European Union Summary Risk Assessment Report

2-BUTOXYETHANOL

CAS No: 111-76-2
EINECS No: 203-905-0

SUMMARY RISK ASSESSMENT

GENERAL NOTE

This document contains two different reports:

- **Volume 68 Part I Environment** (Publication: EUR 22502 EN) – pages 2-27
- **Part II Human Health** (Final approved version awaiting for publication) – pages 28-54

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

Institute for Health and Consumer Protection
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2-BUTOXYETHANOL (EGBE)
Part I – Environment

CAS No: 111-76-2

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Summary Risk Assessment Report

2006 **EUR 22502 EN**

The mission of the IHCP is to provide scientific support to the development and implementation of EU polices related to health and consumer protection. The IHCP carries out research to improve the understanding of potential health risks posed by chemical, physical and biological agents from various sources to which consumers are exposed.

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2-BUTOXYETHANOL (EGBE)

Part I - Environment

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2006

France

The summary of the environmental part of the risk assessment of 2-butoxyethanol (EGBE) has been prepared by Ministry of the Environment (MEDD) on behalf of the European Union.

The scientific work on this report has been prepared by:

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Final report:	**2006**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 2-butoxyethanol (EGBE) that has been prepared by France in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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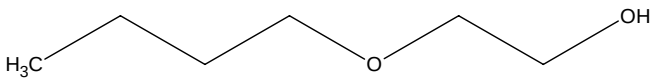
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 111-76-2
EINECS No: 203-905-0
IUPAC Name: 2-butoxyethanol
Synonyms: EGBE (this synonym will be used in the present study to refer to the chemical Ethylene Glycol Butyl Ether). Other synonyms: 2-BE; butoxyethanol; 2-butoxy-1-ethanol; n-butoxyethanol; butyl ethoxol; 3-oxa-1-heptanol; o-butyl ethylene glycol; butyl glycol; butyl monoether glycol; ethylene glycol butyl ether; EGBE; ethylene glycol n-butyl ether; ethylene glycol monobutyl ether; glycol butyl ether
Commercial trade names: Dowanol EB; Butyl Cellosolve; Butyl Icinol; Butyl Oxitol; Eastman EB Solvent
Molecular formula: $C_6H_{14}O_2$
Molecular weight: 118.17 $g.mol^{-1}$
Annex I entry: 603-014-00-0
Structural formula: CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-OH



1.2 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Property	Value
Physical state	Liquid
Melting point	-74.8°C
Boiling point	171°C
Relative density	0.9 at 20°C
Vapour pressure	1.41 hPa, calculated at 25°C (initial value: 1 hPa at 20°C)
Surface tension	26.6 mN/m at 20°C
Water solubility	Highly miscible
Partition coefficient n-octanol/water (log value)	0.8
Granulometry	Not applicable
Flash point	67°C
Autoflammability	244.5°C
Flammability	Upper limit: 12.7% (volume) Lower limit: 1.1% (volume)
Explosive properties	Not explosive
Oxidising properties	No oxidising properties

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties

Property	Value
Viscosity	3.28 mPa.s at 20°C
Henry's constant	0.08 Pa.m^3/mol at 25°C
Conversion factors (101 kPa, 20°C)	1 ppm = 4.9 mg/m^3 1 mg/m^3 = 0.204 ppm

1.3 CLASSIFICATION

1.3.1 Current classification

No classified for the environment.

1.3.2 Proposed classification (environmental part only)

According to the data presented and the criteria of Directive 67/548/EEC EGBE is not classified as dangerous for the environment.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

The chemical 2-butoxyethanol (here referred to as EGBE) belongs to the group of glycol ethers, which are mainly used as solvents. The annual production of EGBE in the European Union has been estimated to be 155,100 tonnes. The production in the European Union is located at five different sites.

EGBE has a wide range of uses as a solvent in paints and surface coatings, detergents and surface cleaners, inks or dyes. A breakdown of the uses of EGBE in Western Europe has been established based on the data collected for years 2001 to 2003 (see **Table 2.1**).

Table 2.1 Breakdown of EGBE uses in Europe

End use	Quantity used (Tonnes)	Percentage of total use
Paints and coatings (including estimation for indirect sales via distributors)	57,000	58.70
Detergents, cleaners	11,000	11.33
Chemicals used in synthesis	10,000	10.30
Captive use (EGBEA production)	9,000	9.27
Printing inks	2,500	2.57
Oilfield chemicals	2,500	2.57
Metal cleaning	2,000	2.06
Electronic industry	600	0.62
Leather treatment operations	500	0.51
Pharmaceuticals	500	0.51
Adhesives	500	0.51
Cosmetics / Personal care	500	0.51
Fire foams	300	0.31
Agricultural products	200	0.21
Paper industry*	0	0.00
Textile manufacture*	0	0.00
Miscellaneous (unknown)*	0	0.00
Rubber, oil industry*	0	0.00
Oil spill dispersants*	0	0.00
Construction chemicals*	0	0.00
Total	97,100	~100

* Use reported in the past or in the literature, for information only

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 Environmental fate

The level of exposure of the environment to a chemical depends on the quantities and compartments of release and subsequent degradation, distribution and accumulation in the environment. This section presents the major characteristics of EGBE relevant for the exposure assessment.

- No experimental data are available on hydrolysis. However, alcohols and ethers are generally resistant to hydrolysis.
- An estimated atmospheric half-life value of ~ 13 hours has been derived for EGBE.
- According to standard tests on ready biodegradation and further experimental data which confirmed high biodegradation rates, EGBE can be regarded as readily biodegradable (half-lives in surface water, soil and sediment can be estimated for EGBE, respectively 15, 30 and 300 days).
- $K_{air\text{-}water}$ of $3.23.10^{-5}$ indicates that volatilisation of EGBE from surface water and moist soil is expected to be very low.
- In view of the BCFs for fish and worm (0.97 and 1.6) calculated based on the log Kow, EGBE is expected to have a low bioaccumulation potential.
- Based on the results from a multimedia fugacity model and the physico-chemical properties of EGBE, the hydrosphere is the preferential target of the substance in the environment (99.2% in water, 0.55% in soil).
- Based on the SIMPLETREAT model, it is anticipated that, after a sewage treatment plant, EGBE will be degraded at a level of 87%, 12.6% of EGBE will remain in water. The remaining fraction of EGBE will be shared between adsorption to sludge and air emission.

3.1.2 Environmental releases

Local releases

Releases from production have been estimated from site-specific information. Generic exposure scenarios are used to estimate the releases from formulation, processing and private use of EGBE, when no other data are available. Specific emission scenarios have been used for the following scenarios: EGBE use in leather finishing operations, for metal cleaning, for the processing of oilfield chemicals and for the use in oil spill dispersants.

The overall releases are shown in **Table 3.1**.

