 mg/l (Table 9). A 96-hour EC_{50} value for growth inhibition in algae of > 500 mg/l has also been reported (Table 10). These data suggest that, to environmental organisms, nBA is slightly toxic to relatively non-toxic.

nBA exhibits a low order of toxicity when administered in single doses to laboratory animals by stomach tube, inhalation or covered application to the skin. Oral LD_{50} values appear to be consistent in different studies using different species (Table 15). By inhalation, the LC_{50} values were > 24,000 mg nBA/m^3 (> 7,800 ppm) in the rat and > 20,000 mg/m^3 (6,600 ppm) in the mouse. A dermal LD_{50} value of 3,400 mg/kgbw has been reported for single 24-hour occluded skin application in rabbits. In general, for both ingestion and inhalation of high doses/exposure concentrations of nBA, the major effect in animals is narcosis. In humans, under normal conditions of handling and use of nBA, this imminent hazard of acute exposure is not to be expected. Even following a catastrophic release of nBA vapour with concentrations approaching saturation (29,000 mg/m^3 or 9,400 ppm), brief exposure would not cause lethal effects although some degree of narcosis might be encountered.

Depending on the method used, different results have been reported for the irritant effects of nBA when applied to the skin of rabbits (Table 18). Dermal exposure, under occlusive conditions precluding evaporation from the skin, caused strong irritation and superficial necrosis. Slight to moderate skin irritation was seen where the test material was uncovered. nBA is irritant to the eyes, depending on the extent of dilution (Table 19).

The effects of repeated oral administration and inhalation exposure of rats to nBA has been studied. When administered by stomach tube for 13 weeks, the major adverse effect was transient ataxia and hypoactivity during the latter 6 weeks of the study. The NOAEL was 125 mg nBA/kg/d (US-EPA, 1986). The human health hazard following prolonged oral exposure to nBA is very low.

In a 3-month study in which rats were exposed to nBA vapour, some haematological (decreased haemoglobin and red blood cell count) and neuromuscular effects were observed. Effects were seen at concentrations as low as 150 mg/m^3 (50 ppm) (Korsak *et al*, 1994). This study is inadequately described and lacks elements of a conventional study for repeated exposure, including histopathological evaluation of tissues; thus it is of limited value. Bernard and David (1996) conducted a more thorough study with *n*-butyl acetate. (*n*-Butyl acetate is cleaved rapidly into nBA and may thus be used as a surrogate, both qualitatively and quantitatively on a molar basis, including equivalent ppm levels of inhalation). The study was conducted according to US EPA and OECD guidelines and under GLP conditions, using exposure concentrations of up to 14,500 mg/m^3 (3,000 ppm) for 13 weeks. Decreased activity during exposure, decreased body weight, food consumption and clinical signs suggestive of irritant effects were seen, particularly in animals exposed to the highest concentration. In contrast to the Korsak *et al* study, haematological studies showed a slight increase in red blood cell count, haematocrit and haemoglobin. The nasal passages and the stomach were identified as target tissues. The effects on nasal tissues are likely to be attributable to the acetate moiety of the molecule. The NOAEL for systemic toxicity was 1,500 mg/m^3 (500 ppm). Based on this result, the human health hazard following prolonged inhalation exposure to nBA is judged by the Task Force to be low.

In general, no mutagenic activity was detected in several tests for gene mutation in both bacteria and mammalian cell lines (Section 8.4.1) and no clastogenic activity was observed in *in vivo* test systems (Section 8.4.2). nBA is thus not genotoxic. Moreover, there is no evidence implicating nBA as a carcinogen in animals or humans.

nBA has been tested in vapour inhalation studies for effects on the developing offspring of rats. Foetotoxicity (decreased foetal weight and slight increases in skeletal variations or malformations) was observed only at exposure concentrations toxic to the mother (Nelson *et al*, 1989a). These effects are generally associated with foetotoxicity and are consistent with non-specific delayed development following maternal toxicity.

The NOAEL for both maternal and foetal toxicity was ~ 10,800 mg nBA/m^3 (3,500 ppm). The developmental toxicity of nBA has also been studied in rats when administered in drinking water (Sitarek *et al*, 1994). The lack of methodological details of this study do not permit a proper evaluation of results. The lack of specific developmental toxicity on the part of nBA is supported by studies conducted with *n*-butyl acetate in rats and rabbits. In these studies no effects attributable to the test compound were observed on the foetuses of rabbits and the minimal effects seen in rats, indicative of retarded development, were observed at exposure concentrations toxic to the mothers (7,200 mg/m^3 or 1,500 ppm).

A limited number of neurobehavioural and neurochemical parameters were affected in neonates of mothers exposed to nBA (Nelson *et al*, 1989b). Again, these effects were noted in the presence of maternal toxicity. No patterns of results characteristic of specific developmental neurotoxicity were seen. The NOAEL was 18,500 mg/m^3 (6,000 ppm).

nBA had no effect on male fertility, as shown in a study in which male rats were exposed to nBA vapour for 6 weeks and then mated with unexposed females. In the same study, reproductive indices of pregnant females exposed during the entire period of gestation were unaffected. The NOAEL for effects on fertility is thus > 18,500 mg/m^3 (> 6,000 ppm) (Nelson *et al*, 1989b). Additional supporting evidence for a lack of effect on fertility is provided by the subchronic study with *n*-butyl acetate (Bernard and David, 1996). The study included extensive investigations on male reproductive tissue and sperm. No effects on either the reproductive organs or sperm were noted at exposure concentrations up to 14,500 mg/m^3 (3,000 ppm).

As shown for single exposures to high doses/concentrations of nBA, narcosis appears to be the most immediate and often the only effect observed following repeated administration. In addition, in longer-term studies with animals, hypoactivity and ataxia were observed suggestive of CNS depression, an effect often associated with other alcohols and esters. In a subchronic oral gavage study in rats, transient effects consistent with CNS depression were noted at 500 mg/kg/d but not at 125 mg/kg/d (US EPA, 1986). In a repeated inhalation study in rats with *n*-butyl acetate (Bernard and David, 1996), the NOAEL for apparent CNS depression was 2,400 mg/m^3 (500 ppm) with hypoactivity noted only during exposure at concentrations of 7,200 mg/m^3 (1,500 ppm) and greater. No gross changes were observed in other specific measures for evaluation of neurotoxcity (SCOB, NP, MA and FOB) even at the highest exposure concentration (14,500 mg/m^3; 3,000 ppm).

NOAEL and LOEL values for various endpoints are summarised in Table 23. Based on the available information the most sensitive endpoint of toxicity would appear to be CNS depression. No specific target organs have been identified in the more reliable studies conducted with nBA and the pattern of findings from studies conducted by repeated exposure are generally limited to non-specific effects, i.e. decreased weight gain and decreased food consumption.

Table 23: NOAEL and LOEL values

Endpoint	**NOAEL** (mg/kg/d)		**LOEL** (mg/kg/d)		**Effect**
Repeated oral administration (gavage)	125		500		CNS depression
	(mg/m^3)	(ppm)	(mg/m^3)	(ppm)	
Repeated inhalation (*n*-butyl acetate [a])	2,400	500	7,200	1,500	CNS Depression, decreased body weight and food consumption
Foetal toxicity	10,800	3,500	18,500	6,000	Decreased foetal weight
Maternal toxicity	10,800	3,500	18,500	6,000	Decreased food consumption
Fertility	> 18,500	6,000	ND	ND	
Specific neurotoxicity (*n*-butyl acetate [a])	> 14,500	3,000	ND	ND	

[a] Equivalent to nBA on a molar (ppm) basis

ND Not determined

12. FIRST AID AND SAFE HANDLING ADVICE

12.1 First aid and medical treatment

There is no specific treatment or antidote for over-exposure to nBA. Supportive medical treatment as indicated by the patient's condition is recommended.

12.1.1 Skin and eye injuries

Clothing contaminated with nBA should be removed and either discarded or laundered before re-use. Affected areas of skin should be washed with copious quantities of water for at least 10 minutes. If the eyes are splashed with nBA, they should be irrigated immediately and for at least 10 minutes with eye-wash solution or clean water, holding the eyelids apart. A physician should be consulted.

12.1.2 Inhalation

The subject over-exposed to nBA vapours should be taken into fresh air, kept warm and at rest if difficulty in breathing is experienced. If a patient stops breathing, artificial respiration should be administered until qualified medical personnel are able to take over. Medical aid should be summoned immediately.

12.1.3 Ingestion

If nBA has been swallowed, do not induce vomiting as aspiration into the lungs may cause chemical pneumonitis. Never administer anything by mouth to an unconscious person. A physician should be consulted immediately.

12.2 Safe handling

12.2.1 Safety at work

In order to avoid danger of fire and explosion, good ventilation at the workplace and in storage is essential. Usual industrial hygiene standards must be regarded. Gloves (rubber) and eye protection (close-fitting protective goggles) should be worn. Contamination of skin and clothes is to be avoided.

12.2.2 Storage safety

The material is to be stored in tightly closed vessels under cool and dry conditions.

12.2.3 Fire safety and extinguishers

A fire extinguisher should be kept at hand. Suitable extinguishing media: water spray, dry media, alcohol-resistant foam or CO_2. Containers should be kept cool by spraying with water if exposed to fire. Foam should be applied in large quantities, since it is subject to degradation by the product.

12.2.4 Protection against fire and explosion

Measures to avoid electrostatic charges should be introduced. Avoid sources of open fire and ignition.

12.3 Management of spillage and waste

Ensure adequate ventilation and extinguish ignition sources. Dam off and pump larger amounts into containers, soak residues with absorbent material and dispose of in accordance with local regulations.

13. BIBLIOGRAPHY

13.1 Databases consulted

ECB, 1996. IUCLID data sheet CAS No 71-36-3, butan-1-ol, date of last update 19-Dec 95. European Chemical Bureau, Ispra, Italy.

Literature search from 1995 via DIMDI host including TOXLINE, TOXBIO, IPA and TOXCAS.

Literature search from 1995 via STN host including CHEMID, HSDB, RTECS, TRIFACTS, DART, CHEMTOX, DATALOG, BIOLOG, CHEMFATE, BIODEG, AQUIRE, TOXLINE, CHEM ABS and CHEMLIST.

13.2 References quoted

Aarstad K, Zahlsen K, Nilsen OG. 1985. Inhalation of butanols: changes in the cytochrome p 450 enzyme system. *Arch Toxicol Suppl* 8:418-421.

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 TLVs and BEIs, Threshold limit values for chemical substances and physical agents and biological exposure indices. ACGIH, Cincinnati, OH, USA, p18.

AFS (Arbetarskyddsstyrelsens Författningssamling). 1996. Occupational exposure limit values. (Hygieniska gränsvärden), AFS 1996:2. Swedish national board of Occupational Safety and Health (Arbetarskyddsstyrelsen), Solna, Sweden, p18.

Amoore JE, Hautala E. 1983. 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 Toxicol* 3:272-290.

Arbeidstilsynet. 1997. Administrative normer for forurensning i arbeidsatmosfære. Veiledning til arbeidsmiljøloven 361, rev. mars 1997. Tiden Norsk Forlag, Oslo, Norway, p7.

Arbejdstilsynet. 2000. Grænseværdier for stoffer og materialer, At-vejledning C.0.1 Oktober 2000 erstatter At-anvisning 3.1.0.2 af december 1996. Arbejdstilsynet, København, Denmark [http://www.at.dk].

Åstrand I, Övrum P, Lindquist T, Hultengren M. 1976. Exposure to butyl alcohol: uptake and distribution in man. *Scand J Work Environ Health* 3:165-175.

Auty RM, Branch RA. 1976. The elimination of ethyl, *n*-propyl, *n*-butyl, and iso-amyl alcohols by the isolated perfused rat liver. *J Pharm Exp Ther* 197:669-674.

Bagley DM, Gardner JR, Holland G, Lewis, Vrijhof H, Walker AP. 1999. Eye Irritation, updated reference chemicals data bank. *Toxicology in vitro* 13:505-510.

BASF. 1979. Bericht über die gewerbetoxikologische Grundprüfung, Substanz 78/305, *n*-Butanol. Unpublished report by Zeller H, Gelbke P, Klimisch JH, Freisberg KO, with appendix by Schreiber G. 1979. Bericht über die Prüfung von Butanol 78/305 auf Schleimhautreizwirkung. Unpublished report by Fraunhofergesellschaft, Institut für Aerobiologie, Schmallenberg, Germany. BASF Gewerbehygiene und Toxikologie, Ludwigshafen, Germany.

BASF. 1990. Prüfung auf Ökotoxizität: Hemmung der Algen-Zellvermehrung nach DIN 38412 L9. Unpublished report by Noack U, Laboratorium für angewandte Biologie, Hildesheim, Germany. BASF Abt. DUU/O, Ludwigshafen, Germany.

BASF. 1999. Sicherheitsdatenblatt gemäß 91/155/EWG, *n*-butanol. BASF, Ludwigshafen, Germany.

BASF. 2000a. Verfahren zur Bestimmung von *n*-Butanol in der Luft in Arbeitsbereichen. Personal communication by Dr. Krämer, Labor für Umweltanalytik. BASF, Ludwigshafen, Germany.

BASF. 2000b. *n*-Butanol, workplace air measurements (BASF, 1979 - 1999). Unpublished results, summary. BASF, Ludwigshafen, Germany.

Bengtsson BE, Renberg L, Tarkpea M. 1984. Molecular structure and aquatic toxicity, an example with C_1 - C_{13} aliphatic alcohols. *Chemosphere* 13:613-622.

Bernard LG, David RM. 1994. *n*-Butyl acetate, an acute inhalation neurotoxicity study in the rat. Unpublished report HAEL 93-0305 by Health and Environmental Laboratories, Eastman Kodak, Rochester, NY, USA. Oxo Process Panel, Chemical Manufacturers Association, Washington, DC, USA.

