

Special Report

No 7

Butoxyethanol Criteria Document

**Including a Supplement for
2-Butoxyethyl Acetate**

April 1994

ISSN-0773-8072-7

ECETOC

SPECIAL REPORT

No. 7

BUTOXYETHANOL CRITERIA DOCUMENT

**Including a Supplement For
2-Butoxyethyl Acetate**

April 1994

ECETOC SPECIAL REPORTS

No. Title

- No. 1 Existing Chemicals, Guidance for Completing the ECC Data Set
- No. 2 Existing Chemicals, Recommendations for Priority Setting
- No. 3 Studies on Toxicokinetics and Macromolecular Binding of Styrene
- Vol. 1 Study on the Kinetics of Styrene and Styrene Oxide in Rats and Mice.
- Vol. 2 Investigation of the Adduct Formation between Styrene or Styrene Metabolites and Hemoglobin or Blood Proteins in Rats and Mice (in vitro and in vivo).
- Vol. 3 Investigation of the Adduct Formation between Styrene (S) or Styrene-7,8 Oxide (SO) and Deoxyribonucleic Acid (DNA) in Rats, Mice, and in vitro.
- No. 4 1,3-Butadiene, Criteria Document.
- No. 5 Environmental Health Criteria for Methylene Chloride.
- No.6 Special Report : Interpretation - Evaluation of the Neurotoxic Potential of Chemicals in Animals.

PREFACE

This report has been prepared by ECETOC for use by the Commission of the EC DG V and its Scientific Expert Group. It contains an original review and assessment of toxicological data and quantitative risk assessments to provide a scientific basis for an occupational exposure limit for 2-butoxyethanol and 2-butoxyethyl acetate. Information on occurrence, production and use, exposure and uptake, and measurement techniques has been drawn largely from existing literature.

ECETOC Special Report No.7

© Copyright - ECETOC, 1994

Application for permission to reproduce or translate all or part of this publication should be made to the Director. ECETOC welcomes such applications. Reference to the document, its title and summary may be copied or abstracted in data retrieval systems without subsequent reference.

This document has been prepared and reviewed with all possible care by experts on behalf of ECETOC. It is provided solely for information. ECETOC cannot accept any responsibility and does not provide a warranty for use or interpretation of the material contained in the publication.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), 4 avenue Van Nieuwenhuysse, Bte. 6, 1160-Brussels, Belgium.

CONTENTS

1. SUBSTANCE IDENTIFICATION	1
1.1. IDENTITY	1
2. CHEMICAL AND PHYSICAL PROPERTIES	2
2.1. CONVERSION FACTORS	2
3. OCCURRENCE	3
3.1. EMISSIONS	3
3.2. OCCURRENCE IN THE WORKPLACE	3
3.3. BACKGROUND ENVIRONMENT	3
4. PRODUCTION AND USE DATA	4
4.1. PRODUCTION	4
4.2. USE	4
5. QUANTITATIVE INFORMATION ON EXPOSURE AND UPTAKE	5
5.1. EXPOSURE LEVELS OF THE WORKPLACE	5
5.1.1. Number of workers potentially exposed	5
5.1.2. Quantitative exposure data	5
5.2. PERSONAL MONITORING	6
5.3. ENVIRONMENTAL LEVELS	6
6. MEASUREMENT TECHNIQUES AND ANALYTICAL METHODS	7
6.1. AT THE WORKPLACE	7
6.2. ENVIRONMENTAL MONITORING	7
6.3. BIOLOGICAL MATERIALS	7
7. TOXICOLOGY	8
7.1. TOXICOKINETICS	8
7.1.1. General Aspects	8
7.1.2. Uptake	8
7.1.3. Distribution	10
7.1.4. Biotransformation and excretion	10
7.1.5. Physiologically-based pharmacokinetic [PBPK] model	14
7.1.6. Summary and conclusion	17
7.2. TOXICODYNAMICS	17
7.2.1. Acute Toxicity	17
7.2.1.1. Oral administration	17
7.2.1.2. Dermal administration	20
7.2.1.3. Inhalation exposure	20
7.2.1.4. Summary and conclusion	21
7.2.2. Irritation	21
7.2.2.1. Skin irritation	21
7.2.2.2. Eye irritation	21