Table 3.1 Local releases of EGBE

Scenario	Amount released to air (kg/day)	Amount released to waste water (kg/day)	Amount released to soil (kg/day)
Production (worst case scenario)	1.9	1,680	-
Paints I^F: general industrial coatings (water-based)	13.7	8.2	0.3
Paints II^F and Paints III_F: decorative trade coatings (water-based) and decorative retail coatings (water-based)	14.1	8.4	0.3
Paints IV^F: can coatings	51.4	0	0
Paints V^F: coil coatings	14.1	0	0
Paints VI^F: automotive OEM coatings (water-based)	7.1	28.3	0.1
Paints VII^F: anticorrosion coatings	2.5	9.9	0
Paints $VIII^F$: automotive OEM coatings	8.5	0	0
Paints IX^F: wood coatings (water-based)	5.7	2.8	0
Paints I^P: general industrial coatings (water-based) - processing	182.7	22.8	0.2
Paints II^P and Paints III^U: decorative trade coatings (water-based) and decorative retail coatings (water-based)	11.3	2.1	0.1
Paints IV^P: can coatings	230.0	0	7.3
Paints V^P: coil coatings	1.8	1.8	0
Paints VI^P: automotive OEM coatings (water-based)	1.8	17.7	0.2
Paints VII_P: anticorrosion coatings	63.6	1.4	0.1
Paints $VIII^P$: automotive OEM coatings	0.4	0	0
Paints IX^P: wood coatings (water-based)	33.9	0.4	0
Detergents I^F: industrial detergents	0	2.0	7.0
Detergents I^P: industrial detergents	-	7.4	-
Detergents II^F: domestic detergents	0	0.8	2.9
Detergents II^U: domestic detergents	-	1.5	-
Intermediates I^P: intermediate for chemicals synthesis	0.1	58.3	0.8
Inks I^F: printing inks	4.2	16.7	0.1
Inks I^P: printing inks	83.3	0.3	0
Pharm I^P: pharmaceuticals	1.0	20.3	0
Elec I^P: electronic industry	2.5	12.5	25.0
Leather I^P: leather treatment operations	-	44.5	1.3
Adhesives I^F: adhesives	0.8	3.3	0
Adhesives I^P: adhesives	-	0.9	-
Agri I^F: agricultural products	0.3	1.3	0

Table 3.1 continued overleaf

Table 3.1 continued Local releases of EGBE

Scenario	Amount released to air (kg/day)	Amount released to waste water (kg/day)	Amount released to soil (kg/day)
Agri I^P: agricultural products	10	0	0
Oilfield I^F: oilfield chemicals	4.2	16.7	0.1
Oilfield I^P Oilfield chemicals	-	4.5	-
Metal I^F: metal cleaning	5.3	10.7	0.1
Metal I^P: metal cleaning	116.7	0. 8	23.3
Cosmet I^F / Fire I^F: cosmetics, Personal care / Fire foams	1.3	5.3	0
Cosmet I^U: cosmetics, personal care	-	0.2	-
Fire I^P: fire foams	-	0.5	-

P Processing
F Formulation
U Private use

Continental and regional releases

The total continental and regional EGBE emissions from formulation, processing and private uses are given in **Table 3.2**.

Table 3.2 Total continental and regional EGBE emissions

	Air	Water (total / waste water*)	Soil
Continental	$9.69.10^4$ kg/day	$4.90.10^4$ kg/day/ $3.92.10^4$ kg/day	$6.81.10^3$ kg/day
Regional	$1.08.10^4$ kg/day	$5.56.10^3$ kg/day / $4.45.10^3$ kg/day	$7.59.10^2$ kg/day

* It is assumed that 80% of the waste water is treated in a biological STP and the remaining 20% released directly into surface waters

3.1.3 Environmental concentrations

Local predicted environmental concentrations (PEClocal)

The methods in the TGD were used to estimate predicted environmental concentrations (PECs) for water and seawater, sediment, sewage treatment plants (STP), air and soil. Table 3.3 shows the PECs calculated for the various stages of the life cycle of EGBE.

Table 3.3 Local PECs for EGBE

Scenario	PEC_{STP} (µg/L)	Local PEC_{aqua} (µg/L)	Local $PEC_{seawater}$ (µg/L)	Local PEC in agricultural soil averaged over 30 days (µg/kg ww)	$PEC_{local\_air,ann}$ (µg/m^3)
Production (worst case)	490	10.6	0.8	34.25	1.77
Paints I^F / Paints I^P	519 / 1,430	59 / 151	42 / 114	30 / 84	3.25 / 41.50
Paints II^F & III_F	533	61	43	31	3.33
Paints II^P and Paints III^U	132	21	11	9	2.67

Table 3.3 continued overleaf

Table 3.3 continued Local PECs for EGBE

Scenario	PEC_{STP} (µg/L)	Local PEC_{aqua} (µg/L)	Local $PEC_{seawater}$ (µg/L)	Local PEC in agricultural soil averaged over 30 days (µg/kg ww)	$PEC_{local\_air,ann}$ (µg/m³)
Paints IV^{F} / Paints IV^{P}	- / -	7 / 7	1 / 1	4 / 10	11.90 / 51.10
Paints V^{F} / Paints V^{P}	- / 110	7 / 18	1 / 9	2 / 8	3.35 / 0.51
Paints VI^{F} / Paints VI^{P}	1,780 / 1,090	186 / 116	142 / 87	96 / 59	1.73 / 0.51
Paints VII^{F} / Paints VII^{P}	623 / 87	70 / 16	50 / 8	5 / 9	0.68 / 14.30
Paints VIII^{F} / Paints VIII^{P}	- / -	7 / 7	1 / 1	2 / 2	2.05 / 0.19
Paints IX^{F} / Paints IX^{P}	178 / 22	25 / 10	15 / 2	12 / 4	1.40 / 7.62
Detergents I^{F} / Detergents I^{P}	125 / 464	20 / 54	11 / 37	9 / 26	0.22 / 0.12
Detergents II^{F} / Detergents II^{U}	52 / 93	13 / 17	5 / 8	5 / 7	0.16 / 0.12
Intermediates I^{P}	736	26	59	41	0.13
Inks I^{F} / Inks I^{P}	1,050 / 17	112 / 9	84 / 2	57 / 6	1.07 / 18.60
Pharm I^{P}	254	14	21	15	0.14
Elec I^{P}	791	87	63	44	0.14
Leather I^{P}	2,810	288	223	150	0.12
Adhesives I^{F} / Adhesives I^{P}	167 / 55	24 / 13	14 / 5	11 / 5	0.27 / 0.12
Agri I^{F} / Agri I^{P}	82 / -	15 / 7	7 / 1	7 / 3	0.23 / 0.30
Oilfield I^{F} / Oilfield I^{P} Surface and well cleaning Squeeze treatments Hydrotest chemicals	1,050 / 276 - - -	112 / 35 - - -	84 / 23 7,700 2,300 100,000	57 / 17	1.07 / 0.12
Metal I^{F} / Metal I^{P} Metal intermittent	673 / 51 1,500	75 / 12 26	54 / 5 16	38 / 9	1.33 / 26.80
Cosmet I^{F} & Fire I^{F} / Cosmet I^{U}	335 / 14	41 / 9	27 / 3	20 / 3	0.42 / 0.12
Fire I^{P}	32	11	2	4	0.12

P Processing
F Formulation
U Private use

Continental and regional predicted environmental concentrations

Continental and regional computations are done by means of multimedia fate models based on the fugacity concept. The standardised continental and regional environments of the TGD are used. **Table 3.4** shows the calculated continental and regional PECs for air, water and soil using EUSES.

Table 3.4 Regional PECs in air, water and soil (calculations made by EUSES – SIMPLEBOX model)

Compartment	PEC continental	PEC regional
Air	$1.10.10^{-5}$ mg/m^3	$1.15.10^{-4}$ mg/m^3
Water	$9.41.10^{-4}$ mg/L	$7.35.10^{-3}$ mg/L
Agricultural soil	$8.44.10^{-5}$ mg/kg (ww)	$8.74.10^{-4}$ mg/kg (ww)
Pore water of agricultural soils	1.40.10-4 mg/L	1.45.10-3 mg/L
Natural soil	1.82.10-4 mg/kg (ww)	1.89.10-3 mg/kg (ww)
Industrial soil	4.39.10-3 mg/kg (ww)	4.30.10-2 mg/kg (ww)
Sediment	1.16.10-3 mg/kg (ww)	9.08.10-3 mg/kg (ww)
Seawater	6.09.10-7 mg/L	6.12.10-4 mg/L
Marine sediment	7.54.10-7 mg/kg (dw)	7.57.10-4 mg/kg (ww)

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

Calculation of the PNEC for the freshwater compartment

Three long term test results from three species representing three trophic levels will be used to derive the $PNEC_{aqua}$ for EGBE. These tests are gathered in **Table 3.5**.