Bernard LG, David RM. 1996. *n*-Butyl acetate: a thirteen-week subchronic inhalation toxicity study in the rat. Unpublished report HAEL 94-0305I7 by Health and Environmental Laboratories, Eastman Kodak, Rochester, NY, USA. Oxo Process Panel, Chemical Manufacturers Association, Arlington, VA, USA.

Bianchi AP, Varney MS. 1992. Sampling and analysis of volatile organic compounds in estuarine air by gas chromatography and mass spectrometry. *J Chromatography* 643:11-23.

Billig E. 1992. Butyl alcohols. In Kroschwitz JF, Howe-Grant M, eds, *Kirk-Othmer encyclopedia of chemical technology, bearing materials to carbon*. 4th ed, Vol 4. John Wiley, New York, USA, pp691-700.

Bloom SE. 1981. Detection of sister chromatid exchanges *in vivo* using avian embryos. In Hsu TC ed, *Cytogenetic assays of environmental mutagens*. Allanheld and Osmun, Totowa, NJ, USA, pp137-159.

Blum DJW, Speece RE. 1991. QSAR for chemical toxicity to environmental bacteria. *Ecotoxicol Environ Saf* 22:198/224.

Boman A, Hagelthorn G, Magnusson K. 1995. Percutaneous absorption of organic solvents during intermittent exposure in Guinea pigs. *Acta Derm Venereol* 75:114-119.

Boman A, Wahlberg JE. 1989. Percutaneous absorption of 3 organic solvents in the guinea pig I. Effect of physical and chemical injuries to the skin. *Contact Dermatitis* 21:36-45.

Boman AS, Maibach HI. 1996. Human skin percutaneous absorption of *n*-butanol *in vitro*: effect of pretreatments and cosolvents. *Occup Hyg* 3:427-439.

Bridié AL, Wolff CJM, Winter M. 1979a. BOD and COD of some petrochemicals. *Water Res* 13:627-630.

Bridié AL, Wolff CJM, Winter M. 1979b. The acute toxicity of some petrochemicals to goldfish. *Water Res* 13:623-624.

Bringmann G, Kühn R. 1977a. Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Bakterien (*Pseudomonas putida*) und Grünalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. *Z Wasser- Abwasserforschung* 10:87-98.

Bringmann G, Kühn R. 1977b. Befunde der Schadwirkung wassergefährdender Stoffe gegen *Daphnia magna. Z Wasser- Abwasserforschung* 10:161-166.

Bringmann G, Kühn R. 1978a. Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Blaualgen (*Microcystis aeruginosa*) und Grünalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. *Vom Wasser* 50:45 60.

Bringmann G, Kühn R. 1978b. Testing of substances for their toxicity threshold: model organisms *Microcystis (Diplocystis) aeruginosa and Scenedesmus quadricauda. Mitt Internat Verein Limnol* 21:275 284.

Bringmann G, Kühn R. 1978c. Bestimmung der biologischen Schadwirkung wassergefährdender Stoffe gegen Protozoen. I. Bakterienfressende Flagellaten (Modelorganismus *Entosiphon sulcatum* Stein). *Z Wasser-Abwasserforschung* 11:210-275.

Bringmann G, Kühn R. 1980a. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. *Water Re*s 14:231-241.

Bringmann G, Kühn R. 1980b. Bestimmung der biologischen Schadwirkung wassergefährdender Stoffe gegen Protozoen. II. Bakterienfressende Ciliaten. *Z Wasser- und Abwasserforschung* 13:26-31.

Bringmann G, Kühn R. 1982. Ergebnisse der Schadwirkung wassergefährdender Stoffe gegen *Daphnia magna* in einem weiterentwickelten standardisierten Testverfahren. *Z Wasser- Abwasserforschung* 15:1-6.

Brooke LT, Call DJ, Geiger DL, Northcott CE, eds. 1984. Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*), Vol 1. Center for lake Superior environmental studies, University of Wisconsin-Superior, Superior, Wisconsin, USA, pp 107-108.

Bruckmann P, Mülder W. 1982. Der Gehalt an organischen Spurenstoffen in Deponiegasen. *Schriftenreihe der Landesanstalt für Immissionsschutz des Landes NW* 55:21-28.

Cameron AM, Zahlsen K, Haug E, Nilsen OG, Eik-Nes KB. 1985. Circulating steroids in male rats following inhalation of *n*-alcohols. *Arch Toxicol*, Suppl 8:422-424.

Campbell IM, McLaughlin DF, Handy BJ. 1976. Rate constants for reactions of hydroxyl radicals with alcohol vapors at 292 K. *Chem Phys Lett* 38:262-264.

Carlson GP. 1994a. *In vitro* esterification of fatty acids by various alcohols in rats and rabbits. *Toxicol Lett* 70:57-61.

Carlson GP. 1994b. Formation of esterified fatty acids in rats administered 1-butanol and 1-pentanol. *Research Communications in Molecular Pathology and Pharmacology* 86:111-117.

Carlson GP, Olson RMC. 1995. Comparison of the metabolism of alcohols by rat hepatic and pulmonary alcohol dehydrogenase. *Biochem Mol Biol Int* 37:65-71.

Carpenter CP, Smyth F. 1946. Chemical burns of the rabbit cornea. *Am J Ophtalmol* 29:1363-1372.

Cavanagh LA, Schadt CF, Robinson E. 1969. Atmosphere hydrocarbon and carbon monoxide measurements at Point Barros. *Sci Technol* 3:251-257.

Cederbaum AI, Dicker AI, Cohen G. 1978. Effect of hydroxyl radical scavangers on microsomal oxidation of alcohols and on associated microsomal functions. *Biochemistry* 17:3058-3064.

Cederbaum AI, Dicker E, Rubin E, Cohen G. 1979. Effect of thiourea on microsomal oxidation of alcohols and on associated microsomal reaction. *Biochemistry* 18:1187-1191.

ChemExpo News. 1999. Industry news, chemical profile: *n*-butanol. ChemExpo News, July 5, 1999 [http://www.chemexpo.com/news/profile990705.cfm].

Chen T-H, Kavanagh TJ, Chang CC, Trosko JE. 1984. Inhibition of metabolic cooperation in chinese hamster v79 cells by various organic solvents and simple compounds. *Cell Biology and Toxicology* 1:155-171.

CIR (US Cosmetic Ingredient Review) Expert Panel. 1987. Final report on the safety assessment of *n*-butyl alcohol. *J American College of Toxicology* 6:403-422.

Ciugudeanu M, Gabor S, Gocan M, Ivanescu G, Buzas A. 1985. Cercetari experimentale provind toxicitatea acuta a butanolului, mono-, di- si tributilaminei normale [Experimental research regarding the acute toxicity of butanol, mono-, di-, and tributylamine]. *Revista de Chimie* 36:667-670.

CMA (US Chemical Manufacturers Association). 1999a. Personal communication by Bauer T [e-mail on 1998 production], 6-Dec-99. CMA, Washington DC, USA.

CMA (US Chemical Manufacturers Association). 1999b. Summary of responses to the OECD request for available data on HVP chemicals. Prepared by the Oxo Panel. CMA, Washington DC, USA, pp6-7.

Cogan DG, Grant WM. 1945. An unusual type of keratitis associated with exposure to *n*-butyl alcohol (butanol). *Arch Ophtalmol* 33:106-109.

Cometto-Muñiz JE, Cain WS. 1993. Efficacy of volatile organic compounds in evoking nasal pungency and odor. *Archives of Environmental Health* 48:309-314.

Cometto-Muñiz JE, Cain WS. 1998. Trigeminal and olfactory sensitivity: comparison of modalities and methods of measurement. *Int Arch Occup Environ Health* 71:105-110.

Connor TH, Theiss JC, Hanna HA, Monteith DK, Matney TS. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol Lett* 25:33-40.

Crebelli R, Conti G, Conti L, Carere A. 1989. A comparative study on ethanol and acetaldehyde as inducers of chromosome malsegregation in *Aspergillus nidulans. Mutat Res* 215:187-195.

Dalton P, Wysocki CJ, Brody MJ, Lawley HJ. 1997. The influence of cognitive bial on the preceived odor, irritation and health symptoms from chemical exposure. *Int Arch Occup Environ Health* 69:407-417.

David RM, Tyler TR, Ouellette R, Faber WD, Banton MI, Garman RH, Gill MW, O'Donoghue JL. 1998. Evaluation of subchronic neurotoxicicity of *n*-butyl acetate vapor. *Neurotoxicol* 19:809-822.

De Ceaurriz JC, Micillino JC, Bonnet P, Guenier JP. 1981. Sensory irritation caused by various industrial airborne chemicals. *Toxicol Lett* 9:137-143.

De Zwart D, Sloof W. 1987. Toxicity of mixtures of heavy metals and petrochemicals to *Xenopus laevis. Bull Environ Contam Toxicol* 38:345-351.

Deisinger PJ, English JC. 1997. The *in vivo* pharmacokinetics of *n*-butyl acetate in rats after intravenous administration. Unpublished report HAEL 94-0306 by Health and Environmental Laboratories, Eastman Kodak, Rochester, NY, USA. Oxo Process Panel, Chemical Manufacturers Association, Arlington, VA, USA.

Deisinger PJ, English JC. 2001. Pharmacokinetics of *n*-butyl acetate and its metabolites in rats after intravenous administration. Project 94-0306BT02, final report. Unpublished report by Eastman Kodak Company, Toxicological Sciences Laboratory, Rochester, NY, USA. American Chemistry Council, Arlington, Virginia, USA.

Denkhaus W, Von Steldern D, Botzenhardt U, Konietzko H. 1986. Lymphocyte subpopulations in solvent-exposed workers. *Int Arch Occup Environ Health* 57:109-115.

Derwent RG, Jenkin ME, Saunders SM, Pilling MJ. 1998. Photochemical ozone creation potentials for organic compounds in Northwest Europe calculated with a master chemical mechanism. *Atmospheric Environment* 32:2429-2441.

DFG (Deutsche Forschungsgemeinschaft). 1999. MAK- und BAT-Werte-Liste 1999, Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Mitteilung 35. Wiley-VCH, Weinheim, Germany, 32.

Dilling WL, Bredeweg CJ, Tefertiller NB. 1976. Organic photochemistry, simulated atmospheric photodecomposition rates of methylene chloride, 1,1,1-trichloroethane, trichloroethylane, tetrachloroethylenen and other compounds. *Environ Sci Technol* 10:351-356.

DiVincenzo GD, Hamilton ML. 1979. Fate of *n*-butanol in rats after oral administration and its uptake by dogs after inhalation or skin application. *Toxicol Appl Pharmacol* 48:317-325.

Dugard PH, Walker M, Mawdsley SJ, Scott RC. 1984. Absorption of some glycol ethers through human skin *in vitro*. *Environ Health Perspectives* 57:193-197.

EC (European Commission). 1993. Commission Directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the EC* L258, L258A.

ECETOC. 1998. Eye irritation: reference chemicals data bank, 2nd ed. Technical report 48. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium, pp 72-73.

Ehrig T, Bohren KM, Wermuth B, von Wartburg JP. 1988. Degradation of aliphatic alcohols by human liver alcohol dehydrogenase: effect of ethanol and pharmacokinetic implications. *Alcoholism: Clinical and Experimental Research* 12:789-794.

Elf Atochem. 1996. Safety data sheet *n*-butanol, version 4, date 14.08.96. Elf Atochem, Paris La Défense.

Engelhardt G, Hoffmann HD. 1998. Cytogenetic study *in vivo* with *n*-butanol in the mouse micronucleus test, single oral administration. Report en-db 1740. BASF, Ludwigshafen, Germany.

ExxonMobil. 2000. Material safety data sheet, *n*-butanol. Exxon Mobil Chemical, Brussels, Belgium.

Fiserova-Bergerova V, Pierce JT, Droz PO. 1990. Dermal absorption potential of industrial chemicals: criteria for skin notation. *Am J Ind Med* 17:617-635.

Forsander O. 1967. Influence of some aliphatic alcohols on the metabolism of rat liver slices. *Biochem J* 105:93-97.

Gad SC, Dunn BJ, Dobbs DW, Reilly C, Walsh RD. 1986. Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). *Toxicol Appl Pharmacol* 84:93-114.

Gaillard D, Derache R. 1965. Métabolisation de différents alcools présents dans les boissons alcooliques chez le rat. *Trav Soc Pharm Montpellier* 25:51-62.

Gerarde HW, Ahlstrom DB. 1966. The aspiration hazard and toxicity of a homologous series of alcohols. *Arch Environ Health* 13:457-461.

Gettings SD, Lordo RA, Hintze KL, Bagley DM, Casterton PL, Chudkowski M, Curren RD, Demetrulias JL, Dipasquale LC, Earl LK, Feder PI, Galli CL, Glaza SM, Gordon VC, Janus J, Kurtz PJ, Marenus KD, Moral J, Pape WJW, Renskers KJ, Rheins LA, Roddy MT, Rozen MG, Tedeschi JP, Zyracki J. 1996. The CFTA evaluation of alternatives program: an evaluation of *in vitro* alternatives to the Draize primary eye irritation test. Phase III, surfactant-based formulations. *Fd Chem Toxic* 34:79-117.

Gillette LA, Miller DL, Redman HE. 1952. Appraisal of a chemical waste problem by fish toxicity tests. *Sewage Ind Wastes* 24:1397-1401.

Hackett PL, Brown MG, Buschbom RL, Clark ML, Miller RA, Music RL, Rowe SE, Schirmer RE, Sikov MR. 1982. Teratogenic Study of Ethylene and Propylene Oxide and *n*-Butyl Acetate. Battelle Pacific Northwest Labs, Richland, WA, USA, prepared for the National Inst. For Occupational Safety and Health, Cincinnati, OH, USA. PB83-258038.

Hahn H-D, Dämbkes G, Rupprich N. 1986. Butanols. In Gerhartz W, ed, *Ullmann's encyclopedia of industrial chemistry*, 5th ed, Vol A4, benzyl alcohol to calcium sulfate. VCH, Weinheim, Germany, pp463-474.