7.2.3. Sensitisation	22
7.2.4. Subchronic toxicity	22
7.2.4.1. General aspects	22
7.2.4.2. Oral Administration	22
7.2.4.3. Dermal administration	24
7.2.4.4. Inhalation exposure	24
7.2.4.5. Intraperitoneal injection	26
7.2.4.6. Summary and conclusion	26
7.2.5. Genotoxicity	27
7.2.5.1. <i>In vitro</i>	27
7.2.5.2. <i>In vivo</i>	27
7.2.5.3. Metabolites	27
7.2.5.4. Summary and evaluation	27
7.2.6. Chronic toxicity and carcinogenicity	28
7.2.7. Reproductive toxicity	28
7.2.7.1. Fertility	28
7.2.7.2. Developmental toxicity	28
7.2.7.3. Summary and Conclusion	31
7.2.8. Immunological data	31
7.2.9. Haematological effects	32
7.2.9.1. General aspects	32
7.2.9.2. Mechanisms of haemolysis <i>in vivo</i>	36
7.2.9.3. Haemolysis <i>in vitro</i> and species differences	38
7.2.9.4. Summary and conclusions	38
7.2.10. <i>In vitro</i> cytotoxicity assessments	39
7.3. EFFECTS ON HUMANS	39
7.3.1. Case reports	39
7.3.2. Controlled studies	40
7.3.3. Occupational studies	41
7.3.4. Biological monitoring	42
8. GAPS IN KNOWLEDGE AND ONGOING RESEARCH	43
8.1. HAEMATOLOGICAL EFFECTS	43
8.2. ABSORPTION AND PHARMACOKINETICS	43
8.3. GENOTOXICITY	43
8.4. CARCINOGENICITY	44
9. GROUPS AT EXTRA RISK	45
10. REVIEW OF EXISTING ASSESSMENTS	46
11. EXISTING OCCUPATIONAL EXPOSURE LIMITS	47
12. SUMMARY EVALUATION AND RECOMMENDATION FOR A SCIENTIFICALLY BASED OCCUPATIONAL EXPOSURE LIMIT	48
12.1. SUBSTANCE IDENTIFICATION	48
12.1.1. Identification	48

12.1.2. Chemical and physical properties	49
12.2. PRODUCTION, USE AND EXPOSURE LEVELS	49
12.2.1. Production and use	49
12.2.2. Exposure levels at the workplace	50
12.2.3. Exposure levels in the environment	50
12.2.4. Measuring methods	50
12.3. HEALTH SIGNIFICANCE	51
12.4. FINAL EVALUATION AND RECOMMENDATION	52
12.4.1. Human Inhalation Exposure Studies with 2-Butoxyethanol	52
12.4.2. Determination of an animal NOEL	53
12.4.3. Relevance of Haemolysis to Humans	53
12.4.3.1. Dose-response Relationship	54
12.4.4. Assessing a safe human dose	54
12.4.5. Conclusion	56
12.4.6. Recommendations	56
13. SUPPLEMENT-2-Butoxyethylacetate	57
13.1. SUBSTANCE IDENTIFICATION	57
13.1.1. Identity	57
13.1.2. Chemical and Physical Properties	57
13.2. TOXICOKINETICS	58
13.3. TOXICODYNAMICS	58
13.3.1. Acute toxicity	58
13.3.2. Irritation	59
13.3.3. Sensitization	59
13.3.4. Subacute/subchronic toxicity	59
13.3.5. Carcinogenicity/Genotoxicity/Reproduction/Developmental Toxicity	59
13.4. SUMMARY AND CONCLUSIONS	61
13.5. RECOMMENDATIONS	61
14. BIBLIOGRAPHY	62
14.1. KEY REFERENCES	62
14.2. REFERENCES QUOTED IN THE DOCUMENT	63
14.3. DATABASES CONSULTED	69
14.4. REFERENCES NOT QUOTED IN THE DOCUMENT	70
APPENDIX 1: Members of the ECETOC Task Force	72
APPENDIX 2: Members of the ECETOC Scientific Committee	73