Table 3.5 Toxicity tests retained for the derivation of $PNEC_{aqua}$

Species	Duration	Endpoint	Result (mg/L)	Reference	Lowest short term toxicity result for the same trophic level
Fish: *Brachydanio rerio*	21 days	NOEC	> 100	INERIS, 2001	*Poecilia reticulata* LC_{50} after 7 days = 983 mg/L (Konemann, 1981).
Invertebrates: *Daphnia magna*	21 days	NOEC	100	DeVillers et al., 2002a	*Hydra attenuata* EC_{50} after 72 hours =540 mg/L (Bowden *et al.*, 1995) *Daphnia magna* EC_{50} after 48 hours = 835 mg/L (Dow Chemical Co, 1979)
Algae: *Pseudokirchneriella subcapitata*	72 hours	NOEC	286	INERIS, 1999e	*Pseudokirchneriella subcapitata* EC_{50} after 72 hours = 911 mg/L (INERIS, 1999e)

An assessment factor of 10 is applied to the lowest test result in order to derive the $PNEC_{aqua}$: $PNEC_{aqua}$ = 10 mg/L

To support this assessment, we can add that EGBE is a non-polar narcotic (OECD, 1995) and acts with a non-specific mod of action in organisms. Although a smaller Assessment Factor can be used to derive a PNEC for non polar narcotics, a factor lower than 10 is not recommended by TGD (EC, 2003). Only additional studies, i.e. field data or model ecosystems, could result, after a review on a case by case basis, in a lower assessment factor. Nevertheless, the knowledge of a non-specific mode of action for EGBE seconds the $PNEC_{aqua}$ proposal.

Table 3.6 shows ecotoxicity results calculated from a log K_{ow} of 0.8 and a molar weight of 118.17 g/mol. The equations for non-polar narcotics given in Table 1 of Chapter 4, Part III of TGD (EC, 2003) were used to estimate QSAR ecotoxicity data.

Table 3.6 QSAR ecotoxicity data for EGBE

Species	Endpoint	Result (mg/L)
Fish: *Pimephales promelas*	96-hour LC_{50}	1,006
Fish: *Brachydanio rerio* or *Pimephales promelas*	28, 32-day NOEC	113
Daphnia: *Daphnia magna*	48-hour EC_{50}	983
Daphnia: *Daphnia magna*	16-day NOEC	242
Algae: *Selenastrum capricornutum*	72, 96-hour EC_{50}	1,103

The close relationship between predicted ecotoxicity of EGBE and results from ecotoxicity tests confirms that EGBE does not act with a specific action manner.

Calculation of the PNEC for the seawater compartment

Chronic toxicity data on three freshwater species representing three trophic levels are available. Only acute toxicity data on marine organisms (fish and invertebrates) are available. Nevertheless, the species tested do not show higher sensitivities than freshwater organisms. According to TGD (EC, 2003), both freshwater and seawater species are used to derive the PNEC for seawater. Thus the PNEC for marine organisms is determined from the lowest chronic test result (NOEC (21 days) = 100 mg/L on *Daphnia magna*) to which an assessment factor of 100 is applied as proposed in the TGD. This gives a $PNEC_{saltwater}$ of 1 mg/L.

Calculation of a PNEC for the sediment compartment

As no specific data is available for this compartment, the $PNEC_{sed}$ will be calculated from the $PNEC_{aqua}$ using the equilibrium partitioning method.

This results in: $PNEC_{sed}$ = 13.7 mg/kg (ww)

Calculation of the PNEC for the marine sediment compartment

No test is available on sediment dwelling organisms exposed via sediment. The PNEC for organisms living in marine sediments may provisionally be calculated using the equilibrium partitioning method from the PNEC for the marine aquatic compartment ($PNEC_{saltwater}$).

Thus, the $PNEC_{marine\ sed}$ = 1.4 mg/kg wet weight of marine sediment.

Endocrine disruption

A test has been conducted so as to identify a potential endocrine disrupting effect due to EGBE. The conclusion of this test is that EGBE has no potential for endocrine disruption.

PNEC for micro-organisms in STP

Four EGBE toxicity tests on micro-organisms are quoted. Three tests were conducted with protozoa and one with an individual bacteria species. Studies testing ciliated protozoa can be used for the determination of a $PNEC_{micro\text{-}organisms}$. That is why the test conducted on *Uronema parduzci* will be retained for the PNEC determination.

$PNEC_{micro\text{-}organisms}$ = 463 mg/L.

Terrestrial compartment

Since there are no EGBE toxicity data for terrestrial organisms, no $PNEC_{soil}$ can be derived directly. Therefore, this PNEC was estimated from the PNEC for aquatic organisms using the equilibrium partitioning approach.

This results in: $PNEC_{soil}$ = 6 mg/kg (ww)

Atmosphere

No data are available in order to correctly assess the effect of EGBE for species living in the environment and exposed via the air compartment. In a first attempt to quantify the risk for this compartment, inhalation toxicity data from the human risk assessment have been reported in this section.

In a repeat dose study with rats exposed by inhalation, a NOAEC value of 25 ppm (121 mg/m^3) has been identified from a sub-chronic study. During these studies, haemolysis was consistently observed and sometimes associated with hepatic effects. Effects on body weight gain, on the forestomach and on the WBC sub-populations (T limphocyte) were also observed. In a separate study a LOAEC of 31 ppm (150 mg/m^3) has been determined for mice and rats. Due to the closeness of the apparent LOAEC and NOAEC, it has been considered prudent to take the more conservative LOAEC of 31 ppm forward for the human health risk characterisation (with appropriate assessment factors). However, as the approach taken for the risk characterisation for the environmental section (atmospheric compartment) should be considered as a first tier, the NOAEC will be retained.

Secondary poisoning

No specific data available.

3.3 RISK CHARACTERISATION

Table 3.7 presents the calculated PEC / PNEC ratios for the aquatic compartment and for soil.

Table 3.7 Risk characterisation for micro-organisms in STP, aquatic and soil organisms

Scenario	RCR_{STP}	RCR_{aqua}	$RCR_{seawater}$	$RCR_{agricultural\_soil\_over\_30\_days}$
Production (worst case)	0 (7.10^{-5})	0.001	0 (8.10^{-4})	0.006
Paints I^F / Paints I^P	0 (7.10^{-5}) / 0 (2.10^{-4})	0.006 / 0.015	0.042 / 0.114	0.005 / 0.014
Paints II^F & III^F	0 (7.10^{-5})	0.006	0.043	0.005 / 0.013
Paints II^P and Paints III^U	0 (3.10^{-4})	0.002	0.011	0.002
Paints IV^F / Paints IV^P	- / -	0 (7.10^{-4}) / 0 (7.10^{-4})	0.001 / 0.001	0 (5.10^{-4}) / 0.002
Paints V^F / Paints V^P	- / 0 ($1.4.10^{-5}$)	0 (7.10^{-4}) / 0.002	0.001 / 0.009	0 (3.10^{-4}) / 0.001
Paints VI^F / Paints VI^P	0 (3.10^{-4}) / 0 ($1.4.10^{-4}$)	0.019 / 0.012	0.142 / 0.087	0.016 / 0.011

Table 3.7 continued overleaf

Table 3.7 continued Risk characterisation for micro-organisms in STP, aquatic and soil organisms