Handler JA, Thurman RG. 1988. Catalase-dependent ethanol oxidation in perfused rat liver. Requirement for fatty-acid-stimulated H_2O_2 production by peroxisomes. *Eur J Biochem*176: 477-484.

Hatfield R. 1957. Biological oxidation of some organic compounds. *Industrial and Engineering Chemistry* 49:192-196.

Hill MW, Neale E, Bangham AD. 1981. Acute tolerance to the effects of *n*-butanol and *n*-hexanol in goldfish. *J Comp Physiol* 142:61-65.

Hoffman DJ, Eastin WC. 1981. Effects of industrial effluents, heavy metals, and organic solvents on mallard embryo development. *Toxicol Lett* 9:35-40.

HSE (UK Health and Safety Executive). 2000. EH40/2000 occupational exposure limits 2000. HSE Books, Sudbury, Suffolk, UK, 13.

Hüls. 1995. Meßprogramm (MESPO), Messungen von Schadstoff-Konzentrationen in der Atemluft, gemäß TRGS 402-3. Kontrollmessung für Formaldehyd, Acetaldehyd, Ethylglykol, Ethylglykolacetat, Methanol, *n*-Butanol und Essigsäure. Personal communication by Hermann to Schmidt-Steffen. Hüls, Marl, Germany.

Hüls. 1996a. Mackay-Level 1 [speadsheet calculation following Paterson and Mackay, 1985]. Hüls, Marl, Germany.

Hüls. 1996b. Bestimmung der biologischen Abbaubarkeit von *n*-Butanol im geschlossenen Flaschentest (OECD-Richtlinie 301 D). Unpublished report GF-109 by Diefenbach R, test performed in 1978. Hüls, Marl, Germany.

Hüls. 1996c. Bestimmung der biologischen Abbaubarkeit von *n*-Butanol nach der EG-Richtlinie 84/449/EWG C.3, final report OECD-screening-test. Unpublished report by Diefenbach R, test performed in 1979. Hüls, Marl, Germany.

Hüls. 1996d. Bestimmung der biologischen Abbaubarkeit von *n*-Butanol im Zahn-Wellens-Test, final report. Unpublished report by Diefenbach R, test performed in 1979. Hüls, Marl, Germany.

Hüls. 1997. Meßprogramm (MESPO), Messungen von Schadstoffkonzentrationen in der Atemluft, gemäß TRGS 402-4. Kontrollmessung für Acetaldehyd, Ethylacetat, *i* + *n*-Butanol, Methanol und Chlorwasserstoff. Personal communication by Hermann to Dr. Rues. Hüls, Marl, Germany.

Hüls. 2001. ABBK-*n*-Butanol, Bestimmung der bakterientoxizität von *n*-Butanol nach Bringmann und Kühn. Unpublished report by Enste-Diefenbach R, test performed in 1977. Degussa Infracor, Marl, Germany.

Hüls. n.d. Bestimmung der biologischen Abbaubarkeit von *n*-Butanol im Coupled Units-Test, final report CU-0401. Unpublished report by Enste-Diefenbach R, test performed in 1983. Degussa Infracor Analytisch Technische Services, Marl, Germany.

INRS (Institut National de Recherche et de Sécurité pour la prévention des accidents du travail et des maladies professionnelles). 1999. Alcool *n*-butylique. *Cahiers de notes documentaires - Hygiène et sécurité du travail* 174:67 [www.inrs.fr/indexprodinfo.html ND 2098].

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

Jacobs GA, Martens MA. 1988. The enucleated eye test: A comparison of the use of ultrasonic and optic pachometers. *Toxic in vitro* 2:253-256.

Jacobs GA, Martens MA. 1989. An objective method for the evaluation of eye irritation *in vivo*. *Fd Chem Toxicol* 27:255-258.

Jacobs GA, Martens M, Mosselmans G. 1987. Proposal of limit concentrations for skin irritation within the context of a new EEC Directive on the classification and labeling of preparations. *Regulat Toxicol Pharmacol* 7:370-378.

Jenner PM, Hagan EC, Taylor JM, Cook EL, Fitzhugh OG. 1964. Food flavourings and compounds of related structure. I. Acute Toxicity. *Food Cosmet Toxicol* 2:327-343.

JSOH (Japan Society for Occupational Health). 1999. Recommendation of occupational exposure limits (1999-2000). *J Occup Health* 41:191-206.

Juhnke I, Lüdemann D. 1978. Ergebnisse der Untersuchung von 200 chemischen Verbindungen auf akute Fischtoxizität mit dem Goldorfentest. *Z Wasser- und Abwasserforschung* 11:161 164.

Jung R, Engelhardt G, Herbolt B, Jäckh R, Müller W. 1992. Collaborative study of mutagenicity with *Salmonalla typhimurium* TA 102. *Mutat Res* 278:265-270.

Jüttner F. 1986. Analysis of organic compounds (VOC) in the forest air of the southern black forest. *Chemosphere* 15:985-992.

Kamil IA, Smith JN, Williams RT. 1953. Studies in detoxication 46. The metabolism of aliphatic alcohols. The glucuronic acid conjugation of acyclic aliphatic alcohols. *Biochem* J 53:129-136.

Kane LE, Dombroske R, Alarie Y. 1980. Evaluation of sensory irritation from some common industrial solvents. *Am Ind Hyg Assoc* 41:451-455.

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

Kassam JP, Tang BK, Kadar D, Kalow W. 1989. *In vitro* studies of human liver alcohol dehydrogenase variants using a variety of substrates. *Drug Metab Dispos* 17:567-572.

Kawai T, Okada Y, Odachi T, Horiguchi S, Zhang ZW, Moon CS, Furuki K, Ukai H, Inui S, Ikeda M. 1997. Monitoring of occupational exposure to 1-butanol by diffusive sampling and urinalysis. *Int Arch Environ Health* 69:266-272.

Kennah HE, Hignet S, Laux PE, Dorko JD, Barrow CS. 1989. An objective procedure for quantitating eye irritation based upon changes of corneal thickness. *Fundam Appl Toxicol* 12:258-268.

Khudoley VV, Mizgireuv I, Pliss GB. 1987. The study of mutagenic activity of carcinogens and other chemical agents with *Salmonella typhimurium* assays: Testing of 126 compounds. *Arch Geschwulstforschung* 57:453-462 [with erratum].

Klimisch HJ, Zeller H. 1979. Bericht über die Bestimmung der akuten Inhalationstoxizität LC_{50} von *n*-Butanol, Produkt-Nr. 03331 bei 4-stündiger Exposition an Sprague-Dawley-Ratten. BASF Gewerbehygiene und Toxikologie, Ludwigshafen, Germany.

Klimisch HJ, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulat Toxicol Pharmacol 25:1-5.

König G, Brunda M, Puxbaum H, Hewitt CN, Duckham SC, Rudolph J. 1995. Relative contribution of oxygenated hydrocarbons to the total biogenic VOC emissions of selected mid-European agricultural and natural plant species. *Atmospheric Environment* 29:861-874.

Korsak Z, Swiercz R, Jedrychowski R. 1993. Effects of acute combined exposure to *n*-butyl alcohol and m-xylene. *Polish J Occup Med Environ Health* 6:35-41.

Korsak Z, Wisniewska-Knypl J, Swiercz R. 1994. Toxic effects of subchronic combined exposure to *n*-butyl alcohol and m-xylene in rats. *Int J Occup Med Environ Health* 7:155-166.

Kristiansen U, Vinggaard AM, Nielsen GD. 1988. The effects of *n*-butanol vapour on respiratory rate and tidal volume. *Arch Toxicol* 61:229-236.

Kühn R, Pattard M, Pernak K-D, Winter A. 1989. Results of the harmful effects of selected water pollutants (analines, phenols, aliphatic compounds) to *Daphnia magna*. *Water Res* 23:495-499.

Lasne C, Gu ZW, Venegas W, Chouroulinkov I. 1984. The *in vitro* micronucleus assay for detection of cytogenetic effects induced by mutagen-carcinogens: comparison with the *in vitro* sister-chromatid exchange assay. *Mutat Res* 130:273-282.

Lieber CS, Ohnishi K, Matsuzaki S. 1978. Effect of chronic ethanol consumption: increase of a distinct cytochrome P-450 in liver microsomes with accelerated biotransformation and enhanced mitochondrial toxicity. *Ind Environ Xenobiotics* 274-276.

Lin Chou W, Speece RE, Siddiqui RH. 1979. Acclimation and degradation of petrochemical wastewater components by methane fermentation. *Biotechnol Bioeng Symp* 8:391-414.

Lindén E, Bengtsson BE, Svanberg O, Sundström G. 1979. The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the bleak (*Alburnus alburnus*) and the harpaticoid (*Nitocra spinipes*). *Chemosphere* 8:843-851.

Maickel RP, Nash JF. 1985. Differing effects of short-chain alcohols on body temperature and coordinated muscular activity in mice. *Neuropharmacology* 24:83-89.

Mattson VR, Arthur JW, Walbridge CT. 1976. Acute toxicity of selected organic compounds to fathead minnows. Unpublished report EPA-600/3-76-097, US EPA Environmental Research Laboratory, Duluth, Minnesota, USA [NTIS PB-262 879].

McCann J, Choi E, Yamasaki E, Ames BN. 1975. Detection of carcinogens as mutagens in the Salmonella/microcosme test: Assay of 300 chemicals. *Proc Natl Acad Sci USA* 72:5135-5129.

McGregor DC, Schonbaum E, Bigelow WG. 1964. Acute toxicity studies on ethanol, propanol, and butanol. *Can J Physiol Pharmacol* 42:689-696.

McKinney RE, Jerris JS. 1955. Metabolism of low molecular weight alcohols by activated sludge. *Sewage Industrial Wastes* 27:728-735.

McOmie WA, Anderson HH. 1949. Comparative toxicologic effects of some isobutyl carbinols and ketones. In Anderson HH, ed, *The toxicity of dicyclohexylamine nitrite*. University of California Press, Berkeley, California, USA, pp 217-229.

Merritt AD, Tomkins GM. 1959. Reversible oxidation of cyclic secondary alcohols by liver alcohol dehydrogenase. *J Biol Chem* 234:2778-2782.

Mohler FS, Gordon CJ. 1991. Hypothermic effects of homologous series of short-chain alcohols in rats. *J Toxicol Environ Health* 32:129-139.

Müller W, Engelhardt G, Herbold B, Jäckh R, Jung R. 1993. Evaluation of mutagenicity testing with *Salmonella typhimurium* TA 102 in three different laboratories. *Environ Health Perspect* 101:33-36.

Munch JC. 1972. Aliphatic alcohols and alkyl esters: narcotic and lethal potencies to tadpoles and to rabbits. *Ind Med* 41:31-33.

Nakamura S, Oda Y, Shimada T, Oki I, Sugimoto K. 1987. SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA 1535/pSK1002: examination with 151 chemicals. *Mutat Res* 192:239-246.

Nelson BK, Brightwell WS, Khan A, Burg JR, Goad PT. 1989a. Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fund Appl Toxicol* 12:469-479.

Nelson BK, Brightwell WS, Robertson SK, Khan A, Krieg EF, Massary VJ. 1989b. Behavorial teratology investigation of 1-butanol in rats. *Neurotoxicol Teratol* 11:313-315.

Nelson KW, Ege JF, Ross M, Woodman LE, Silverman L. 1943. Sensory response to certain industrial solvent vapors. *Ind Hyg Toxicol* 25:282-285.

NIOSH (National Institute for Occupational Safety and Health). 1979. Industrial hygiene walk-through survey report on butyl glycidyl ether (BGE) exposure at Celanese Polymer Specialities Company Louisvillen Kentucky, November 7, 1978. NIOSH Publications, 4676 Columbia Parkway, Cincinnati, OH, USA [NTIS PB88-252945].

NIOSH. 1983. Health hazard evaluation report HETA 83-266-1391, McCourt Label Co., Bradford, Pensylvania. National Institute of Occupational Safety and Health, Cincinnati, OH, USA [NTIS PB85-181261].

NIOSH. 1984. Health hazard evaluation report HETA 82-228-1447, Coca Cola Company, Highstown, NJ, USA. National Institute of Occupational Safety and Health, Cincinnati, OH, USA [NTIS PB85-185528].

NIOSH (US National Institute of Occupational Safety and Health). 1986a. Health hazard evaluation report HETA 83-369-1672, Lockheed-Georgia Company, Mariettta, Georgia. Salisbury S, McConnell R, Anger K. NIOSH, Cincinnati, OH, USA [NTIS PB86-223989].

NIOSH (US National Institute of Occupational Safety and Health). 1986b. Health hazard evaluation report HETA 85-518-1737, LCI Excelon Products, Inc., Woodland, Washington, USA. Apol AG. NIOSH, Cincinnati, OH, USA [NTIS PB87-174173].

NIOSH (US National Institute of Occupational Safety and Health). 1986c. Health hazard evaluation report HETA 86-037-1749, Lamiglas, Woodland, Washington, USA. Apol AG. NIOSH, Cincinnati, OH, USA [NTIS PB87-185575].

NIOSH. 1994. Method 1401, Alcohols II. In Cassinelli ME, O'Connor PF, eds, *NIOSH Manual of analytical methods (NMAM)*, 4th ed. Publication 94-113. National Institute of Occupational Safety and Health, Cincinnati, OH, USA.

NIOSH. 1996. *n*-Butyl alcohol. In *Documentation for immediately dangerous to life or health concentrations (IDLHS)*. NIOSH chemical listing and documentation of revised IDLH values (as of 3/1/95). National Institute of Occupational Safety and Health, Cincinnati, OH, USA [www.cdc.gov/niosh/idlh].

NIOSH. 2000. *n*-Butyl alcohol. In *NIOSH pocket guide to chemical hazards*. National Institute of Occupational Safety and Health, Cincinnati, OH, USA [www.cdc.gov/niosh/npgdcas.html].