Table of Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the blood concentration time curve
BAA	2-Butoxyacetic acid
bw	Body weight
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CNS	Central nervous system
d	day(s)
EAA	Ethoxyacetic acid
EC ₅₀	Concentration that allows 50% cell formation
g.d.	Gestation day
Hb	Haemoglobin
Hct	Haematocrit
HGPRT	Hypoxanthine-guanine-phosphoribosyl transferase
i.v.	Intravenous
kg	Kilogram
KTV	Takgränsvärde (Sweden)
l	Litre
LC ₅₀	Lethal concentration for 50% of the exposed animals
LD ₅₀	Lethal dose for 50% of the exposed animals
l/min	Litre per minute
LOAEL	Lowest observable adverse effect level
MAK	Maximale Arbeitsplatzkonzentration (FRG)
MCHb	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
mg	Milligram
mg/m ³	Milligrams per cubic meter

ml	Millilitre
mM	Millimolar
mmol	Millimole
NGV	Nivågränsvärde (Sweden)
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No observable adverse effect level
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PBBK	Physiologically-based pharmacokinetic (Model)
ppm	Parts per million parts of air
RBC	Red blood cell (erythrocyte numbers)
RTECS	Registry of Toxic Effects of Chemical Substances
s.c.	Subcutaneous
REL	Recommended exposure level
STEL	Short term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UDS	Unscheduled DNA synthesis
μ mol	Micromole
WBC	White blood cell
wk	week

1. SUBSTANCE IDENTIFICATION

1.1. IDENTITY

2-Butoxyethanol has the chemical structure: $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$.

The IUPAC name is Ethylene glycol butyl ether and the Chemicals Abstracts Service 8th and 9th nomenclature name is Ethanol, 2-butoxy-. 2-Butoxyethanol is known by a large number of synonyms and trade names. These are detailed in Table I.

2-Butoxyethanol belongs to the family of ethylene glycol monoalkyl ethers represented by the general formula $\text{R}_1\text{OCH}_2\text{CH}_2\text{OR}_2$, where R_1 represents the alkyl (butyl) moiety and R_2 either H or acetate. For the purposes of this Criteria Document the name 2-butoxyethanol is used throughout.

Trade names and synonyms are also given in Table I.

Table I
2-Butoxyethanol - Synonyms and Trade Names

Name	Numbers	Synonyms	Trade Names
2-Butoxyethanol	EINECS ¹⁾ 203-905-0	2-n-Butoxyethanol 2-butoxyethanol Ethanol, 2-Butoxy	Buthyl Ethoxol [®] Dowanol EB [®] Butyl Cellosolve [®]
	EEC Classification number 603-014-00-0	Butyl Glycol	Ektasolve EB [®]
	CAS 111-76-2	Butyl Glycol Ether (BGE)	Jeffersol EB [®]
	RTECS KJ 8575000	Ethylene Glycol Butyl Ether (EGBE)	Butyl Oxitol [®]

1) European Inventory of Existing Chemical Substances

2-Butoxyethanol is classified and labelled in the EC as below.

EC Classification Xn (Harmful) R20/21/22
 Xi (Irritant) R37

EC Labelling Symbol Xn

Risk Phrases: R20/21/22, R37

Harmful by inhalation, in contact with the skin and if swallowed.
Irritating to the respiratory system.

Safety Phrases: S24/25

Avoid contact with skin and eyes.

2. CHEMICAL AND PHYSICAL PROPERTIES

2-Butoxyethanol is a colourless liquid with a mild ether like odour. The odour threshold is 0.10 ppm (Amoore and Hautala 1983). It is soluble in water and most organic solvents. Other chemical and physical properties are listed in Table II.