Scenario	RCR_{STP}	RCR_{aqua}	$RCR_{seawater}$	$RCR_{agricultural\_soil\_over\_30\_days}$
Paints VII^{F} / Paints VII^{P}	0 (7.10^{-5}) / 0 ($1.4.10^{-5}$)	0.007 / 0.002	0.050 / 0.008	0.006 / 0.001
Paints VIII^{F} / Paints VIII^{P}	- / -	0 (7.10^{-4}) / 0 (7.10^{-4})	0.001 / 0.001	0 (2.10^{-4}) / 0 (4.10^{-4})
Paints IX^{F} / Paints IX^{P}	0 (3.10^{-5}) / 0 (4.10^{-6})	0.003 / 0.001	0.015 / 0.002	0.002 / 0 (6.10^{-4})
Detergents I^{F}/Detergents I^{P}	0 (2.10^{-5}) / 0 (7.10^{-5})	0.002 / 0.005	0.011 / 0.037	0.001 / 0.004
Detergents II^{F}/Detergents II^{U}	0 (7.10^{-6}) / 0 (1.10^{-5})	0.001 / 0.002	0.005 / 0.008	0 (7.10^{-4}) / 0.001
Intermediates** I^{P}	0 (1.10^{-4})	0.003	0.059	0.032
Inks I^{F} / Inks I^{P}	0 (1.10^{-4}) / 0 (3.10^{-6})	0.011 / 0 (9.10^{-4})	0.084 / 0.002	0.009 / 0 (9.10^{-4})
Pharm I^{P}	0 (4.10^{-5})	0.001	0.021	0.011
Elec I^{P}	0 (1.10^{-4})	0.009	0.063	0.007
Leather I^{P}	0 (4.10^{-4})	0.029	0.223	0.025
Adhesives I^{F} / Adhesives I^{P}	0 (3.10^{-5}) / 0 (7.10^{-6})	0.002 / 0.001	0.014 / 0.005	0.002 / 0 (7.10^{-4})
Agri I^{F} / Agri I^{P}	0 (1.10^{-5}) / -	0.002 / 0 (7.10^{-4})	0.007 / 0.001	0.001 / 0 (4.10^{-4})
Oilfield I^{F} / Oilfield I^{P}	0 (1.10^{-4}) / 0 (4.10^{-5})	0.011 / 0.004	0.084 / 0.023	0.009 / 0.003
Metal I^{F} / Metal I^{P} Metal intermittent	0.001 / 0 (1.10^{-4}) 0.003	0.007 / 0.001 0 (5.10^{-4})	0.054 / 0.005 0 (5.10^{-4})	0.008 / 0.002
Cosmet I^{F} & Fire I^{F} / Cosmet I^{U}	0 (5.10^{-5}) / 0 (2.10^{-6})	0.004 / 0 (9.10^{-4})	0.027 / 0.003	0.003 / 0 (3.10^{-4})
Fire I^{P}	0 (5.10^{-6})	0.001	0.002	0 (4.10^{-4})

* Captive use not included
P Processing
F Formulation
U Private use

According to **Table 3.7** no risk is identified for all end uses even when both formulation and processing can be considered at a same site.

For sediments (freshwater and marine sediments), as neither monitoring data on levels of EGBE in sediment nor ecotoxicity data for benthic organisms are available, no risk characterisation is conducted. In addition, the partition coefficient between sediment and water for EGBE is low. So it can be assumed that the risk assessment for the sediment is covered by that for surface water (freshwater and seawater).

Conclusions to the risk assessment for the aquatic compartment (including STP and sediments) and soil

Conclusion (ii).

Conclusion (ii) is applied to all levels of the life cycle of EGBE: production, formulation, processing and private use.

Atmosphere

No specific effect data are available in order to accurately assess the risk for the atmospheric compartment. However, due to the volatility of EGBE, direct emissions to air should not be overlooked. In a first attempt to quantify the risk for the air compartment, a NOAEC of

121 mg/m^3 will be compared to the PECs calculated for air. This NOAEC has been determined in a study where rats where exposed via inhalation.

The worst $PEC_{local\_air,ann}$ of 51 µg/m^3 has been calculated for the scenario Paint IV_P (use in can coatings).

Using the methodology described in the risk characterisation for consumers, a minimal margin of safety (MOS) can be calculated as follows:

Interspecies differences	0.1 (based on rationale described in the risk characterisation for workers part to account for relative species sensitivity to critical end point)
Intraspecies differences	10 (default for consumers)
Type of effect	1
Confidence of the database	1
Minimal MOS required	1

The ratio between the threshold retained in the effect assessment and this worst case exposure is about a factor of 2,400. This rough risk characterisation for the air compartment leads to no concern by a sufficiently large margin that a more accurate assessment is not considered necessary.

Conclusions to the risk assessment for atmosphere

Conclusion (ii).

Secondary poisoning

Conclusion (ii).

4 HUMAN HEALTH

(to be added later).

5 RESULTS

5.1 ENVIRONMENT

Conclusions to the risk assessment for the aquatic compartment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is applied to all levels of the life cycle of EGBE: production, formulation, processing and private use.

Conclusions to the risk assessment for the terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is applied to all levels of the life cycle of EGBE: production, formulation, processing and private use.

Conclusions to the risk assessment for the atmospheric compartment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is applied to all levels of the life cycle of EGBE: production, formulation, processing and private use.

Conclusions to the risk assessment for secondary poisoning

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is applied to all levels of the life cycle of EGBE: production, formulation, processing and private use.

5.2 HUMAN HEALTH

(to be added later).

European Commission
DG Joint Research Centre, Institute of Health and Consumer Protection
European Chemicals Bureau

EUR 22502 EN **European Union Risk Assessment Report**
2-butoxyethanol (EGBE) – Part I – Environment

Editors: S.J. Munn, K. Aschberger, O. Cosgrove, S. Pakalin, A. Paya-Perez, B. Schwarz-Schulz, S. Vegro

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The report provides the comprehensive summary of the risk assessment of the substance 2-butoxyethanol (EGBE). It has been prepared by France in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I – Environment

The evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

The environmental risk assessment for 2-butoxyethanol (EGBE) concludes that there is at present no concern for the atmosphere, the aquatic ecosystem, the terrestrial ecosystem or for microorganisms in the sewage treatment plant. There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

This part of the evaluation will be added later.

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European Commission – Joint Research Centre
Institute for Health and Consumer Protection
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European Union Risk Assessment Report

2-butoxyethanol (EGBE)
Part I – environment

CAS No: 111-76-2 EINECS No: 203-905-0

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2-BUTOXYETHANOL

CAS-No.: 111-76-2

EINECS-No.: 203-905-0

SUMMARY RISK ASSESSMENT REPORT

FINAL APPROVED VERSION

Final report, 2008

France

Rapporteur for the risk assessment of 2-butoxyethanol is BERPC for the risk evaluation and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by:

Human health risk assessment

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Date of Last Literature Search : **[2003]**
Review of report by MS Technical Experts finalised: **[07-2007]**
Final report: **[2008]**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 2-butoxyethanol that has been prepared by France in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

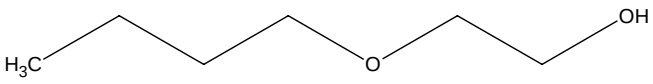
CAS No: 111-76-2

EINECS No: 203-905-0

IUPAC Name: 2-butoxyethanol

Molecular formula: $C_6H_{14}O_2$

Structural formula: CH3-CH2-CH2-CH2-O-CH2-CH2-OH



Molecular weight: 118.17 $g.mol^{-1}$

Synonyms: EGBE (this synonym will be used in the present study to refer to the chemical 2-butoxytehanol). Other synonyms: butoxyethanol ; 2-butoxy-1-ethanol ; n-butoxyethanol ; butyl ethoxol ; 3-oxa-1-heptanol ; o-butyl ethylene glycol ; butyl glycol ; butyl monoether glycol ; ethylene glycol butyl ether ; 2-BE ; ethylene glycol n-butyl ether ; ethylene glycol monobutyl ether ; glycol butyl ether
Commercial trade names : Dowanol EB ; Butyl Cellosolve ; Butyl Icinol ; Butyl Oxitol ; Eastman EB Solvent

In this assessment, the name 2-butoxyethanol (EGBE) will be used for the substance as this is the most common name.