Obe G, Ristow HJ. 1977. Acetaldehyde, but not ethanol, induces sister chromatid exchanges in Chinese hamster cells *in vitro*. *Mutat Res* 56:211-214.

Oxeno. 2000. Safety data sheet (EC), *n*-butanol, revision 07.04.00. Degussa-Hüls, Marl, Germany.

Paterson S, Mackay D. 1985. In Hutzinger G, ed, *The fugacity concept in environmental modelling: The handbook of environmental chemistry*, Springer-Verlag, Berlin, Germany, pp 121-140.

Pellizzari ED, Hartwell TD, Harris III BSH, Waddell RD, Whitaker DA, Erickson MD. 1982. Purgeable organic compounds in mother's milk. *Bull Environ Contam Toxicol* 28:322-328.

Peters T. 1958. Augenschäden durch eine wasserlösliche, starke butanolhaltige Druckfarbe. *Zentralblatt für Arbeitsmedizin und Arbeitschutz* 8:208.

Pitter P. 1976. Determination of biological degradability of organic substances. *Wat Res* 10:231-235.

Price KS, Waggy GT, Conway RA. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. *J Water Pollut Control Fed* 46:63-77.

Purchase FH. 1969. Studies on Kaffircorn malting and brewing. XII. The acute toxicity of some fuel oil found in Bantu beer. *S A Tydskrif vir Geneeskunde* (S. A. Medical Journal) 53:795-462.

Revici E, Ravich R. 1953. Anti-hemorrhagic action of *n*-butanol in advanced cancer. *Angiology* 4:510-515.

Rietbrock N, Abshagen U. 1971. Pharmakokinetik und Stoffwechsel aliphatischer Alkohole. *Arzneimittelforsch* 21:1309-1319.

Rowe VK, McCollister SB. 1982. Alcohols. In Clayton GD, Clayton FE, eds. *Patty's Industrial Hygiene and Toxicology* 3rd ed, vol 2c. Wiley-Inserscience, John Wiley, New York NY, USA. pp 4571-4578.

Royster L. 1993. Review of the paper "Audiologic impairment due to *n*-butyl alcohol exposition" by J. Velazquez, R. Escobar and A. Almarez. Published in the proceedings of the XVI International Congress on Occupational Health, September 22-27, 1969 in Tokyo, Japan. Personal communication, Environmental Noise Consultants. CMA, Washington DC, USA.

RTECS. 1990. *n*-Butyl alcohol. In *Registry of Toxic Effects of Chemical Substances* (RTECS). US National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH, USA.

RTECS. 2000. Butyl-alcohol-. In *Registry of Toxic Effects of Chemical Substances* (RTECS). US National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH, USA.

Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc* J 47:142-151.

Salthammer T. 1997. Emission of volatile organic compounds from furniture coatings. *Indoor air* 7:189-197.

Schafer EW, Bowles WA, Hurlbut J. 1983. The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. *Arch Environ Contam Toxicol* 12:355-382.

Schaper M. 1993. Development of a database for sensory irritants and its use in establishing occupational exposure limits. *Am Ind Hyg Assoc J* 54:488-544.

Scheuplein RJ, Blank IH. 1973. Mechanism of percutaneous absorption. IV. Penetration of nonelectrolytes (Alcohols) from aqueous solutions and from pure liquids. *Journal of Investigative Dermatology* 60:286-296.

Schreiber G. 1979. Bericht über die Prüfung von Butanol 78/305 auf primäre Hautreizwirkung. Unpublished report, Fraunhofergesellschaft, Institut für Aerobiologie, Hannover, Germany. BASF Gewerbehygiene und Toxikologie, Ludwigshafen, Germany.

Sdu. 1999. De nationale MAC lijst 2000. Ministerie van Sociale Zaken en Werkgelegenheid. Sdu Uitgeverij, Den Haag, Netherlands, p 19.

Seitz B. 1972. Vertiges graves apparus après manipulation de butanol et d'isobutanol. A propos de trois cas. *Arch Maladies Professionelles* 33:393-395.

Shell. 1993. Material safety data sheet, normal butyl alcohol. MSDS 5430-11, T 06/15/93. Shell Oil, Houston, TX, USA.

Silva ML, Malcata FX, De Revel G. 1996. Volatile contents of grape marcs in Portugal. *Journal of Food Composition and Analysis* 9:72-80.

Sitarek K, Berlinska B. 1996. Effect of exposure to *n*-butanol in drinking water on fertility and prenatal development of rats. *Teratol* 53:36A.

Sitarek K, Berlinska B, Baranski B. 1994. Assessment of the effect of *n*-Butanol given to female rats in drinking water on fertility and prenatal development of their offspring. *Int J Occup Med Environ Health* 7:365-370.

Smyth HF, Carpenter CP, Weil CS. 1951. Range-finding toxicity data: List IV. *Arch Ind Hyg Occup Med* 4:119-122.

Snider JR, Dawson GA. 1985. Tropospheric light alcohols, carbonyls and acetonitrile: concentrations in the southwestern United States and Henry's law data. *Journal of Geographical Research* 90:3797-3805.

SRC (Syracuse Research Corporation). 2000. Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) version 1.87. SRC Environmental Science, North Syracuse NY, USA [http://esc.syrres.com/interkow/aop.htm].

Staples CA. 1998: *n*-Butanol, an environmental fate and aquatic effects assessment. Assessment Technologies, Fairfax, VA, USA. Oxo Process Panel, CMA, Arlington, VA, USA.

Sterner JH, Crouch HC, Brockmyre HF, Cusack M. 1949. A ten-year study of butyl alcohol exposure. *Am Ind Hyg Assoc Quarterly* 10:53-59.

Sugai S, Murata K, Kitagaki T, Tomita I. 1990. Studies on eye irritation caused by chemicals in rabbits 1, a quantitative structure-activity relationships approach to primary eye irritation of chemicals in rabbits. *J Toxicol Sci* 15:245-262.

Swiercz R, Korsak Z, Rydzynski K. 1995. Kinetics of *n*-butyl alcohol and m-xylene in blood during single and combined inhalation exposure in rats. *International Journal of Occupational Medicine and Environmental Health* 8:361-365.

Tabershaw IR, Fahy JP, Skinner JB. 1994. Industrial exposure to butanol. *J Ind Hyg Toxicol* 26:328-330.

Tatsuka K, Suekane S Sakai Y, Sumitani H. 1990. Volatile constituents of kiwi fruit flowers: simultaneous distillation and extraction versus headspace sampling. *J Agric Food Chem* 38:2176-2180.

Teschke R, Hamasura Y, Lieber CS. 1974. NADPH-dependent oxidation of methanol, ethanol, propanol, and butanol by hepatic microsomes. *Biochem Biophys Res Comm* 60:851-857.

Teschke R, Hasumura Y, Lieber CS. 1975. Hepatic microsomal alcohol-oxidizing system. Affinity for methanol, ethanol, propanol, and butanol. *J Biol Chem* 250:7397-7404.

Treon JF. 1967. Alcohols. In Patty FA, ed, *Industrial hygiene and toxicology*, vol 2. Wiley-Interscience, New York NY, USA, pp 1441-1445.

Triebig G, Schaller KH, Weltle D. 1992. Neurotoxicity of solvent mixtures in spray painters. I. Study design, workplace exposure and questionnaire. *Int Arch Occup Environ Health* 64:353-359.

Union Carbide. 1998. Material safety data sheet, butanol. MSDS 758, 07/20/1998. Union Carbide, Danbury, CT, USA.

US-EPA. 1986. Rat oral subchronic toxicity study of normal butanol. Unpublished report TRL study 032-006 by Toxicity Research Laboratories Muskegon, Michigan USA. Environmental Protection Agency, Washington DC, USA.

US-EPA. 1994. Chemical summary for 1-butanol. Report EPA 749-F-94-007a. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington DC, USA.

US-EPA. 1995, Final Water Quality Guidance for the Great Lakes System. Environmental Protection Agency final rule. *Federal Register* 60:15366-15425.

US-EPA. 1999a. TRI chemicals in water, by chemical, 1997. In Toxics release inventory (TRI), 1997 public data release, chapter 2. Environmental Protection Agency, Washington, DC, USA, 65 [www.epa.gov/opptintr/ tri/tri97/pdf/chap2.pdf].

US-EPA. 1999b. Technology transfer network, Chief clearing house for inventories and emission factors. Environmental Protection Agency, Washington, DC, USA [www.epa.gov/ttn/chief].

US-EPA. 2001. Reference Dose (RfD) for chronic oral exposure, *n*-butanol, last revised 09/01/1990. In IRIS integrated risk information system. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington DC, USA [www.epa.gov/iriswebp/iris/subst/0140.htm].

Veith GD, Call DJ, Brooke LT. 1983a. Estimating the acute toxicity of narcotic industrial chemicals to fathead minnows. In Bishop WE *et al*, eds, *Aquatic toxicology and hazard assessment*, 6th Symposium of the American Society for Testing of Materials. Report STP 802. ASTM, Philadelphia, PA, pp90-97.

Veith GD, Call DJ, Brooke LT. 1983b. Structure-toxicity relationships for the fathead minnow, *Pimephales promelas*: narcotic industrial chemicals. *Can J Fish Aquat Sci* 40:743-748.

Velazquez J, Escobar R, Almaraz A. 1969. Audiologic impairment due to *n*-butyl alcohol exposition. Presented at: XVI. Int. Cong. Occup. Health, 22-27 September 1969, Tokyo, 231-234.

Verschueren K. 1986. n-Butanol. In *Handbook of Environmental Data on Organic Chemicals*, 3rd ed. Van Nostrand Reinhold, New York, NY, USA, p351.

Veulemans H, Groeseneken D, Masschelein R, Van Vlem E. 1987. Survey of ethylene glycol ether exposure in Belgian industries and workshops. *Am Ind Hyg Assoc* J 48: 671-676.

Videla LA, Fernandez V, De Marinis A, Fernandez N, Valenzuela A. 1982. Liver lipoperoxidative pressure and glutathione status following acetaldehyde and aliphatic alcohols pretreatments in the rat. *Biochem Biophys Res Commun* 10:965-970.

Vincent R, Poirot P, Subra I, Rieger B, Cicolella A. 1994. Occupational exposure to organic solvents during paint stripping and painting operations in the aeronautical industry. *Int Arch Occup Environ Health* 65:377-380.

Von Wartburg JP, Bethane JL, Vallee BL. 1964. Human liver alcohol dehydrogenase: kinetic and physiochemical properties. *Biochemistry* 3:1775-1782.

Wakabayashi T, Horiuchi M, Sakaguchi M, Onda H, Iijima M. 1984. Induction of metamitochondria in the rat liver by *n*-propyl alcohol and *n*-butyl alcohol. *Acta Pathol Jpn* 34:471-480.

Weast RC, Astle MJ, Beyer WH. 1989. CRC handbook of chemistry and physics, 69th ed. CRC, Boca Raton, FL, C-174.

Weil CS, Scala RA. 1971. Study of intra- and interlaboratory variability in the results of rabbit eye and skin irritation tests. *Toxicol Appl Pharmacol* 19:276-360.

Welt B. 1950. *n*-Butanol: its use in control of postoperative pain in otorhinolaryngological surgery. *Arch Otolaryngol* 52:549-564.

Wise LD, Petrere J. 1996. MARTA (Middle Atlantic Reproduction and Teratology Association) and MTA (Midwest Teratology Association) 1992-1994 historical control project, correction notice [on database of pre-clinical developmental teratology and reproductive toxicity parameters]. MARTA, Reston Virginia, USA and MTA, Kalamazoo, Michigan, USA [www.hcd.org].
Wysocki CJ, Dalton P. 1996. Odor and irritation thresholds for 1-butanol in humans. Unpublished report, Monell Chemical Senses Center, Philadelphia, PA, USA. Oxo Process Panel, CMA, Washington, DC, USA.

Yasuhara A. 1987. Identification of volatile compounds in poultry manure by gas chromatography-mass spectrometry. *Journal of Chromatography* 387:371-378.

Yasuhara A, Shiraishi H, Tsuji M., Okuno T. 1981. Analysis of organic substance in highly polluted water by mass spectrometry. *Environ Sci. Technol* 15:570-573.

13.3 References not quoted

The following references were consulted by the Task Force, but not quoted for the specific reasons indicated.

Abernethy SG, MacKay D. 1988. "Volume fraction" correlation for narcosis in aquatic organisms: the key role of partitioning. *Environ Toxicol Chem* 7:469-481 [Review, does not provide new data or aspects for evaluation].

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. *n*-Butyl alcohol. In *Documentation of threshold limit values and biological exposure indices*, 5th ed. ACGIH, Cincinatti, OH, USA [Review].

Aitio A. 1977. Inhibition of ethoxycumarin deethylation by organic solvents. *Res Commun Chem Pathol Pharmacol* 1:773-776 [Potential disturbance of *in vitro* assay, no toxicity data].

Alexander HC, McCarthy WM, Bartlett EA, Syverud AN. 1982. Aqueous odor and taste threshold values of industrial chemicals. *Res Technol J* AWWA 74:95-599 [Review].

Ames BN, McCann J, Yamasake M. 1975. Methods for detecting carcinogens with the *Salmonella*/mammalian-microsome mutagenicity test. *Mutat Res* 31:347-364 [Method only, no pertinent data].

Ashford MLJ, Wann KT. 1979. A comparison of the effects of butanol and benzyl alcohol on the frog end-plate conductance. *J Physiol* 295:86-87 [Pharmaceutical effect at ≥ 10 mM *in vitro*].

Baer G. 1898. Beitrag zur Kenntnis der acuten Vergiftung mit verschiedenen Alkoholen. *Arch Anat Physiol* 283-296 [Historical, non-specific data].

Bagley DM, Botham PA, Gardner JR, Holland G, Kreiling R, Lewis RW, Stringer DA, Walker AP. 1992. Eye irritation: reference chemicals data bank. *Toxicology in vitro* 6:487-491 [Superseded by Bagley *et al*, 1999].

