European Union Summary Risk Assessment Report

2-BUTOXYETHYL ACETATE

(EGBEA)

CAS No: 112-07-2
EINECS No: 203-933-3

SUMMARY RISK ASSESSMENT

GENERAL NOTE

This document contains two different reports:

- **Volume 69 Part I Environment** (Publication: EUR 22477 EN) – pages 2-25
- **Part II Human Health** (Final approved version awaiting for publication) – pages 26-50

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

Institute for Health and Consumer Protection
European Chemicals Bureau
I-21020 Ispra (VA) Italy

2-BUTOXYETHANOL ACETATE (EGBEA)
Part I – Environment

CAS No: 112-07-2

EINECS No: 203-933-3

Summary Risk Assessment Report

2006 **EUR 22477 EN**

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European Commission
Directorate-General Joint Research Centre
Institute of Health and Consumer Protection (IHCP)
European Chemicals Bureau (ECB)

Contact information:

Institute of Health and Consumer Protection (IHCP)
Address: Via E. Fermi 1 – 21020 Ispra (Varese) – Italy
E-mail: ihcp-contact@jrc.it
Tel.: +39 0332 785959
Fax: +39 0332 785730
http://ihcp.jrc.cec.eu.int/

European Chemicals Bureau (ECB)
E-mail:esr.tm@jrc.it
http://ecb.jrc.it/

Directorate-General Joint Research Centre
http://www.jrc.cec.eu.int

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2-BUTOXYETHANOL ACETATE (EGBEA)

Part I - Environment

CAS No: 112-07-2

EINECS No: 203-933-3

SUMMARY RISK ASSESSMENT REPORT

Final report, 2006

France

The summary of the environmental part of the risk assessment of 2-butoxyethanol acetate (EGBEA) 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:

Institut National de l'Environnement Industriel et des Risques (INERIS)
Direction des Risques Chroniques
Unité Evaluation des Risques Ecotoxicologiques
Parc Technologique ALATA
BP n°2
60550 Verneuil-en-Halatte
France

Date of Last Literature Search:	**2004**
Review of report by MS Technical Experts finalised:	**2005**
Final report:	**2006**

PREFACE

This report provides a summary, with conclusions, of the environmental part of the risk assessment report of the substance 2-butoxyethanol acetate (EGBEA) 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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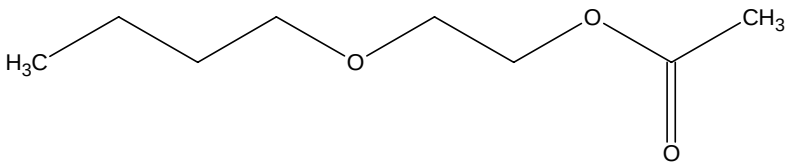
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 112-07-2
EINECS No: 203-933-3
IUPAC Name: 2-butoxyethanol acetate
Synonyms: EGBEA (this synonym will be used in the present study to refer to the chemical 2-butoxyethanol acetate). Other synonyms: Butyl Glycol Acetate; 2-butoxyethyl acetate; butoxyethyl acetate; butyl ethoxol acetate; Embkanol AEG; ethylene glycol butyl ether acetate (EGBEA); ethylene glycol monobutyl ether acetate; glycol monobutyl ether acetate
Commercial trade names: Butyl Cellosolve Acetate; Butyl Ethoxyl Acetate; Butyl Oxitol Acetate; Eastman EB acetate
Molecular formula: $C_8H_{16}O_3$
Molecular weight: 160.21 $g.mol^{-1}$
Annex I entry: 607-038-00-2
Structural formula: CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-O-C-O-CH_3



1.2 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Property	Value
Physical state	Liquid
Melting point	-64°C
Boiling point	192.3°C
Relative density	0.94, at 20°C
Vapour pressure	0.56 hPa, calculated at 25°C (initial value: 0.4 hPa, at 20°C)
Surface tension	30 mN/m, at 20°C
Water solubility	16,100 mg/L, calculated at 25°C (initial value: 15,000 mg/L, at 20°C)
Partition coefficient n-octanol/water (log value)	1.51
Granulometry	n.a.
Flash point	75°C, closed cup
Autoflammability	340°C
Flammability	0.88% (at 93°C) – 8.54% (at 135°C) – volume