1.2 PURITY/IMPURITIES, ADDITIVES

1.3 PHYSICO-CHEMICAL PROPERTIES

The physical and chemical properties of EGBE are summarized below in Table 1:

Table 1: Summary of physical and chemical properties of EGBE

Property	Value
Physical state	Liquid
Melting point	-73.4°C
Boiling point	170.5°C
Relative density	0.9 at 20°C
Vapour pressure	1 hPa at 20°C
Surface tension	26.6 mN/m at 20°C
Water solubility	Miscible (~1.10^6 mg/L)
Partition coefficient n-octanol/water (log value)	0.8
Granulometry	Not applicable
Flash point	63.2°C
Autoflammability	244.5°C
Flammability	Upper limit: 12.7 % (volume) Lower limit: 1.1 % (volume)
Explosive properties	Not explosive
Oxidising properties	No oxidising properties
Viscosity	3.28 mPa.s at 20°C
Henry's constant	0.08 $Pa.m^3/mol$ at 25°C
Conversion factors (101 kPa, 20°C)	1 ppm = 4.9 mg/m^3 1 mg/m^3 = 0.204 ppm

1.4 CLASSIFICATION

Human health effects (adopted classification)

Classification was adopted and included in the 28th TPA of directive 67/548/EEC (human health) with:

Classification: Xn; R 20/21/22

Xi; R 36/38

Labelling: Xn; R 20/21/22, 36/38

S 2 – 36/37 - 46

Environmental effects

To be updated

2 GENERAL INFORMATION ON EXPOSURE

3 ENVIRONMENT

4 HUMAN HEALTH

4.1 Human health (toxicity)

4.1.1 EXPOSURE ASSESSMENT

Exposure may occur during manufacture and use as intermediate in the chemical and pharmaceutical industries, and during formulation and use of products and indirectly via the environment. EGBE is a solvent used in many industrial activities or consumer applications. The main uses are in paints or surface coatings (solvent-based or water-based), followed by cleaners and printing inks.

Workers and consumers are primarily exposed via inhalation and dermal routes. EGBE is readily absorbed through the skin including absorption from direct contact with liquid or aerosol form or contact with vapours. Because this compound has a relatively low vapour pressure (0.1 kPa at 20°C), dermal absorption after direct contact with the liquid may be predominant or may contribute significantly to overall exposure.

OCCUPATIONAL EXPOSURE

The major occupational routes of exposure to EGBE are inhalation and skin contact. Assuming proper hygiene measures are applied, oral exposure would normally not occur in the workplace.

Environmental monitoring of breathing zone or air concentrations in the work area has been found to be inadequate to assess overall exposures: the total exposure to EGBE should take into account the respiratory uptake of vapours and aerosols and the dermal absorption of EGBE in liquid, vapour and aerosol form. Biological monitoring of the common toxic urinary metabolite, 2-butoxyacetic acid (BAA), is considered necessary for a complete assessment. Limited data on urinary BAA concentrations are available for occupationally exposed groups of the population. Biomonitoring data in the general population are not available.

Occupational exposure assessment has been carried out through three main categories of scenarios:

(a) the manufacture of EGBE and its use as an intermediate;

(b) the formulation of products containing EGBE;

(c) the use of products containing EGBE.

The third category focuses on particular sub-scenarios for exposure in the most frequent type of use, or particular pattern of use, when relevant.

Occupational exposure limits (8-hour TWA) range from 2 ppm to 25 ppm in the EU.

The worst-case estimates generated in the exposure assessment are considered to be reasonable worst-case estimates, as they describe high-end or maximum exposures in feasible but not unrealistic situations. They are not intended to account for extreme or unusual use scenarios. The majority of exposures are expected to be well below these estimates.

Inhalation exposure is mainly based on measured data issued from literature, producers or manufacturers surveys or documentation prepared by national or international bodies. EASE model (Estimation and Assessment of Substances Exposure) was used in a comparative way.

A few measured dermal exposure data are available for EGBE or analogous substances. They are considered together with modelling to predict occupational dermal exposure to EGBE. Many of the references stress the importance of dermal exposure, particularly during use of products. All sections on dermal exposure deal with liquid exposure.

1.1.1.1.1 MANUFACTURE AND USE AS INTERMEDIATE

EGBE is manufactured continuously, either full-time during the year or within periodic campaigns of several weeks or months. Workers may be exposed approximately 8 hours for 5 days per week of campaign but typically there are no personnel working constantly on the plant, with only occasional visits from fitters, engineers and other technical staff. The process is enclosed as extensive precautions are taken to prevent and minimize exposure to workers in the production area, due to the toxicity of the ethylene oxide feedstock.

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).

Exposure during transfer to tankers or drums is generally minimized by the use of automated filling, where the operator is segregated from the area during transfer, and the use of local exhaust ventilation. Accidental exposure may occur when the process is breached or when spills occur. Exposure may also occur during maintenance and cleaning activities; however, the purging of plant and equipment is generally standard practice.

1.1.1.1.2 FORMULATION OF PRODUCTS CONTAINING EGBE

During the formulation of products containing EGBE, workers may be exposed during pre-weighing before mixing, during transfer to the mixing tank, during mixing and during the filling of containers with products. The whole operation is generally carried out at room temperature. Because of the similarity of scenarios, it will be assumed that exposure during formulation is the same whatever the final use of products is.

Exposure strongly depends on the process, which may be enclosed or relatively open. When the transfer of EGBE to the mixing vessel is carried out in a sealed system, potential exposure will be minimal, but when the operator adds the raw materials directly by drum to the mixing tank, exposure may be greater due to possible splashing and vapour and/or aerosol generation.

While during preweighing and transfer to the mixing tank, workers are potentially exposed to pure EGBE, they are exposed to a more dilute form during filling. However, the frequency and duration of exposure may be greater. As operators may be involved in both mixing and filling, assessment of exposure is for the formulation process as a whole.

Inhalation exposure is based on many measurements and was set at 3.2 ppm (15.7 mg/m^3) as a worst case approach.

Very few data are available for dermal exposure to EGBE. So a mean dermal exposure was estimated from biological monitoring data. A reasonable worst-case was established using this mean dermal exposure and a factor 4 to take into account between-worker variability. This factor 4 is issued from RISKOFDERM database analysis.

1.1.1.1.3 USE OF PRODUCTS CONTAINING EGBE

EGBE is used in a wide variety of products. The following scenarios are considered as representative:

- use of paints and coatings

- use of printing inks

- use of cleaners

Cleaning related to painting and printing activities are included in the first and second scenarios.

- Scenario 3-1 Painting/Surface coatings

EGBE is used as a solvent in paints and surface coatings, particularly in water-based type. It is the main application of EGBE and due to the high volume use, a large number of workers are potentially exposed.

Coatings and paints are applied by brushing, rolling, spraying or dipping in different industrial and skilled trade sectors, e.g. coating of metal and wood, vehicle production and repair, building trade.

Two assessments are presented. The first covers spray applications and the second is a generic assessment for others paint applications.

Inhalation exposure assessment uses EGBE measurement data. Dermal exposure assessment is based on an analogous approach with DEGBE data from RISKOFDERM

- Scenario 3-2 Printing

EGBE is a solvent in a range of specialist inks particularly silk-screen inks used by professional trades. However there is a trend from solvent based inks to UV curing inks that contain no solvents.

Two scenarios are presented for printing. One for silk screening and the other for general applications. Inhalation and dermal exposure Assessments for silk screening are based on measurement data. For general application, inhalation exposure is based on measures too whereas dermal exposure is based on EASE model.

- Scenario 3-3 Cleaning

Exposure during cleaning is extremely variable, due to differences in frequency and duration of use, strength of solution used, method of application and precautions taken during use…

A distinction is made between spray application and wiping. Spray application leads to lower exposure than wiping. As for paint application analogous approach with DEGBE data is used for dermal exposure assessment.

1.1.1.1.4 SUMMARY OF EXPOSURE DATA

The following table presents exposure value for reasonable worst-case situations.