Baikov BK, Khachaturyan MKh. 1973. Hygenic assessment of the reflex action on a body of small concentration of butyl alcohol in the atmosphere. *Gig i Sanit* 12:7-11 [Russian; CoR 4d].

Barilyak IR, Kozachuk SY. 1988. Studies in cytogenetic action of some monohydric alcohols on the rat bone marrow cells. *Tsitol Genet* 22:49-52 [Russian; CoR 4d].

Barroso-Moguel R, Hernandez JV. 1989. Experimental neuropathy produced in rats with industrial solvents (thinner). *J Arch Invest Med* 20:53-60 [Mixed exposure, effects caused by *n*-hexane].

Benigni R, Andreoli C, Guiliani A. 1989. Structure-activity studies of chemical carcinogens: use of an electrophilic reactivity parameter in a new QSAR model. *Carcinogenesis* 10:55-61 [Review, no toxicity data].

Bernard LG, David RM. 1994. *n*-Butyl acetate: A two-week inhalation probe study in the rat. Unpublished report, Oxo-13.0-BA-Kodak. Oxo Process Panel, Chemical Manufacturers Association, Washington, DC, USA [Covered by Bernard and David, 1994].

BgVV (Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin). 2000. Hauptname, 1 Butanol, CAS-Nr. 71-36-3. In CIVS, *Chemikalieninformationssystem zu Verbraucherrelevanten Stoffen*. BgVV, Berlin [http://www.bgvv.de/fbs/chem/civs/7136.htm] [Safety information, covered by Section 12].

BIA (Berufsgenossenschaftliches Institut der Arbeitssicherheit). 2000. 1-Butanol. In *GESTIS-Stoffdatenbank, Gefahrstoffinformationssystem der gewerblichen Berufsgenossenschaften*. BIA, Sankt Augustin, Germany [www.hvbg.de/d/bia/fac/zesp/zesp.htm] [Safety information, covered by Section 12].

Birkett DJ. 1974. Interaction of some drugs, metal ions, and alcohols with rat liver microsomes as studied with a fluorescent probe. *Clin Exp Pharmacol Physiol* 1:415-427 [Disturbance of *in vitro* assay, no toxicity data].

Boman A, Mellström G. 1989a. Percutaneous absorption of 3 organic solvents in the guinea pig. III) Effect of barrier creams. Contact Dermatitis 21:134-140 [Not relevant, see Boman and Wahlberg, 1989].

Boman A, Mellström G. 1989b. Percutaneous absorption of 3 organic solvents in the guinea pig. IV) Effect of protective gloves. *Contact Dermatitis* 21:260-266 [Not relevant, see Boman and Wahlberg, 1989].

Boman A. 1989. Percutaneous absorption of 3 organic solvents in the guinea pig. V) Effect of "accelerants". *Contact Dermatitis* 21:304-311 [Not relevant, see Boman and Wahlberg, 1989].

Bridié A, Winter M, Wolff CJM. 1973. Determination of acute toxicity to fish of Shell chemicals II. Shell Oil, Washington DC [NTIS PB87-8210130] [Covered by Bridié *et al*, 1979b].

Brightwell WS, Nelson BK, MacKenzie PT. 1987. Lack of teratogenicity of three butanol isomers administered by inhalation to rats. *Teratology* 35:56A [Abstract, covered by Nelson *et al*, 1989a].

Brightwell WS, Robertson SK, Nelson BK, Khan A, Krieg EF, Massari VJ. 1988. Behavioral teratology investigation of 1-butanol administered by inhalation to rats. *Teratology* 37:523 [Abstract, covered by Nelson *et al*, 1989b].

Browning E. 1965. Toxicity and metabolism of industrial solvents, butanols, butanol-1. Elsevier Publishing, Amsterdam, The Netherlands, pp342-348 [Review].

Cater BR, Cook MW, Gangolli SD, Grasso P. 1977. Studies on dibutyl phthalate-induced testicular atrophy in the rat: effect on zinc metabolism. *Toxicol Appl Pharmacol* 41:609-614 [The active agent is a phthalate ester, subchronic testicular toxicity is covered by more comprehensive studies].

Ciugudenau M, Gabor S, Buzas A. 1986a. Actiunea iritativa a butanolului, mono-, di- si tributilaminei normale [The irritative effects of butanol, and of normal mono, di- and tributylamide]. *Igenia* 35:63-73 [Romanian language, probably covered by Ciugudenau *et al*, 1985].

Ciugudenau M, Gabor S, Gocan M, Ivanescu G, Buzas A. 1986b. Experimental researches regarding the acute toxicity of butanol, mono-, di-, and tributylamine. *Toxicology Abstracts* 9:44 [Abstract; CoR 4a].

Clark CR, Marshall WF, Seizinger DE, Naman TM. 1980. Influence of nonpetroleum fuel extenders on mutagenicity of diesel exhaust particulate extracts. In Diel JH, Bice DE, Martinez BS, eds, *Annual Report of the Inhalation Toxicology Research Institute*, Biomedical Research Institute, Lovelace, USA, pp188-190 [Abstract; nBA, among other additives, decreases mutageniity of exhaust particles].

Clegg DJ. 1964. The hen egg in toxicity and teratogenicity studies. *Fd Cosmet Toxicol* 2:717-727 [More reliable rodent studies are available].

Daubert TE, Danner RP. 1985. Tables, 1-butanol. In *Data compilation tables of properties of pure compounds*. American Institute of Chemical Engineers. American Institute of Chemical Engineeers, New York, NY, USA, n.p [Review].

De Ceaurriz JC, Desiles JP, Bonnet P, Marignac B, Muller J, Guener JP. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. *Toxicol Appl Pharmacol* 67:383-389 [Covered by De Ceaurriz *et al*, 1981].

DECOS (Dutch Expert Committee on Occupational Standards). 1994. 1-, 2- and *t*-Butanol, health based recommended occupational exposure limit. Report GR 1994/10. Gezondheidsraad, Den Haag, The Netherlands [Review; CoR 4b].

DECOS (Dutch Expert Committee on Occupational Standards). 2001. *n-*, *iso-*, *sec-*, *tert-*Butylacetate, health based recommended occupational exposure limit. Report 2001/03OSH. Gezondheidsraad, Den Haag, The Netherlands [Review; CoR 4b].

DeFelice A, Wilson W, Ambre J. 1976. Vasoactive effects of methanol and sodium formate on isolated canine basilar artery. *Toxicol Appl Pharmacol* 36:515-601 [Pharmacological assay *in vitro*, not relevant].

DFG (Deutsche Forschungsgemeinschaft). 1995. Schwangerschaft, 1-butanol. In Greim H, ed, *Toxikologisch-medizinische Begründungen von MAK-Werten*. VCH, Weinheim, Germany, p6 [Review].

DFG (Deutsche Forschungsgemeinschaft). 1999. 1-Butanol. In Greim H, ed, *Gesundheitsschädliche Arbeitsstoffe, toxikologisch-arbeitsmedizinische Begründung von MAK-Werten*, 28th ed. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. VCH, Weinheim, Germany, pp 1-16 [Review].

Diericks PJ. 1989. Cytotoxicity testing of 114 compounds by the determination of the protein content in HEP G2 cell cultures. *Toxicol in vitro* 3:189-193 [Validation programme, no specific cytotoxicity of nBA].

DiVincenzo GD, Krasavage WJ. 1974. Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. *Am Ind Hyg Assoc J* 35:21-29 [Validation programme for hepatotoxicity assay, no specific effects for nBA at LD_{50}].

Donnelly MK, Sekellick MJ. 1990. Alcohols induce interferon in primary chick embryo cells. *J Interferon Res* 20:25-30 [No relevant data on toxicity].

Doré M, Brunet N, Legube B. 1975. Participation de différents composés organiques à la valeur des critères globaux de pollution. Centre Belge d'Etude et de Documentation des Eaux 374:3-11 [Review, no relevant data or new aspects for evaluation].

Dubina ON, Maksimov GG. 1976. Testing the use of golden hamsters in toxicological research. *Gig Tr Ohkhr Zdorov'ya Rab Neft Neftekhim Prom-sti* 9:100-103 [Russian; CoR 4c,d].

Dumont JP, Adda J. 1978. Occurrence of sesquiterpenes in mountain cheese volatiles. *J Agric Food Chem* 26:364-367 [Cited by US-EPA, 1994].

Edelfors S, Ravn-Jonsen A. 1990. The effects of alcohols *in vitro* on the nervous cell membrane measured by changes in the (Ca2+/Mg2+) ATPase activity and fluidity of the synaptosomal membrane. *Pharmacol Toxicol* 67:56-60 [*in vitro* pharmacological assay].

EC. 1998. CAS No 71-36-3, butan-1-ol; *n*-butanol. In Annex to Commission directive 98/98/EEC of 15 December 1998 adapting to technical progress for the twenty-fifth time Council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities* L355:197 [Covered by Section 2.2].

Egorov YL. 1972. Dependence of dermal toxicity of alcohols on solubility index: oil/water. *Toksikol Gig Prod Neftekhim Yarosl* 98-102 [Russian; CoR 4d].

Etlin SN, Lakhonina GM, Irlina IS, Popova LA, Malygin SA. 1987. Correlation study of the parameters of chemical substance toxicity for Tetrahymena pyriformis infusoria and animals. *Gig Sanit* 9:80-82 [Russian; CoR 4d].

Falbe J, Weber J. 1986. Butanole. In Gerhartz W, ed, *Ullmann's encyclopedia of industrial chemistry*, 5th ed, Vol A4 - benzyl alcohol to calcium sulfate. VCH, Weinheim, Germany, pp25-33 [Technical survey, no new data].

Fazzalari FA. 1978. Compilation of odor and taste threshold values data. Committee E-18 on sensory evaluation of materials and products. American Society for Testing and Materials, Philadelphia, PA, USA, pp23-24 [Review].

Franco G, Fonte R, Tempini G, Candura F. 1987. Assessment of early hepatotoxicity during exposure to solvent mixtures. *Occup Environ Chem Hazards* 17:173-177 [Serum bile level in workers as a toxicity parameter, no specific data].

Gaillard D, Derache R. 1965. Effect of acute intoxication, by various alcohols, on hepatic lipid fractions in female rats. *CR Hebd Seances Acad Sci* 261:3880-3883 [No additional, significant information].

Gaillard D, Derache R. 1966. Action de quelques alcools aliphatiques sur la mobilisation de différentes fractions lipidiques chez la rate [Effect of some aliphatic alcohols on the mobilization of various lipid fractions in the rat]. *Food Cosmet Toxicol* 4:515-520 [French; no additional, significant information].

Gao C, Govind R, Tabak HH. 1996. Predicting soil sorption coefficients of organic chemicals using a neural network model. *Environ Toxicol Chem* 15:1089-1096 [Non-linear estimation of K_{oc}; nBa not mentioned].

Geppert E von, Sturz J, Haase W, Isselhard W. 1976. Effect of *n*-Butanol on the metabolic status of certain rat organs and on the circulation of the rabbit. *Arzneim Forsch* 26:1333-1337 [Subchronic intramuscular injection of 100 mg nBA/kg/d increased glycogen and kreatine in rats, and lowered blood pressure in rabbits; no additional, significant information].

Gerhold RM, Malaney GW. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. *J Water Poll* 35:562-578 [Review, no new information on degradation].

Glass LR, Connor TH, Theiss JC, Dallas CE, Matney TS. 1986. Genotoxic evaluation of the offgassing products of particle board. *Toxicol Lett* 31:75-83 [Effects on TA100 caused by formaldehyde].

Gold LS, Slone TF, Ames BH. 1997. Summary of the carcinogenic potency database by chemical. In Gold LS, Zeiger E, eds, *Handbook of carcinogenic potency and genotoxicity databases*. CRC Press, Boca Raton, Florida, USA, pp 621-659 [No conclusive or convincing evidence of potency of nBA].

Graedel TE. 1978. Chemical compounds in the atmosphere. Academic Press, New York, NY, USA [Not available; CoR 4c].

Gu Z, Wang Y. 1988. Evaluation of genotoxic effect of 16 chemicals using the micronucleus asssay *in vitro*. *Weisheng Dulixue Zazhi* 2:1-4 [Chinese; CoR 4c; Chem Abstr 112, 93613w].

Guseinov VG. 1986. Comparison of the toxicological characteristics of saturated monohydric normal and isoalcohols of C3-C5 aliphatic series. *Azerb Med* Zh 63:44-48 [Russian; CoR 4c; Chem Abstr 107, 34622X].

Hamilton ML, DiVincenzo GD. 1978. The fate of *n*-butanol in rats after oral administration and its uptake by dogs after inhalation of skin application. Unpublished report. Eastman Kodak, Rochester, NY, USA [Covered by DiVincenzo *et al*, 1986].

Handler JA, Bradford BU, Glassmann EB, Forman DT, Thurman RG. 1987. Inhibition of catalase-dependent ethanol metabolism in alcohol dehydrogenase-deficient deermice by fructose. *Biochem J* 248:415-421.

Hansch C, Leo AJ. 1985. The log P database. Medchem project, issue 26. Pomona College, Claremont, CA, USA. Technical Database Services, New York, NY, USA, p 1 [Cited by Staples, 1998].

Hartung J. 1987. Testing the antimicrobial activity of compounds from the air or animal houses using the microtox test. *Toxicity assessment* 2:1-14 [Validation programme of *in vitro* cytotoxicity test, no specific data].

Henry BJ, Schaper KL. 1990. PPG's safety and health index system: a 10-year update of an in-plant hazardous materials identification system and its relationship to finished product labeling, industrial hygiene, and medical programs. *Am Ind Hyg Assoc J* 51:475-484 [No specific information on nBA].

Henson EV. 1960. The toxicology of some aliphatic alcohols. Part II. *J Occup Med*, October, 497-502 [Review].