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties

Property	Value
Explosive properties	Not explosive
Oxidising properties	No oxidising properties
Viscosity	1.8 mPa.s
Henry's constant	0.55 Pa.m^3/mol at 25°C
Conversion factors (101 kPa, 20°C)	1 ppm = 6.65 mg/m^3 1 mg/m^3 = 0.15 ppm

1.3 CLASSIFICATION

1.3.1 Current classification

There is no classification for the environment.

1.3.2 Proposed classification (environmental part only)

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

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

Glycol ethers and their acetates consist of a large group of organic solvents that are widely used in formulating paints, lacquers and cleaning products. As far as butyl glycol ether acetate (EGBEA) is concerned, about 13.4 kt were produced in Europe, in 2003, whereas the consolidation of sales in Europe for the same period gives a volume of 12.8 kt. For comparison, the most recent data available show a total use of 2-butoxyethanol (EGBE) of about ~ 97 kt/year in Europe.

2.2 USES

A breakdown of the uses of EGBEA 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 EGBEA uses in Europe

End use	Quantity used (tonnes)	Percentage of total use
Paints and coatings (including estimation for indirect sales via distributors)	11,500	89.84
Metal cleaning	400	3.13
Screen printing inks	350	2.73
Detergents, cleaners	250	1.95
Leather finishing	150	1.17
Intermediates	150	1.17
TOTAL	12,800	~ 100

EGBEA is primarily used as a solvent in paints. This principal use covers about 90% of its total volume. The remaining 10% are scattered within several other uses. It is used, for example, as a solvent in metal cleaning, screen printing inks and in leather processing industry or as a cleaning agent in detergents.

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 EGBEA 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 ~18.5 hours has been derived for EGBEA.
- According to standard tests on ready biodegradation, EGBEA 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 $2.32.10^{-4}$ indicates that volatilisation of EGBEA from surface water and moist soil is expected to be very low.
- In view of the BCFs for fish and worm (3.8 and 6.5) calculated based on the log Kow, EGBEA is expected to have a low bioaccumulation potential.
- Based on the results from a multimedia fugacity model and the physico-chemical properties of EGBEA, the hydrosphere is the preferential target of the substance in the environment (89.5% in water, 7.85% in air, 2.57% in soil).
- Based on the SIMPLETREAT model, it is anticipated that, after a sewage treatment plant, EGBEA will be degraded at a level of 86.7%, 12.5% of EGBEA 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 EGBEA, when no other data are available. A specific emission scenario has been used for the use of EGBEA for metal cleaning.

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

Table 3.1 Local releases of EGBEA

Scenario	Amount released to air (kg/day)	Amount released to waste water (kg/day)	Amount released to soil (kg/day)
Production (worst case scenario)	0.15	90	-
Paints F - Paints and coatings	9.9	0.05	-
Paints P - Paints and coatings	172.5	3.8	0.2
Paints U - Paints and coatings	-	0.1	-
Metal F - Metal cleaning	1	4	0.02
Metal P - Metal cleaning	53.3	0.8	10.7
Printing F - Screen printing inks	0.5	1.9	0 (9.10^{-3})
Printing P - Screen printing inks	1.9	0.2	0.1
Detergents F - Detergents and cleaners	0 (2.10^{-3})	0.1	0.3
Detergents P - Detergents and cleaners	-	0.2	-
Detergents U - Detergents and cleaners	-	0.1	-
Leather P - Leather finishing	-	-	-
Intermediates P - Intermediates for chemical synthesis	0 (1.10^{-2})	19.5	0.1

P Processing
F Formulation
U Private use

Continental and regional releases

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

Table 3.2 Total continental and regional EGBEA emissions

	Air	Water (total / waste water*)	Soil
Continental	$2.69.10^4$ kg/day	$2.06.10^3$ kg/day/$1.65.10^3$ kg/day	$1.36.10^2$ kg/day
Regional	$2.98.10^3$ kg/day	$2.29.10^2$ kg/day/$1.83.10^2$ kg/day	16 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 EGBEA.