Table -2: Summary of proposed reasonable worst case occupational exposures

Scenario	8-hour TWA inhalation (mg/m3)	Dermal worst case derived from biomonitoring data (mg/day)	External dermal (mg/day)	Dermal worst case, EASE & Riskofderm & biomonit. Retained values for risk characterisation (mg/day)
1 - Manufacture	12	No data	42b	42
2 - Formulation	15.7	500	11,600c	2,000e
3 - Use of products				
3.1.1.1 - Coating/Painting – industrial: spraying	58.1		2,000c	2,000
3.1.1.2 - Coating/Painting – industrial: other works	30.4	430 (metal painting)	240c	430
3.1.2 - Coating/Painting- decorative	30.4	70	36c	70
3.2.1 – Printing - silk screening	20	Negligible	23b	23
3.2.2 – Printing - general printing	5	Negligibled	168b	168
3.3.1 – Cleaning - spraying	49		250c	250
3.3.2 – Cleaning - wiping	49	1,040	1,000c	1,040

Nota b : modelled data from EASE

Nota c : data derived from measurements with a less volatile solvent (DEGBE)

Nota d: in this case, due to a probable negative bias (see text), it is proposed to apply the low end of the EASE assessment.

Nota e: extrapolated from biomonitoring data

CONSUMER EXPOSURE

1.1.1.1.5 EXPOSURE FROM USES

EGBE is used as a solvent in many products available for consumers as, paints, paints thinners and cleaning products.

- Scenario 1: Household surface cleaners

Cleaning products which contain EGBE include general surface cleaners, floor strippers, window cleaners, carpet cleaners, spot cleaners, rust removers, oven and grease trap cleaners, laundry detergent, cars cleaners, bathrooms and toilets cleaners and disinfectants, ink and resin removers. One generic exposure assessment is presented for all household surface cleaner. This assessment is based on measurement data.

- Scenario 2: Measurements in indoor air

Consumers can be exposed via release of EGBE to indoor air. For this assessment only exposure by inhalation of indoor air is taken into account. The scenario considers a room with walls covered by paint containing EGBE and a covering floor containing EGBE. Release values issue from literature.

- Scenario 3: Painting

Paints that contain EGBE are both waterborne paints and solvent-borne paints including varnishes and products to preserve wood. A reasonable worst case inhalation is based on measurement data for a paint containing 1.5% of EGBE. Dermal exposure is assessed with model of Technical Guidance Document.

1.1.1.1.6 SUMMARY OF EXPOSURE DATA

The following table presents exposure value for reasonable worst-case situations.

Table -3: Summary of proposed "reasonable worst-case" consumer exposures in the main scenarios

Scenario	Inhalation (mg/kg/d)	Skin (mg/kg/d)
1 – Household surface cleaners	0.09	7
2 – Indoor air	0.1	
3 – Painting	10	4.2

For risk characterisation, internal exposures will be estimated for each scenario.

As a consumer is also exposed to indoor air when he paints, or uses household cleaners, we will also include in the risk characterisation, the scenarios:

- household surface cleaners + indoor air

- paints + indoor air

Table -4: Summary of combined worst case scenarios

Scenario	Inhalation (mg/kg/d)	Skin (mg/kg/d)
Household surface cleaners + indoor air	0.19	7
Paintings + indoor air	10.1	4.2

HUMANS EXPOSED VIA THE ENVIRONMENT

Generic exposure scenarios are used to estimate the releases from formulation, processing and private use of EGBE, as no actual data are available.

Both local and regional levels are taken into consideration and the estimation of local environmental exposures has been performed for all generic exposure scenarios. Concerning the production step, only the worst case has been reported. Calculations have been performed using default parameters in EUSES except for the use of an absorption factor via inhalation of 60% and a body weight of 60 kg.

The highest indirect exposure is estimated for the processing of can coating: $3.73.10^{-2}$ $mg.kg^{-1}.day^{-1}$. It can also be noted that the highest exposures are to be expected through intake of drinking water and plants (leaves and roots). Moreover, based on the regional concentrations, the total daily intake for humans is $3.32.10^{-4}$ $mg.kg^{-1}.day^{-1}$.

4.1.2 EFFECTS ASSESSMENT

Toxicokinetics, metabolism and distribution

Oral administration of EGBE leads to a quite complete absorption. Via inhalation route, a “wash in / wash out” mechanism limits the absorption to 55 – 60 % of the administrated concentration.

From dermal absorption studies, a wide range of absorption values were observed depending on the species (rats having a greater dermal penetration than humans), the dilution of EGBE (40 % or 80 % water solutions of EGBE being absorbed at twice the rate compared to lower dilutions or undiluted EGBE), physical state of EGBE and occlusion status of administration. In two rat studies, dermal absorption of liquid EGBE varies between 20 to 30 % of the applied dose. In human, dermal studies with liquid EGBE give penetration uptakes which varies of a factor of 10 between different subjects exposed to EGBE with the same experimental conditions with a percentage of absorption of about 12 % in one study using EGBE at 5 and 10 % in water. For dermal absorption of vapour EGBE, studies on volunteers have shown a percentage of internal dose due to dermal absorption of 11 to 39 % (depending on the conditions of exposure). Overall, dermal absorption of EGBE vapour is estimated to contribute for 27 % of the total EGBE body burden in normal uses and 39 % if extreme conditions are expected. EGBE reaches a maximum blood concentration rapidly after exposure whichever the route of exposure. EGBE is rapidly metabolised. Target organs are the liver, kidneys, thymus and stomach, in particular forestomach in the rat whichever the route of administration (oral and inhalation route, no data for dermal route). The main metabolism pathway leads to the formation of BAA (Butoxy Acetic Acid) via Alcohol dehydrogenase and Aldehyde dehydrogenase in a saturable mechanism. With increasing doses of EGBE, the formation of glucuronide conjugate of EGBE or BAA is enhanced.

Elimination is rapid and mainly via urinary route (80 to 90 % of the metabolites). The plasmatic half-life of metabolites is about 4 hours. Any renal injury will enhance BAA toxicity by increasing its blood persistence. However if renal integrity is respected, a repeated administration of EGBE leads to metabolism adaptation. In this case, elimination of BAA occurred more rapidly. This mechanism of extra hepatic adaptation is also described for action of EGBE on red blood cells, especially on erythrocyte deformability.

It is considered that the PBPK model for EGBE is sufficiently well developed to justify its used to derive animal to man toxicokinetic extrapolation factors for the inhalation route. These factors are based on the toxicokinetics of BAA since this is the metabolite that causes the critical toxic effects.

Acute toxicity

For the inhalation route, the 4 hour LC_{50} in rats, which are susceptible to haemolysis, was in the region of 450 ppm (2,214 mg/m^3) with higher values reported in other species. For the dermal route, great differences were seen between the tested species and the mode of occlusion. The rabbit seems to be the most sensitive species with LD_{50} of about 500 mg/kg with an occlusive application. For the oral route, available studies show LD_{50} values upwards from 1,000 mg/kg. According to the data available, a classification Xn; R20/21/22 is needed for all three routes of exposure.

A number of human case studies are available from attempted suicides which suggest that the human LOEL is in the region of 400 mg/kg bw. In the reported cases, patients exhibited SNC depression and metabolic acidosis. Signs of hemolysis were seen in some cases but this finding was not systematic. Human data is preferred for EGBE risk characterisation, because its haematotoxicity is more marked in animals than in humans. A worst case estimation of the LOEL is used in the risk characterisation part in which is derived from the Mc Kinney paper where the possible range of exposure was between 0.4 and 1.2 g/kg bw.

Summary haematotoxicity

In studies performed *in vivo*, the same signs of toxicity seen in acute toxicity studies (LD50 studies) were recorded with thrombosis in various localisations sometimes leading to necrosis due to an infarction mechanism. Mechanistic studies have shown that BAA is responsible for *in vivo* haematotoxicity. Some species were very sensitive to EGBE- or BAA-induced haemolysis: rat, mouse, hamster and baboon whereas other species were resistant to these effects: dog, guinea pig, pig, cat, rabbit and humans (30 x less sensitive than rats). In one study, dogs were very sensitive to EGBE but not to BAA.