Hesketh TR, Keightley CA, Metcalfe JC, Richards CD. 1978. Long-chain alcohols (C_{10}-C_{12}) can block nerve impulse. *J Physiol* 278:5-6 [Nerve blockade *in vitro* by alcohols 30 mM].

Hine J, Mookerjee PK. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. *J Org Chem* 40:292 298 [Review].

Ho CT, Lee KN, Jin QZ. 1983. Isolation and identification of volatile flavor compounds in fried bacon. *J Agric Food Chem* 31:336-342 [Cited by US-EPA, 1994].

Hoffmann DJ. 1990. Embryotoxicity and teratogenicity of environmental contaminants to bird eggs. In Hoffmann DJ, Ware GW, eds, *Reviews of Environmental Contamination and Toxicology* 115:39-89 [Covered by Hoffman and Eastin, 1981].

Hoh A, Maier K, Dreher RM. 1987. Multilayered keratinocyte culture used for *in vitro* toxicology. *Mol Toxicol* 1:537-546 [Potency ranking correlated with *in vivo* irritancy].

Indorato AM, Snyder KB, Usinowicz PJ. 1983. Toxicity screening using Microtox™. Presented at the First international symposium on toxicity testing using bacteria, National Water Research Institute, Burlington, Ontario, 17-19 May 1983. Air Products and Chemicals, Allenntown, PA, USA [NTIS PB 87-8213668] [Validation programme of *in vitro* cytotoxicity test, no specific data].

IPCS (International Programme on Chemical Safety). 1987. 1-Butanol health and safety guide 3. WHO, Geneva, Switzerland [Review covered by IPCS, 1987 and Section 12].

Ishikawa F, Okada Y, Kimura I. 1986. Effect of alcohol on natural killer cell activity. *Igaku to Seibutsugaku* 113:253-256 [Chem Abstr 107, 002450y] [Japanese; probably *in vitro* immuno-pharmacology].

Jacobs G, Martens M. 1987. Evaluation of the enucleated eye test against the *in vivo* eye irritation test in the rabbit. Unpublished report, depot D/1987/2505/36. Institute of Hygiene and Epidemiology, Brussels, Belgium [Covered by Jacobs and Martens, 1989].

Jacobs GA, Castellazzi A, Diericks PJ. 1989. Evaluation of a non-invasive human and an *in vitro* cytotoxicity method as alternative to the skin irritation test on rabbits. *Contact Dermatitis* 21:239-244 [Method validation, results do not change present evaluation].

Jacobs GA, Diericks PJ, Martens MA. 1988. Evaluation of the *in vitro* uridine uptake inhibition assay in comparison with the *in vivo* eye irritation test as prescribed by the EEC. ATLA 15:290-296 [Data cannot be interpreted].

JECFA (Joint FAO/WHO Expert committee of Food Additives). 1994. Butan-1-ol. In *Summary of evaluations performed by the JECFA*. FAO, Rome, and WHO, Geneva. B-12 [Review; CoR 4b].

Juliano RL, Gagalang E. 1979. Relative sensitivity of three daphnid species to selected organic and inorganic chemicals. *J Cell Physiol* 98:483-490 [CoR 4c].

Kamlet MJ, Doherty RM, Taft RW, Abraham MH, Veith GD, Abraham DJ. 1987. Solubility properties in polymers and biological media. 8. An analysis of the factors that influence toxicities of organic nonelectrolytes to the Golden Orfe Fish (*Leuciscus idus melanotus*). *Environ Sci Technol* 21:149-155 [Review, QSAR on acute fish toxicity data].

Kennah HE, Albulescu D, Hignet S, Barrow CS. 1989. A critical evaluation of predicting ocular irritancy potential from an *in vitro* cytotoxicity assay. *Fundam Appl Toxicol* 12:281-290 [Review including results of Kennah, Hignet *et al*, 1989].

Kim YK, Lee SH, Goldinger JM, Hong SK. 1986. Effect of ethanol on organic ion transport in rabbit kidney. *Toxicol Appl Pharmacol* 86:411-420 [Pharmacological effect *in vitro* at 0.5 - 1%].

Kinlin TE, Muralidhara R, Pittet AO, Sanderson A, Walradt JP. 1972. Volatile components of roasted filberts. *J Agr Food Chem* 20:1021-1028 [Cited by US-EPA, 1994].

Kinnby B, Könsberg R, Larsson A. 1988. Immunogenic potential of some mercury compounds in experimental contact allergy of the rat oral mucosa. *Scand J Dent Res* 96:60-68 [nBA used as negative solvent control; not an establsihed test system].

Klimisch HJ. 1988. The inhalation hazard test; principle and method. *Arch Toxicol* 61:411-416 [Redundant since LC_{50} values are available].

Klopman G, Frierson MR, Rosenkranz HS. 1990. The structural basis of the mutagenicity of chemicals in *Salmonella typhimurium*, the gene-tox data base. *Mutat Res* 228:1-50 [QSAR consideration, no unpredicted mutagenicity].

Knobeloch LM, Blondin GA, Read HW, Harkin JM. 1990. Assessment of chemical toxicity using mammalian mitochondrial electron transport particles. *Arch Environ Contam Toxicol* 19:828-835 [Mitochondrial function assay without capacity for biotransformation].

Lahti A. 1980. Non-immunologic contact urticaria. *Acta Dermato-Venereologica* 60:1-49 [On page 22, nBA appears to be not or less active than other well-known materials].

Lambert WJ, Higuchi WI, Knutson K, Krill SL. 1989. Effects of long-term hydration leading to the development of polar channels in hairless mouse stratum corneum. *J Pharm Sci* 78:925-928 [Skin passage of nBA facilitated by long hydration; general dermatopharmacology and therapy].

Lampinen J, Korpela M, Saviranta P, Kroneld R, Karp M. 1990. Use of *Escherichia coli* cloned with genes encoding bacterial luciferase for evaluation of chemical toxicity. *Toxic Assess* 5:337-350 [Development of *in vitro* cytotoxicity assay: no additional information on nBA].

Lendle L. 1928. Untersuchungen über die Narkosegeschwindigkeit homologer und isomerer einwertiger Alkohole. *Naunyn-Schmiedeberg's Arch Exp Pathol Pharmakol* 129:85 [Narcotic potency of alcohols in fish; inadequate description of methodology and dosing].

Lewis DFV. 1987. Quantitative structure-activity relationships in a series of alcohols exhibiting inhibition of cytochrome P-450-mediated aniline hydroxylation. *Chem Biol Interactions* 62:271-280 [QSAR consideration, unclear description of (secondary) data used as biological parameters].

Lipnick RL, Watson KR, Strausz AK. 1987. A QSAR study of the acute toxicity of some industrial organic chemicals to goldfish. Narcosis, electrophile and proelectrophile mechanisms. *Xenobiotica* 17:1011-1025 [QSAR based on LC_{50} values quoted in this report].

Lovegren NV, Fisher GS, Legendre MG, Schuller WH. 1979. Volatile constituents of dried legumes. *J Agric Food Chem* 27:851-853 [Cited by US-EPA, 1994].

Lovinger DM, White G, Weight FF. 1990. NMDA receptor-mediated synaptic excitation selectively inhibited by ethanol in hippocampal slice from adult rat. *J Neurosci* 10:1372-1379 [Physiology and pharmacology of alcohols; no new information on nBA].

Lundberg P, Löf A, Johanson G, Wennberg A, Högberg J, Holmberg B. 1991. New Swedish occupational standards for some organic solvents. *Am J Ind Med* 19:559-567 [Review].

Macht DI. 1920. A toxicological study of some alcohols, with special reference to isomers. *J Pharmakol Exp Ther 16:1-10* [Investigation in isolated tissues; inadequate description of methods].

Mackay D. 1991. Phase equilibrium. In *Multimedia environmental models: the fugacity approach*. Lewish Publishers, Chelsea, MI, USA, pp67-112 [Review; this report cites Paterson and Mackay, 1985].

Maickel RP, McFadden DP. 1979. Acute toxicology of butyl nitrites and butyl alcohols. *Res Commun Chem Pathol Pharmakol* 26:75-83 [No lethal dose achieved after i.p. injection of 1,000 mg/kgbw into mice. Insufficient description of methodology].

Marcus RJ, Winters WD, Hultin E. 1976. Neuropharmacological effects induced by butanol, 4 hydroxybutyrate, 4-mercaptobutyric acid thiolactone, Tetrahydrofuran, Pyrrolidine, 2-deoxy-d-glucose and related substances in the rat. *Neuropharmacology* 15:29-38 [Central nervous depression by organic solvents; no specific information].

McCarty LS. 1987. Relationship between toxicity and bioconcentration for some organic chemicals. II. Application of the relationship. Kaiser KLE, ed, *QSAR in Environ Toxicology II*, pp221-229 [Review].

McLaughlin J, Marliac JP, Verrett MJ, Mutchler MK, Fitzhugh OG. 1964. Toxicity of fourteen volatile chemicals as measured by the chick embryo method. *J Am Ind Hyg Assoc* May-June:282-284 [Devalidated as prenatal toxicity test].

McLaughlin J, Marliac JP, Verrett MJ, Mutchler MK, Fitzhugh OG. 1963. The injection of chemicals into the yolk sac of fertile eggs prior to incubation as a toxicity test. *Toxicol Appl Pharmacol* 5:760-771 [Devalidated as prenatal toxicity test].

Meylan WM, Howard PH. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. *Chemosphere* 26:2293-2299 [Covered by SRC, 2000].

Mikheev MI, Frolova AD, Lyublina EI. 1977. Physiochemical properties and toxokinetics of some representatives of a homologous series of alcohols. *Nek Vopr Eksperim Prom Toksikol* 11-17 [Russian; CoR 4c,d].

Mrak RE, North PE. 1989. Triphasic effects of short chain *n*-alcohols on synaptic membrane transport of choline and of gamma-aminobutyric acid. *Biochim Biophys Acta* 984:97-103 [Pharmacologic effects *in vitro*; not relevant].

Muir CK. 1983. The toxic effect of some industrial chemicals on rabbit ileum *in vitro* compared with eye irritancy in vivo. Toxicol Lett 19:309-312 [Invalidated *in vitro* test system].

Munch JC, Schwartze EW. 1925. Narcotic and toxic potency of aliphatic alcohols upon rabbits. *J Lab Clin Med* 10:985-996 [Insufficient description of dosing and methodology].

Muñoz R, Ferreras JM, Iglesias R, Merino MJ, Girbés T. 1990. Adaptation of *in vitro* rat brain protein synthesis to long-term ingestion of *n*-butanol. *Brain Res* 517:330-332 [Biological meaning unclear since body weights decreased to 46% of controls].

Nakahiro M, Arakawa O, Narahashi T. 1990. Ethanol and longer chain alcohols enhance GABA-activated chloride current in rat dorsal root ganglion neurons. Poster presented at 74th Annual Meeting of the Fed. Am. Soc. Exp. Biol. Part II, April 11-15, 1990, Washington DC, USA. *FESAB Journal* 4:A1201 [Abstract].

Naruse M, Aoyama M. 1989. Acute toxicity caused by the exposure to organic solvents in adhesives currently available on the market. *Igaku to Seibutsugaku* 119:35-37 [Japanese; Chem Abstr 111,148298j] [Abstract].

National Institute for Water Supply, TNO. n.d. Compilation of odour threshold values in air and water. Unpublished report. RID, Voorburg, Netherlands, Central Institute for Nutrition and Food Research TNO, Zeist, Netherlands, p13 [Review; covered by other references].

Nelson BK, Brightwell WS, Krieg EF. 1990. Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. *Tox Ind Health* 6:373-387 [Covered by Nelson *et al*, 1989a,b].

Nelson BK, Brightwell WS, Krieg EF. 1996. Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. *J Occup Med Immun Tox* 5:29-42 [Covered by Nelson *et al*, 1989a,b].

NIOSH (National Institute for Occupational Safety and Health) and OSHA (Occupational Safety and Health Adminstration). 1978. Occupational health guideline for butyl alcohol. US Department of Health and Human Services, US Department of Labor, USA [Summary].

NIOSH (US National Institute of Occupational Safety and Health). 1992. Occupational safety and health guideline for *n*-butyl alcohol. Publication 94-113. NIOSH, Cincinnati, OH [Justification for NIOSH, 2000].

Obe G, Ristow HJ, Herha J. 1977. Chromosomal damage by alcohol *in vitro* and *in vivo*. A*dv Exp Med Biol* 85a:47-70 [Uptake of RNA-/DNA-precursors into the cells; not relevant to assess the genotoxic potential of nBA].

Okolo B. 1987. Toxicity of ethanol, *n*-butanol and iso-amyl alcohol in saccharomyces cerevisiae when supplied separately and in mixtures. *Biotechnology Letters* 9:431-434 [Cytotoxicity assay without metabolic capacity].

Önfelt A. 1987. Spindle disturbances in mammalian cells. III. Toxicity, c-mitosis and aneuploidy with 22 different compounds. Specific and unspecific mechanisms. *Mutat Res* 182:135-154 [Mechanism of chemically-induced spindle disturbances and abnormal chromosome separation; nBA presumably used as negative reference compound].

Osterloh J, Goldfield D. 1984. Butyl nitrite transformation *in vitro*, chemical nitrosation reactions, and mutagenesis. *J Analyt Toxicol* 8:164-169 [Ames test with TA98 and TA100; nBA only 16 mg/plate].

Panganamala RV, Sharma HM, Heikkila RE, Geer JC, Cornwell DG. 1976. The role of hydroxyl radical scavengers dimethyl sulfoxide, alcohols, and methional in the inhibition of prostaglandin biosynthesis. *Prostaglandins* 11:599-607 [Review; no useful information on nBA].

Petrov VV, Okorokov LA. 1990. Increase of the anion and proton permeability of *Saccharomyces carlsbergensis plasmalemma* by *n*-alcohols as a possible cause of its de-energization. *Yeast* 6:311-318 [Abstract].