2.1. CONVERSION FACTORS

1 ppm = 4.91 mg/m³ (20°C; 1014 h Pa)

1 mg/m³ = 0.204 ppm (20°C; 1014 h Pa)

Table II
Chemical and physical properties of 2-butoxyethanol ¹⁾

Property	Value
Molecular weight	118.2
Molecular formula	C ₆ H ₁₄ O ₂
Specific gravity at 25°/4°C	0.898
Evaporation rate (butyl acetate = 1.00)	0.1
Boiling point °C	170.8
Freezing Point °C	-77
Vapour pressure (hPa at 25 °C)	1,17
Refractive index	1.417
Flash point (°C), closed cup	62
Autoignition temperature (°C)	238
Flammability limits (volume % in air)	1.10 - 12.7
Water solubility	Soluble
Vapour density (air = 1)	4.1
ppm in saturated air (25°C)	1,200
Surface tension (mN/m at 25°C)	27.4

¹⁾ Adapted from Rowe and Wolf (1982).

3. OCCURRENCE

3.1. EMISSIONS

No data available

3.2. OCCURRENCE IN THE WORKPLACE

Exposure to 2-butoxyethanol occurs during production and during the end use of formulated products; see Section 5.1 for the available details.

3.3. BACKGROUND ENVIRONMENT

2-Butoxyethanol was listed as a contaminant found in drinking water samples analysed between September 1974 and January 1980 in a survey of US cities. No concentrations were given (Lucas, 1984).

2-Butoxyethanol was detected at a concentration of 23 ppb in one of 7 groundwater samples collected in February 1974 near the "Valley of the Drums", Kentucky, a contaminated site (Stonebreaker and Smith, 1980).

In 1980 2-butoxyethanol was detected in Hayashida River water (Matubara area in Tatsuno City, Hyogo prefecture) at concentrations of 1,310 and 5,680 ppb. The river water was contaminated with effluents from the leather industry. It was one of the most contaminated rivers in Japan. The two figures represent levels detected after steam distillation and vacuum distillation respectively (Yasuhara *et al*, 1981).

4. PRODUCTION AND USE DATA

4.1. PRODUCTION

2-Butoxyethanol is the most widely produced glycol ether with a production capacity in the European Community of approximately 70,000 tonnes per year. It is usually synthesised by a reaction of ethylene oxide with butyl alcohol. Ethylene glycol monoalkyl ethers are not formed as pure compounds but must be separated from the monoethers of diethylene glycol, triethylene glycol and the higher glycols. Temperature, pressure, reactant molar ratios, and catalysts are selected to give the product mix desired.

4.2. USE

In most applications 2-butoxyethanol is used because it is an excellent coupling agent. It is a small yet vital component of many water borne coating and cleaning formulations, allowing reformulation from volatile organic hydrocarbon solvents to water based systems. It is used in the formulation of many industrial and consumer products such as inks, coatings, cleansers, and fuel additives and as a solvent in surface coatings such as paints, spray lacquers, quick-dry lacquers, enamels and varnish removers. 2-Butoxyethanol is employed as an intermediate in 2-butoxyethanol acetate production, as a component in herbicides and some specialised automotive brake fluids.

5. QUANTITATIVE INFORMATION ON EXPOSURE AND UPTAKE

5.1. EXPOSURE LEVELS OF THE WORKPLACE

5.1.1. Number of workers potentially exposed

During production a few people are exposed to 2-butoxyethanol. Typically there are no personnel working constantly on the plant, only occasional visits from fitters, engineers and other technical staff take place. There is the potential for exposure to the chemical in control rooms but this is minimal (2 to 4 people per shift per production facility). There are several plants producing 2-butoxyethanol in the European Community.

In the USA, the National Occupational Exposure Survey (NOES) estimated that during the period 1981-1983, approximately 1.7 million workers were occupationally exposed to 2-butoxyethanol and 124,000 workers were occupationally exposed to 2-butoxyethanol acetate. Among industries labelled by the four digit Standard Industrial Code, 375 were identified as having workers potentially exposed to 2-butoxyethanol, and 104 were identified as having workers potentially exposed to 2-butoxyethanol acetate. NOES identified 222 occupations as having workers potentially exposed to 2-butoxyethanol, and 62 occupations as having workers potentially exposed to 2-butoxyethanol acetate (NIOSH, 1983).