In vivo or *in vitro*, haemolysis was due to a decrease of erythrocyte deformability due to erythrocyte swelling. The mechanism leading to erythrocyte swelling and loss of deformability is for the moment unknown. Newly formed erythrocytes were more resistant than old ones. It was also showed that EGBE pre-treatment gave a relative “protection” against higher doses administered later. Moreover, an adaptive mechanism of “protection” occurs when animals have a period of recovery time before a re-exposure to EGBE. In humans, slight effects were seen with doses of 8 mM and 4 mM of BAA *in vitro.*

Irritation

Human data on skin irritation is not available. All the studies performed on rabbits and guinea-pigs have shown that EGBE have caused moderate irritation when applied occlusively on the skin of rabbits and guinea-pigs. When EGBE was applied on scarified skin or for a longer period of time, signs of severe irritation sometimes leading to necrosis were reported. Overall, in

animals, EGBE can be considered to be a skin irritant. EGBE is classified "Xi; Irritant" with "R38; Irritating to skin". In the available rabbit eye irritation studies, EGBE was irritant or severely irritant to the eyes of rabbits with effects both on conjunctivae, iris and cornea. EGBE is classified "Xi; Irritant" with "R36; Irritating to eyes". It was demonstrated that dilution of EGBE in water decreases its irritant properties as well as rinsing of the eyes in case of exposure. Animal studies available did not show any signs of significant respiratory irritation. No classification is required for this end point. From the human data it is apparent that the NOEC is greater than 50 ppm whilst the NOEC (based on effects of discomfort) is lower than 100-200ppm. A NOEC of 50 ppm is derived for respiratory irritation.

Sensitisation

No signs of skin sensitisation were seen in two animal studies or in a human patch test. Moreover, considering Structure Activity Relationship (SAR) in the glycol ether family, the wide dispersive use of EGBE and that EGBE has never been associated with cases of skin sensitisation, it can be considered that skin sensitisation cannot be expected and is not relevant for risk assessment. No classification is needed for this end point.

Repeated dose toxicity

Since all key effects are induced by haemolysis in rodents, a NOAEL based on haemotoxicity will be used in the risk characterisation. In rats and mice, haemolysis was consistently observed (whichever the route of administration) and was sometimes associated with hepatic effects (Kupffer cell pigmentation and absolute and relative liver weight increases), effects on body weight gain, hyaline degeneration of the olfactive epithelium (by inhalation), effects on the forestomach and effects on the WBC (White Blood Cell) sub-populations (T lymphocyte). Effects on spleen (including spleen fibrosis) were also observed which can be related to haemolysis. Effects on the forestomach of rodents do not appear to be relevant for humans. With regard to the increased incidence of hyaline degeneration of the olfactory epithelium observed in rodents, this appears to be an adaptive response, the severity of the lesion being unaffected by increasing exposure concentrations.

In the available animal studies and for the inhalation route, no NOAEC was identified for mice, whereas a NOAEC value of 25 ppm (121 mg/m^3) in rats was identified. In a separate study a LOAEC value of 31 ppm (150 mg/m^3) can be established in rats, based on haemolysis and Kupffer cell pigmentation. Due to the closeness of the apparent LOAEC and NOAEC, it is considered prudent to take the more conservative LOAEC of 31 ppm forward for risk characterisation. However, the likelihood that this figure is close to the NOAEC will be taken into account in deriving appropriate assessment factors. For the dermal route, a NOAEL of 150 mg/kg bw/d (the highest dose tested) has been determined from a 13-week study in rabbits. For the oral route, a LOAEL of 69 and 82 mg/kg/day for male and female rats respectively, was derived in a 13 week drinking water study (haemolytical effects).

Haemotoxicity is the end point chosen for the risk characterisation, keeping in mind the interspecies differences (human/rodents). No other lesions has been identified which can be specifically attributed to treatment with EGBE.

Mutagenicity

EGBE is not mutagenic in bacteria, not withstanding a significant response according to one report in *S. typhimurium* TA97a. This was not substantiated by another study specifically designed to investigate this finding. Neither BAL (Buthoxy aldehyde) nor BAA was mutagenic in bacteria. Two of three mammalian cell mutation assays did not indicate any mutagenic activity for EGBE and a significant result was obtained in an assay using a very high concentration (20 mM) that was poorly reported.

Sister chromatid exchanges induction and cell transformation were observed but the results were inconsistent and these results could be artefacts due to cell cycle delay. Some indication of inhibition of gap-junctional intercellular communication is given in a single study with EGBE and its two major metabolites.

No evidence for chromosomal aberration induction has been found in a number of mammalian cell culture studies with EGBE, or in one with BAL (Buthoxy aldehyde) or BAA, whereas weak aneugenic effects were obtained in the only available study with EGBE and BAL, but not with BAA. Micronuclei found in long exposure in vitro studies with BAL and, to a much lesser extent with EGBE itself, but not with BAA appear to be due to aneuploidy, rather than chromosomal breakage.

In vivo, there is no evidence for micronucleus induction in bone marrow cells or interaction with DNA in several organs of rats. The balance of the evidence suggests that EGBE dose not exhibit a significant mutagenic potential in vivo.

Reproductive toxicity

Unlike EGME (Ethylene Glycol Methyl Ether) and EGEE (Ethylene Glycol Ethyl Ether), EGBE seems to have no specific effects on fertility (no effects were seen in the continuous breeding study and neither macroscopic nor microscopic effects on reproductive organs in the repeated dose toxicity studies at doses which does not exhibit severe general toxicity.) A NOAEL of 720 mg/kg was derived from the continuous breeding study for fertility effects. The effects seen at the higher dose tested are certainly due to general toxicity.

For developmental toxicity, studies performed on animals via various administration routes did not demonstrate any teratogenic potential, but foetotoxicity and embryotoxicity (lethality and resorptions) were often observed in relation with maternal toxicity (regenerative haemolytic anaemia). Other effects seen on foetuses were an increase in the incidence of skeletal variations which are generally described as ossification delays. *In vitro* studies showed some adverse effects on development with EGBE and its metabolite BAA, but only in conjunction with growth effects. Effects seen in foetuses are certainly related to maternal toxicity. Some studies have previously shown a relationship between maternal haemotoxicity and effects seen with EGBE (resorption, growth retardation and variations).

In human, all the epidemiological studies, except one, studying glycol ethers, showed an increased risk of malformation (cleft lip, neural tube defect). For EGBE, these studies did not allow to draw any conclusion about its potential effects on human because no studies are able to distinguish clearly an unique source of glycol ether, usually studies described co-exposure to various glycol ethers, including known developmental toxins such as EGME and other chemicals as well.

Overall, it is not possible to obtain a suitable NOAEL for developmental toxicity relevant for humans and based on animals studies. Regarding kinetic properties and SAR with other glycol ethers, it can be assumed that developmental toxicity due to EGBE in humans could not be expected without maternal toxicity. Consequently, there is no concern for this end-point and no need for risk characterisation.

No specific effects were seen for fertility. In the continuous breeding study a NOAEL of 720 mg/kg was set based on non specific effects observed at the higher doses tested. This NOAEL is used in the risk characterisation part.

Carcinogenicity

No oral or dermal carcinogenicity study is available. Inhalation rodent carcinogenicity were conducted with EGBE. In male rats, there was no evidence for carcinogenicity of EGBE by inhalation and equivocal evidence for carcinogenicity in female rats based on a slight increase of benign or malignant phaeochromocytoma (combined) of the adrenal medulla at 125 ppm. EGBE is carcinogenic in male B6C3F1 mice by inhalation, where it causes a slight increase of the incidence of haemangiosarcomas, and in female mice, where it causes an increased incidence of forestomach tumours (squamous cell papillomas or carcinomas) at 250 ppm.

Hypotheses have been proposed and supported by experiment data in an attempt to explain the carcinogenic responses. In the case of forestomach tumours, the fundamental differences in physiology and function between rodent forestomach, on the one hand, and the human stomach and the rodent glandular stomach, on the other hand, point to the low probability that the latter would be targets for neoplasia by this mechanism. This is substantiated by the lack of any neoplastic response in the glandular stomach of mice exposed to EGBE under conditions that produce forestomach tumours.