Plunkett ER. 1976. Butyl alcohol. In *Handbook of Industrial Toxicology*. Industrial Health Services, Barberton, OH, USA, pp70-71 [Review].

Poitrast BJ, Keller WC, Elves RG. 1988. Estimation of chemical hazards in breast milk. *Aviation, Space and Environmental Medicine*, A87-A92 [No data on nBA toxicity].

Prabhala RH, Watson RR. 1990. Effects of various alcohols applied *in vitro* on human lymphocyte subtypes and mitogenesis. *Prog Clin Biol Res* 325:155-163 [Abstract].

Protic M, Sablijc A. 1989. Quantitative structure-activity relationships of acute toxicity of commercial chemicals on fathead minnows: effect of molecular size. *Aquatic Toxicity* 14:47-64 [QSAR based on secondary data].

Puskin JS, Martin T. 1978. Effects of anesthetics on divalent cation binding and fluidity of phosphatidylserine vesicles. *Mol Pharmacol* 14:454-462 [*In vitro* influence of solvents (30 mM nBA) on pharmacologic models].

Reinhardt K, Koch L, Schunk W, Bollmann J, Malchow J. 1986. Zum Einfluß ausgewählter Lösungsmittel auf die osmotische Hämolyse menschlicher Erythrozyten. *Z gesamte Hyg* 32:678-679 [No good positive control such as butoxyethanol, data not relevant to nBA toxicity].

Riddick JA, Bunger WB, Sakano TK. 1986. 1-Butanol. In *Organic solvents, physical properties and methods of purification. Techniques of chemistry series*, 4th ed, Vol 2. Wiley-Interscience, New York, NY, USA, pp198-199 [Review, covered by other references].

Rosenkranz HS, Klopman G. 1990a. Structural basis of carcinogenicity in rodents of genotoxicants and non-genotoxicants. *Mutat Res* 228:105-124 [QSAR consideration without new data].

Rosenkranz HS, Klopman G. 1990b. Identification of rodent carcinogens by an expert system. *Progress in Clinical and Biological Research* 340B:23-48 [QSAR consideration without new data].

Rosenkranz HS, Klopman G. 1990c. New structural concepts for predicting carcinogenicity in rodents: an artificial intelligence approach. *Teratog Carcinog Mutagen* 10:73-88 [Abstract].

Rowe VK, McCollister SB. 1963. Alcohols, 1-butanol. In *Industrial Hygiene and Toxikology*, Patty FA, ed, 2nd ed, Vol 2. J Wiley, New York, NY, USA, pp 4571-4578 [Review, superseded by Rowe *et al* 1982].

Rumyanstev AP, Lobanova IYA, Tiunova LV, Chernikova VV. 1979. Toxicology of butyl alcohol. *Khim Prom-st Ser Toksikol Sanit Khim Plastmass* 2:24-26 [Russian; CoR 4c,d].

Rumyantsev AP, Ostroumova NA, Kustova SA, Lobanova LU, Tiunova LV, Dhernikova VV, Koleshnikov PA. 1976. Sanitary-toxicological features of butyl alcohol under conditions of prolonged inhalation route entry. *Gig i Sanit* 11:12-15 [Russian; CoR 4d].

Saad SF. 1976. Effects of aliphatic alcohols on gamma-aminobutyric acid levels in the cerebral hemispheres of rats. *IRCS med-sci Libr Compend* 4:499 [Paper suggests increased GABA involved in CNS depression, and details pharmacological mechanism of this solvent-induced aspecific state. Beyond terms of reference of this report].

Saito M. 1975. Studies on the metabolism of lower alcohols. *Nichidai Igaku Zasshi* 34:569 [Japanese; English translation] [Few data on nBA covered by other references cited].

Savelev AI, Babanov AG, Skobei NA, Troitskaya IA. 1975. Adaptation reactions of white rats after prolonged administration of small concentrations of butyl alcohol. In Zaikina MG, ed, *Pathophysiology of the cardiovascular system*. Yaroslav Medical Institute, *Journal* 59-62, 76-80 [Russian; CoR 4c,d; journal not stated].

Schulze GE, Dougherty JA. 1987. Neurobehavioral toxicity of 2,4-d-n-butyl ester (2,4-d ester): tolerance and lack of cross-tolerance. *Neurotoxicology and Teratology* 10:75-79 [No new aspect to CNS depressing activity of nBA].

Schulze GE. 1988. 2,4-D-n-butyl ester (2,4-d ester) induced ataxia in rats: role for *n*-butanol formation. *Neurotox Teratol* 10:81-84 [No new aspect to CNS depressing activity of nBA].

Sexton K, Webber LM, Hayward SB. 1986. Characterization of particle composition, organic vapor constituents, and mutagenicity of indoor air pollutant emissions. *Environ Internat* 12:351-362 [nBA not detected].

Shehata M, Saad S. 1978. The effect of aliphatic alcohols on certain vitamins of the B-complex group in the liver of the rat. *Pol J Pharmacol Pharm* 30:35-39 [Slight effects attributed to nBA after 7 high doses].

Shopsis C, Sathe S. 1984. Uridine uptake inhibition as a cytotoxicitiy test: correlations with the Draize test. *Toxicology* 29:195-206 [Methodology development, unvalidated system; nBA moderately irritant to the eye: no additional information].

Silverman J, Pennisi S. 1987. Evaluation of *Tetrahymena thermophila* as an *in vitro* alternative to ocular irritation studies in rabbits. *Toxicol Cut Ocular Toxicol* 6:33-42 [Methodoloy development; unvalidated system; nBA moderately irritant to the eye: no additional information].

Smyth HF, Smyth HF Jr. 1928. Inhalation experiments with certain lacquer solvents. *J Ind Hyg* 10:261-271 [Superseded by Smyth *et al*, 1951].

Stark DM, Shopsis C, Borenfreund E, Walberg J. 1983. Alternative approaches to the Draize assay-chemotaxis, cytology, differentiation and membrane transport studies. In Goldberg A, ed, *Product safety and evaluation*, Mary Ann Liebert, New York, NY, USA, pp 180-203 [*Validation basis of proposed system too small compared to established systems*.].

Tabata K, Saito T. 1988. Dicofol detoxification products in resistant citrus red mite *Panonychrus citri* (McGregor) and mouse. *Appl Ent Zool* 23:202-205 [No data on nBA toxicity].

Tabershaw IR, Utidijan HMD, Kawahara BL. 1977. Chemical hazards, *n*-butyl alcohol. In *Occupational diseases, a guide to their recognition*, section 7. US Department of Health, Education and Welfare, NIOSH. US Government Printing Office, Washington DC, USA, pp 153-154 [Review].

Taylor PM, Winfield AJ. 1987. Penetration enhancement through neonatal rat stratum corneum by a homologous series of alcohols. *Journal of Pharmacy* and Pharmacology 39:139 [Unvalidated test system, arteficial conditions; no additional information].

Theorell H, Bonnichsen R. 1951. Studies on liver alcohol dehydrogenase. I. Equilibria and initial reaction velocities. *Acta Chem Scand* 5:1105-1126 [Enzyme kinetics on ADH; few data on nBA covered by other references cited].

Thomas M, Boura ALA, Vijayakumar R. 1980. Prostaglandin release by aliphatic alcohols, from the rat isolated lung. *Clin Exp Pharmacol Physiol* 7:373-381 [Pharmacologic investigation in isolated perfused rat lungs; not related to nBA toxicity].

Tichý M, Trcka V, Roth Z, Krivucová M. 1985. QSAR analysis and data extrapolation among mammals in a series of aliphatic alcohols. *Environ Health Persp* 61:321-328 [Review].

Treon JF, Stasile MJ. 1983. Alcohols. In Parmeggiani L, ed, *Encyclopaedia of occupational health and safety*, 3rd ed. International Labour Office, Geneva, Switzerland, pp109-112 [Review, covered by Billig, 1992].

Turner FC, Seymour KG, Jackson JB. n.d. Topical application of various solvents and solutions to evaluate dermal irritation. Agricultural Research Department, The Dow Chemical Company, Lake Jackson, TX, USA [NTIS PB86-870000226] [No new information on nBA].

Vaishnav DD, Korthals ET. 1990. Comparative toxicities of selected industrial chemicals to microorganisms and other aquatic organisms. *Arch Environ Contam Toxicol* 19:624-628 [Review; data covered by Veith *et al*, 1983].

Vaishnav DD. 1986. Chemical structure-biodegradation inhibition and fish acute toxicity relationships for narcotic industrial chemicals. *Tox Assess* 1:227-240 [Review; data covered by Veith *et al*, 1983].

Valvani SC, Yalkowski SH, Roseman TJ. 1981. Solubility and partitioning. IV. Aqueous solubility and octanol-water partition coefficients of liquid nonelectrolytes. *J Pharma Sci* 70:502-507 [Review; QSAR consideration based on secondary data].

Van den Berg AP, Noordhoek J, Koopman-Kool E. 1979a. The relation between the sex-dependency of type I binding of ethylmorphine and the 1-butanol-induced spectral change in mouse liver microsomes. *Biochem Pharmacol* 28:31-36 [Relevance to nBA toxicity unclear].

Van den Berg AP, Noordhoek J, Koopman-Kool E. 1979b. The use of competitive inhibition of substrate binding to cytochrome P-450 in the determination of spectral dissociation constants for substrates with multiple types of binding, as illustrated with 1-butanol. *Biochem Pharmacol* 28:37-41 [Relevance to nBA toxicity unclear].

Vaughan DJ, Baptista JA, Perdomo GR, Krepinsky JJ. 1989. The involvement of dimethyl sulfoxide in a bacteriotoxic response of the Ames assay tester strains TA 98 and TA 100. *Mutat Res* 226:39-42 [Validation of solvents in Ames assay; no data on nBA toxicity].

Viel G, Béchard P, Jolicoeur C, Beaubien A. 1987. Toxicity effects of alcohols on *Saccharomyces cerevisiae*: A flow microcalorimetry investigation. *Biotech Techniques* 1:73-78 [Cytotoxicity assay without metabolic activation].

Von Oettingen WF. 1943. The aliphatic alcohols, their toxicity and potential dangers in relation to their chemical constitution and their fate in metabolism. *US Public Health Service Public Health Bulletin* 281:122-125 [Earlier review with little description of methodology].

Walberg J. 1983. Exfoliative cytology as a refinement of the Draize eye irritancy test. *Toxicol Lett* 18:49-55 [Methodology development].

Wallgren H. 1960. Relative intoxicating effects on rats of ethyl, propyl and butyl alcohols. *Acta Pharmacol Toxicol* 16:217-222 [Drinking water study with many details lacking; no additional information].

Wang TT, Farres J, Weiner H. 1989. Liver mitochondrial aldehyde dehydrogenease: *In vitro* expression, *in vitro* import and effect of alcohols on import. *Arch Biochem Biophys* 272:440-449 [*in vitro* investigation of substrate specificity of ADH; no new information on nBA].

Weese H. 1928. Vergleichende Untersuchungen über die Wirksamkeit und Giftigkeit der Dämpfe niedrerer aliphatischer Alkohole. *Naunyn-Schmiedeberg's Arch Exp Pathol Pharmakol* 135:119-130 [Insufficient methodological details].

Wei YH, Huang JY, Lee CH. 1988. Effects of alcohols on mitochondrial respiration and oxidative phosphorylation are determined by the chain length of the alcohols. *J Chin Biochem Soc* 17:85-95 [*In vitro* assay without metabolic activation].

Welke B, Ettlinger K, Riederer M. 1998. Sorption of volatile organic chemicals in plant surfaces. *Environ Sci Technol* 32:1099-1104 [Partitioning of VOC between water and plant cuticle: Koc = 1.90; no significant additional information].

Winer AD. 1958. A note of the substrate specificity of horse liver alcohol dehydrogenase. *Acta Chem Scand* 12:1695-1696 [SAR consideration based on secondary data].

Wolff T, Wanders H, Guengerich FP. 1989. Organic solvents as modifiers of aldrin epoxidase in reconstituted monooxygenase systems and in microsomes. *Biochem Pharmacol* 38:4217-4224 [Influence of solvents on enzyme assays].

Wolff T. 1978. *In vitro* inhibition of monooxygenase dependent reactions by organic solvents. *Int Congr Ser-Excerpta Med* 440:196-199 [Influence of solvents on enzyme assays].

Yashuda Y, Cabral AM, Antonio A. 1976. Inhibitory action of aliphatic alcohols on smooth muscle contraction. *Pharmacology* 14:473-478 [Pharmacological investigation *in vitro*].

Yonezawa Y, Urushigawa Y. 1979. Chemico-biological interactions in biological purification systems. V. Relation between biodegradation rate constants of aliphatic alcohols by activated sludge and their partition coefficients in a 1-octanol-water system. *Chemosphere* 3:139-142 [QSAR based on log P_{ow} and biodegradation rate].

Yoshiyama Y, Nagai K, Some H, Tamura G. 1973. Selection inhibition by pantoyl lactone and butyl alcohol of the initiation of DNA replication. *E coli Agric Biol Chem* 37:1317-1320 [Invalidated toxicity assay].