5.1.2. Quantitative exposure data

The potential occupational exposure routes are inhalation and dermal (see also 7.3). Manufacturers of 2-butoxyethanol monitor production areas to ensure that occupational exposure standards are met. The results of such monitoring show very low workplace levels. For example, personal exposures at a number of production sites during 1988-1993 gave results in the a range 0.1-1.6 ppm and a mean of typically 0.13 ppm (data received from CEFIC, 1993).

The main reason for such low figures is that the plants on which 2-butoxyethanol is manufactured are designed to contain the primary feedstock, ethylene oxide. Data from production areas are therefore not a reliable indication of the level of the majority of occupational exposures to 2-butoxyethanol and to formulations containing 2-butoxyethanol during use.

There are a few reports of quantitative workplace (non production area) exposure studies. Recently, an analytical method for 2-butoxyethanol has been developed and used to determine systemic dose after exposure to formulated products by automobile and window cleaners (Vincent *et al*, 1993). The formulated cleaning products contained 2-butoxyethanol at concentrations ranging from 1 - 21%. The results indicate that inhalation exposure was a minor component of the systemic dose (highest mean air concentration about 5 ppm; mean air concentration 0.3 - 2.3 ppm), and that dermal absorption of the liquid formulation was the major contributor.

Veulemans *et al* (1987) examined 2,654 air samples from 336 different plants in Belgium for the presence of various glycol ethers. Though most exposure levels were below the current hygiene standards, in approximately 25% cases these levels were exceeded and sometimes extreme values were obtained (up to 370 ppm = 1,775 mg/m³). Values at painting and printing facilities ranged from 3.4 - 93.6 mg/m³ (0.7 - 19 ppm) and 1.5 -17.7 mg/m³ (0.3 - 3.6 ppm) respectively. A median-value from car repair areas was 5.9 mg/m³ (1.2 ppm) (see also 7.3.3.).

5.2. PERSONAL MONITORING

Where data is available this is given in Section 5.1.2

5.3. ENVIRONMENTAL LEVELS

See Section 3.3

6. MEASUREMENT TECHNIQUES AND ANALYTICAL METHODS

6.1. AT THE WORKPLACE

The major methods for the analysis of 2-butoxyethanol, its acetate and other glycol ethers rely upon adsorption of the solvent onto a suitable adsorbent. The adsorbent can be charcoal (from a variety of sources) or a proprietary substance such as Tenax[®]. In all cases a measured volume of sample air is drawn through a glass or metal tube packed with adsorbent. The collected vapours are desorbed by a suitable solvent and the solution is analysed with a gas chromatograph. Full details of the available methods are given in the Handbook of Occupational Hygiene (instalment 15), UK-HSE (1984a) and NIOSH (1990) which details method 1403 for 2-butoxyethanol. The limit of detection of such a method varies upon the volume of air drawn over the adsorbent, and the nature of the adsorbent. Tenax[®] tubes give the lowest limit of detection, typically 0.1 ppm v/v, whereas charcoal systems give a limit of detection between 0.2 and 2 ppm. The methods are suitable for sampling over periods between 10 minutes and 8 hours.

6.2. ENVIRONMENTAL MONITORING

The principle methods given above for the occupational exposure monitoring can be adapted for the environmental monitoring for 2-butoxyethanol and its acetate (NIOSH, 1990).

6.3. BIOLOGICAL MATERIALS

No specific methods for the detection of 2-butoxyethanol in biological tissues are detailed in the literature. For the analysis of butoxyacetic acid in urine either fluoroanhydride derivatisation after extraction of the tetrabutylammonium ionpair (Smallwood *et al*, 1984), extractive alkylation with pentafluorobenzyl bromide (Johanson and Johnsson, 1991) or diazomethane derivatization after urine lyophilisation (Groeseneken *et al*, 1989) were used or, more recently, a combination of these methods.

The use of other methods is described in Section 7.3.4.