The data available are consistent with the proposal that haemangiosarcomas observed in male mice could arise in mice of both sexes as a result of haemolysis leading to haemosiderin deposition. These deposits form nuclei for oxygen radical production that can damage many cellular components, including DNA, unless there is sufficient antioxidant protection. When this deposition in the sinusoidal cells of the liver reaches a certain level, the oxidative defence mechanisms available to the cells are overwhelmed, creating the conditions for neoplastic responses in the endothelial cells of the hepatic blood vessels. Since man is much less sensitive to the haemolytic effects of EGBE, damage to blood cells not having been observed except in cases of very high exposure found in attempted suicides, the low level of haemangiosarcomas induced in male mice, but not in either female mice or in rats of either sex might have no significance for human risk assessment. In conclusion, given the species and sex specificity of the neoplastic responses and the current evidence supporting the hypothesis that the more likely mechanism of action is based on haematotoxicity, then EGBE is unlikely to be a human carcinogen. Moreover, as the mechanism of haemangiosarcomas in male mice is related to haemotoxicity, the risk characterisation made for repeated dose toxicity is considered sufficient to also cover carcinogenicity. The other tumours (mouse forestomach) are considered not relevant to humans; no risk characterisation is needed for them.

4.1.3 RISK CHARACTERISATION

The human population may be exposed to EGBE at the workplace or from use of consumer products and indirectly via the environment. From the oral absorption studies, it is estimated that oral absorption is complete. For dermal absorption of liquid EGBE, it can be assumed 30 % of applied dose. For dermal absorption of vapour a value of 39 % of the internal dose due to dermal absorption can be taken into account. For inhalation route, 60 % inhalation absorption is estimated.

For toxicological end-points with relevant quantitative MOS (Margin of Safety) values are calculated as quotients of experimental NOAEL or (LOAEL) and workplace exposure assessments. For dose transformation, a breathing volume of 10 m^3 per day is assumed at work. Scientifically based assessment factors describe the stepwise extrapolation of animal data to the worker population. The value of the minimal MOS, as decision mark between conclusion (ii) and (iii), results from the multiplicative combination of the different assessment factors.

For extrapolation between different species (rat to human) an overall factor of 10 is derived for the oral route based on a comparison of rat and human effect data. This factor includes correction for metabolic rate differences which does not apply for inhalation. Species extrapolation of that route therefore uses a factor of 2.5. For each toxicological endpoint an additional uncertainty factor is determined which takes into account aspects like the reliability of the database, the biological relevance of the observed effects, the slope of the dose response curve or the variability of the human population. Intraspecies differences are not accounted for with an extra assessment factor.

Regarding repeated dose toxicity, since all key effects are induced by haemolysis in rodents andhumans are less sensitive to BAA than rats (or mice), the selection of an appropriate interspecies chemical safety assessment factor must take this into account. The toxicokinetic factor is taken account by use of the PBPK (Physiologically Based PharmacoKinetic) model which allows the concentration of the proximate toxicant (BAA) to be predicted following either inhalation or oral exposure to EGBE. The data available on the most sensitive measure (pre-haemolytic changes) suggests that a value of 0.01 would be realistic. However, a more cautious and conservative initial approach was followed with a value of 0.1.

In the following, risks at the workplace are considered specifically for each toxicological endpoint. Summary Table -5 containing all scenarios is given at the end of this section.

WORKERS

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and the inhalation routes of exposure. An overview of the MOSs and conclusions with respect to occupational risk characterisation for EGBE is given in Table -5. Conclusion (ii): no concern is drawn for all the end-points and the identified scenarios.

Table -5: Overview of the MOSs and conclusions with respect to occupational risk characterisation for EGBE

		Acute toxicity			Eye and respiratory tract irritation (vapour)	Sensitisation	Repeated dose toxicity Systemic			Mutagenicity	Carcinogenicity	Fertility		
		Inhalation	Dermal	Combined	Inhalation	*Dermal*	Inhalation	Dermal	Combined			Inhalation	Dermal	Combined
1 - Manufacture	**MOS**	237	2220	213	20		39	250	22			426	4000	385
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
2 - Formulation	**MOS**	181	47	37	16		30	5	3.8			327	84	67
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3- Use of end products														
3.1 Coating/ painting														
3.11 -Industrial														
-spraying	**MOS**	49	47	24	4.2		8	5	2.4			88	84	43
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
-other works	**MOS**	94	217	65	8		16	24	6.6			168	381	118
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.12 - decorative	**MOS**	94	1333	87	8		16	150	8.8			168	2286	157
	Concl.	ii	ii		ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.2 Printing														
3.21 Silk screening	**MOS**	142	4039	137	12		24	454	14			256	6957	247
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.22 General printing	**MOS**	569	555	281	50		95	62	29			1029	1000	507
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.3 Cleaning														
- spraying	**MOS**	58	373	50	5		10	42	5.1			104	640	90
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
- wiping	**MOS**	58	90	35	5		10	10	3.6			104	154	63
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii

[1] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

CONSUMERS

EGBE is used as a solvent in many products available for consumers as paints, paints thinners and cleaning products. Assuming that oral exposure could only be accidental by ingestion of a product, the risk characterisation for consumers is limited to the dermal and the inhalation routes of exposure.

Conclusion (ii): no concern is drawn for all the end-points and identified scenarios (see Table -6 below).

Table -6 Overview of the MOSs and conclusions with respect to consumer risk characterisation for EGBE

		Acute toxicity			**Eye and respiratory tract irritation (vapour)**	***Sensitisation***	**Repeated dose toxicity Systemic**			**Mutagenicity**	**Carcinogenicity**	**Fertility**		
		Inhalation	Dermal	Combined	Inhalation	*Dermal*	Inhalation	Dermal	Combined			Inhalation	Dermal	Combined
1 – Household surface cleaners	**MOS**	7407	190	185	906		2,633	31	30			20,000	500	488
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
2 – Indoor air	**MOS**	6667		6667	816		1580		750			12,000		12,000
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3 – Painting	**MOS**	67	308	55	8		592	1250	230			4,500	20,000	3,673
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
4 – Household surface cleaners + indoor air	**MOS**	3508	190	180	430		987	31	29			7,500	500	469
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
5 – Painting + indoor air	**MOS**	66	308	54	8		431	1,250	176			3,273	20,000	2,813
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii

HUMAN EXPOSED VIA THE ENVIRONMENT

The key health effect is repeated dose toxicity. Irritation (via dermal or ocular routes)) is of low concern since exposure is dissipated throughout the environment. Comparison of the total internal dose of 94.8 $mg.kg^{-1}$ (corresponding to the LOAEC of 31 ppm for RDT via inhalation route corrected with PbPk modelling to obtain human internal dose see also calculation of internal NOAEL by inhalation in the consumer part in chapter 4.1.3.3.4.) with the highest estimated exposure at regional ($3.22.10^{-4}$ $mg.kg^{-1}.day^{-1}$) and local ($3.73.10^{-2}$ $mg.kg^{-1}.day^{-1}$) levels leads to margins of safety of, respectively, $2.9.10^{5}$ and $2.5.10^{3}$ which do not lead to concern (compared to the minimal MOS of 3 calculated for consumers) **conclusion (ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

EGBE has a low vapour pressure and is moderately flammable (flash point is 60°C). It has no explosive or oxidising properties. However, it is noted that oxidation by air may involve peroxidation of the substance, which may increase explosive properties. A general warning to this effect is recommended. The use of antioxidants reduces the potential to peroxidation. It can be concluded that there is no concern for human health with regard to physico-chemical properties **(conclusion ii)**.

5 RESULTS[2]

5.1 Environment

5.2 Human health toxicity

5.2.1 WORKERS

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.2 CONSUMERS

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.3 HUMANS EXPOSED VIA THE ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.3 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.

[2] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.