APPENDIX A: ABBREVIATIONS

ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
BCF	Bioconcentration factor
bw	Body weight
CNS	Central nervous system
COD	Chemical oxygen demand
CoR	Code of reliability (Appendix B)
FID	Flame ionisation detector
FOB	Functional observational battery
GC	Gas chromatography
h	Hour
HPLC	High-pressure liquid chromatography
IDLH	Immediately dangerous to life or health
LOEL	Lowest observed effect level
MA	Motor activity
min	Minute
MS	Mass spectrometry
NADPH	Nicotine-amide adenine dinucleotide phosphate hydrogenase
NOAEL	No-observed adverse effect level
NP	Neuropathology
NS	Not stated
OEL	Occupational exposure limit (value)
POCP	Photochemical ozone creation potential
QSAR	Quantitative structure-activity relationship
RfD	Reference dose
s	Second
SCOB	Schedule-controlled operand behaviour
sp.	Species
STEL	Short-term exposure limit (value)
TOC	Total organic carbon (including dissolved and particulate organic matter)
TWA	Time-weighted average (concentration)
VOC	Volatile organic compound
wk	Week
WWTP	Wastewater treatment plant
y	Year

APPENDIX B: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

Code of Reliability (CoR)	Category of reliability
1	**Reliable without restriction**
1a	GLP guideline study (OECD, EC, EPA, FDA, etc...)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, etc...)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	**Reliable with restrictions**
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	**Not reliable**
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	**Not assignable**
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated (e.g. Russian)
4e	Documentation insufficient for assessment

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[a] Part-time

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[a] Steward responsible for primary review

[b] Presently consultant, UK - Stoke Gabriel, Devon

ECETOC PUBLISHED REPORTS

Monographs

No.	Title
No. 1	Good Laboratory Practice
No. 2	A Contribution to Strategy for Identification and Control of Occupational Carcinogens
No. 3	Risk Assessment of Occupational Chemical Carcinogens
No. 4	Hepatocarcinogenesis in Laboratory Rodents: Relevance for Man
No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology)
No. 6	Acute Toxicity Tests, LD_{50} (LC50) Determinations and Alternatives
No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies
No. 8	Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment (Summary)
No. 9	Assessment of Mutagenicity of Industrial and Plant Protection Chemicals
No. 10	Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man
No. 11	Eye Irritation Testing
No. 12	Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity/teratogenicity)
No. 13	DNA and Protein Adducts: Evaluation of their Use in Exposure Monitoring and Risk Assessment
No. 14	Skin Sensitisation Testing
No. 15	Skin Irritation
No. 16	Early Indicators of Non-Genotoxic Carcinogenesis
No. 17	Hepatic Peroxisome Proliferation
No. 18	Evaluation of the Neurotoxic Potential of Chemicals
No. 19	Respiratory Allergy
No. 20	Percutaneous Absorption
No. 21	Immunotoxicity: Hazard Identification and Risk Characterisation
No. 22	Evaluation of Chemicals for Oculotoxicity
No. 23	Receptor Mediated Mechanisms in Chemical Carcinogenesis
No. 24	Risk Assessment for Carcinogens
No. 25	Practical Concepts for Dose Selection in Chronic Toxicity and Carcinogenicity Studies in Rodents
No. 26	Aquatic Toxicity Testing of Sparingly Soluble Volatile and Unstable Substances
No. 27	Aneuploidy
No. 28	Threshold-Mediated Mutagens - Mutation Research Special Issue
No. 29	Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment
No. 30	Genetic Susceptibility to Environmental Toxicants
No. 31	Guidance on Evaluation of Reproductive Toxicity Data
No. 32	Use of Human Data in Hazard Classification for Irritation and Sensitisation
No. 33	Application of Physiological - Toxicokinetic Modelling to Health Hazard Assessment of Chemcial Substances

Technical Reports

No.	Title
No. 1	Assessment of Data on the Effects of Formaldehyde on Humans
No. 2	The Mutagenic and Carcinogenic Potential of Formaldehyde
No. 3	Assessment of Test Methods for Photodegradation of Chemicals in the Environment
No. 4	The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man
No. 5	Toxicity of Ethylene Oxide and its Relevance to Man
No. 6	Formaldehyde Toxicology: An Up-Dating of ECETOC Technical Reports 1 and 2
No. 7	Experimental Assessment of the Phototransformation of Chemicals in the Atmosphere
No. 8	Biodegradation Testing: An Assessment of the Present Status
No. 9	Assessment of Reverse-Phase Chromatographic Methods for Determining Partition Coefficients
No. 10	Considerations Regarding the Extrapolation of Biological Data in Deriving Occupational Exposure Limits
No. 11	Ethylene Oxide Toxicology and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 5
No. 12	The Phototransformation of Chemicals in Water: Results of a Ring-Test
No. 13	The EEC 6th Amendment: A Guide to Risk Evaluation for Effects on the Environment
No. 14	The EEC 6th Amendment: A Guide to Risk Evaluation for Effects on Human Health
No. 15	The Use of Physical-Chemical Properties in the 6th Amendment and their Required Precision, Accuracy and Limiting Values
No. 16	A Review of Recent Literature on the Toxicology of Benzene
No. 17	The Toxicology of Glycol Ethers and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 4
No. 18	Harmonisation of Ready Biodegradability Tests
No. 19	An Assessment of Occurrence and Effects of Dialkyl-o-Phthalates in the Environment
No. 20	Biodegradation Tests for Poorly-Soluble Compounds
No. 21	Guide to the Classification of Carcinogens, Mutagens, and Teratogens under the 6th Amendment
No. 22	Classification of Dangerous Substances and Pesticides in the EEC Directives. A Proposed Revision of Criteria for Inhalational Toxicity
No. 23	Evaluation of the Toxicity of Substances to be Assessed for Biodegradability
No. 24	The EEC 6th Amendment: Prolonged Fish Toxicity Tests
No. 25	Evaluation of Fish Tainting
No. 26	The Assessment of Carcinogenic Hazard for Human Beings exposed to Methylene Chloride
No. 27	Nitrate and Drinking Water
No. 28	Evaluation of Anaerobic Biodegradation
No. 29	Concentrations of Industrial Organic Chemicals Measured in the Environment: The Influence of Physico-Chemical Properties, Tonnage and Use Patterns
No. 30	Existing Chemicals: Literature Reviews and Evaluations (Fifth Edition) (No longer available)
No. 31	The Mutagenicity and Carcinogenicity of Vinyl Chloride: A Historical Review and Assessment
No. 32	Methylene Chloride (Dichloromethane): Human Risk Assessment Using Experimental Animal Data
No. 33	Nickel and Nickel Compounds: Review of Toxicology and Epidemiology with Special Reference to Carcinogenesis
No. 34	Methylene Chloride (Dichloromethane): An Overview of Experimental Work Investigating Species Differences in Carcinogenicity and their Relevance to Man
No. 35	Fate, Behaviour and Toxicity of Organic Chemicals Associated with Sediments
No. 36	Biomonitoring of Industrial Effluents
No. 37	Tetrachlorethylene: Assessment of Human Carcinogenic Hazard
No. 38	A Guide to the Classification of Preparations Containing Carcinogens, Mutagens and Teratogens
No. 39	Hazard Assessment of Floating Chemicals After an Accidental Spill at Sea

No. 40 Hazard Assessment of Chemical Contaminants in Soil
No. 41 Human Exposure to N-Nitrosamines, their Effects and a Risk Assessment for N-Nitrosodiethanolamine in Personal Care Products
No. 42 Critical Evaluation of Methods for the Determination of N-Nitrosamines in Personal Care and Household Products
No. 43 Emergency Exposure Indices for Industrial Chemicals
No. 44 Biodegradation Kinetics
No. 45 Nickel, Cobalt and Chromium in Consumoducts: Allergic Contact Dermatitis
No. 46 EC 7th Amendment: Role of Mammalian Toxicokinetic and Metabolic Studies in the Toxicological Assessment of Industrial Chemicals
No. 47 EC 7th Amendment "Toxic to Reproduction": Guidance on Classification
No. 48 Eye Irritation: Reference Chemicals Data Bank (Second Edition)
No. 49 Exposure of Man to Dioxins: A Perspective on Industrial Waste Incineration
No. 50 Estimating Environmental Concentrations of Chemicals using Fate and Exposure Models
No. 51 Environmental Hazard Assessment of Substances
No. 52 Styrene Toxicology Investigation on the Potential for Carcinogenicity
No. 53 DHTDMAC: Aquatic and Terrestrial Hazard Assessment (CAS No. 61789-80-8)
No. 54 Assessment of the Biodegradation of Chemicals in the Marine Environment
No. 55 Pulmonary Toxicity of Polyalkylene Glycols
No. 56 Aquatic Toxicity Data Evaluation
No. 57 Polypropylene Production and Colorectal Cancer
No. 58 Assessment of Non-Occupational Exposure to Chemicals
No. 59 Testing for Worker Protection
No. 60 Trichloroethylene: Assessment of Human Carcinogenic Hazard
No. 61 Environmental Exposure Assessment
No. 62 Ammonia Emissions to Air in Western Europe
No. 63 Reproductive and General Toxicology of some Inorganic Borates and Risk Assessment for Human Beings
No. 64 The Toxicology of Glycol Ethers and its Relevance to Man
No. 65 Formaldehyde and Human Cancer Risks
No. 66 Skin Irritation and Corrosion: Reference Chemicals Data Bank
No. 67 The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and Related Food Webs
No. 68 Assessment Factors in Human Health Risk Assessment
No. 69 Toxicology of Man-Made Organic Fibres
No. 70 Chronic Neurotoxicity of Solvents
No. 71 Inventory of Critical Reviews on Chemicals (Only available to ECETOC members)
No. 72 Methyl tert-Butyl Ether (MTBE) Health Risk Characterisation
No. 73 The Value of Aquatic Model Ecosystem Studies in Ecotoxicology
No. 74 QSARs in the Assessment of the Environmental Fate and Effects of Chemicals
No. 75 Organophosphorus Pesticides and Long-term Effects on the Nervous System
No. 76 Monitoring and Modelling of Industrial Organic Chemicals, with Particular Reference to Aquatic Risk Assessment
No. 77 Skin and Respiratory Sensitisers: Reference Chemicals Data Bank
No. 78 Skin Sensitisation Testing: Methodological Considerations
No. 79 Exposure Factors Sourcebook for European Populations (with Focus on UK Data)
No. 80 Aquatic Toxicity of Mixtures
No. 81 Human Acute Intoxication from Monochloroacetic Acid: Proposals for Therapy
No. 82 Risk Assessment in Marine Environments
No. 83 The Use of T25 Estimates and Alternative Methods in the Regulatory Risk Assessment of Non-threshold Carcinogens in the European Union
No. 84 Scientific Principles for Soil Hazard Assessment of Substances
No. 85 Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies

No. 86 Derivation of Assessment Factors for Human Health Risk Assessment
No. 87 Contact Sensitisation: Classification According to Potency
No. 88 Environmental Risk Assessment of Difficult Substances
No. 89 (Q)SARS: Evaluation of the commercially available software for human health and environmental endpoints with respect to chemical management applications
No. 90 Persistence of Chemicals in the Environment
No. 91 Aquatic Hazard Assessment II

Joint Assessment of Commodity Chemicals (JACC) Reports

No. Title

No. 1 Melamine
No. 2 1,4-Dioxane
No. 3 Methyl Ethyl Ketone
No. 4 Methylene Chloride
No. 5 Vinylidene Chloride
No. 6 Xylenes
No. 7 Ethylbenzene
No. 8 Methyl Isobutyl Ketone
No. 9 Chlorodifluoromethane
No. 10 Isophorone
No. 11 1,2-Dichloro-1,1-Difluoroethane (HFA-132b)
No. 12 1-Chloro-1,2,2,2-Tetrafluoroethane (HFA-124)
No. 13 1,1-Dichloro-2,2,2-Trifluoroethane (HFA-123)
No. 14 1-Chloro-2,2,2-Trifluoromethane (HFA-133a)
No. 15 1-Fluoro 1,1-Dichloroethane (HFA-141B)
No. 16 Dichlorofluoromethane (HCFC-21)
No. 17 1-Chloro-1,1-Difluoroethane (HFA-142b)
No. 18 Vinyl Acetate
No. 19 Dicyclopentadiene (CAS: 77-73-6)
No. 20 Tris-/Bis-/Mono-(2 ethylhexyl) Phosphate
No. 21 Tris-(2-Butoxyethyl)-Phosphate (CAS:78-51-3)
No. 22 Hydrogen Peroxide (CAS: 7722-84-1)
No. 23 Polycarboxylate Polymers as Used in Detergents
No. 24 Pentafluoroethane (HFC-125) (CAS: 354-33-6)
No. 25 1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (CAS No. 2837-89-0)
No. 26 Linear Polydimethylsiloxanes (CAS No. 63148-62-9)
No. 27 n-Butyl Acrylate (CAS No. 141-32-2)
No. 28 Ethyl Acrylate (CAS No. 140-88-5)
No. 29 1,1-Dichloro-1-Fluoroethane (HCFC-141b) (CAS No. 1717-00-6)
No. 30 Methyl Methacrylate (CAS No. 80-62-6)
No. 31 1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)
No. 32 Difluoromethane (HFC-32) (CAS No. 75-10-5)
No. 33 1,1-Dichloro-2,2,2-Trifluoroethane (HCFC-123) (CAS No. 306-83-2)
No. 34 Acrylic Acid (CAS No. 79-10-7)
No. 35 Methacrylic Acid (CAS No. 79-41-4)
No. 36 n-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9)
No. 37 Methyl Acrylate (CAS No. 96-33-3)
No. 38 Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3)
No. 39 Tetrachloroethylene (CAS No. 127-18-4)
No. 40 Peracetic Acid (CAS No. 79-21-0) and its Equilibrium Solutions

Special Reports

No.	Title
No. 8	HAZCHEM; A Mathematical Model for Use in Risk Assessment of Substances
No. 9	Styrene Criteria Document
No. 10	Hydrogen Peroxide OEL Criteria Document (CAS No. 7722-84-1)
No. 11	Ecotoxicology of some Inorganic Borates
No. 12	1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0)
No. 13	Occupational Exposure Limits for Hydrocarbon Solvents
No. 14	n-Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document
No. 15	Examination of a Proposed Skin Notation Strategy
No. 16	GREAT-ER User Manual
No. 17	Risk Assessment Report for Existing Substances Methyl tertiary-Butyl Ether

Documents

No.	Title
No. 32	Environmental Oestrogens: Male Reproduction and Reproductive Development
No. 33	Environmental Oestrogens: A Compendium of Test Methods
No. 34	The Challenge Posed by Endocrine-disrupting Chemicals
No. 35	Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances
No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction
No. 43	Contact Sensitisation: Classification According to Potency, A Commentary