Table 3.3 Local PECs for EGBEA

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)
Production (worst case)	110	1	0.14	48.1	$4.92.10^{-2}$
Paints F	2.9	0.6	0.26	1.0	2.29
Paints P	238	24.1	19.1	37.0	39.10
Paints U	6.9	1.0	0.6	1.1	0.03
Metal F	251	25.4	20.1	31.8	0.15
Metal P	50	5.3	4.0	7.6	6.12
Metal P (intermittent release)	1,500	19.1	15.0	-	-
Printing F	117	12.0	9.4	14.9	0.14
Printing P	11.8	1.5	1.0	1.8	0.47
Detergents F	4.7	0.8	0.4	0.8	0.03
Detergents P	13.9	1.7	1.1	2.0	0.03
Detergents U	8.4	1.1	0.7	1.3	0.03
Leather P	This use is already covered by the painting scenario				
Intermediates P**	250	6.6	20.0	31.7	0.03

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	$3.40.10^{-6}$ mg/m³	$3.31.10^{-5}$ mg/m³
Water	$3.82.10^{-5}$ mg/L	$3.00.10^{-4}$ mg/L
Agricultural soil	$9.87.10^{-6}$ mg/kg (ww)	$9.59.10^{-5}$ mg/kg (ww)
Pore water of agricultural soils	$7.92.10^{-6}$ mg/L	$7.70.10^{-5}$ mg/L
Natural soil	$2.48.10^{-5}$ mg/kg (ww)	$2.41.10^{-4}$ mg/kg (ww)
Industrial soil	$1.34.10^{-4}$ mg/kg (ww)	$1.36.10^{-3}$ mg/kg (ww)
Sediment	$7.67.10^{-5}$ mg/kg (ww)	$6.02.10^{-4}$ mg/kg (ww)
Seawater	$1.33.10^{-7}$ mg/L	$2.85.10^{-5}$ mg/L
Marine sediment	$2.61.10^{-7}$ mg/kg (dw)	$5.61.10^{-5}$ mg/kg (ww)

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

Calculation of the PNEC for the freshwater compartment

Acute toxicity data are available for three trophic levels (fish, crustacean and algae). Two long term test results from two species representing two trophic levels (primary consumers and primary producers) will be used to derive the $PNEC_{aqua}$ for EGBEA. 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)	Lowest short term toxicity result for the same trophic level
Fish	-	-	-	*Oncorhynchus mykiss* LC_{50} after 96 hours = 28.3 mg/L
Invertebrates: *Ceriodaphnia dubia*	7 days	NOEC	16.4	*Daphnia magna* EC_{50} after 48 hours = 37 mg/L
Algae: *Pseudokirchneriella subcapitata*	72 hours	NOEC	300	*Pseudokirchneriella subcapitata* EC_{50} (growth rate) after 72 hours = 1,570 mg/L

An assessment factor of 100 should be applied to the lowest chronic test result for it has not been generated from the trophic level showing the lowest acute test result. However, there appears to be very little difference between the sensitivity of fish (96-hour LC_{50} = 20-40 mg/l) and *Daphnia* (48-hour EC_{50} = 37 mg/L and 67.5 mg/L in the two valid studies available). Therefore the assessment factor will be lowered to 50 (recommended assessment factor when chronic toxicity test results are available for two trophic levels).

This gives a $PNEC_{aqua}$ of 328 µg/L.

Calculation of the PNEC for the seawater compartment

Chronic toxicity data on two freshwater species representing two trophic levels are available. No toxicity data on marine organisms (fish and invertebrates) are available. According to the TGD, freshwater species can be used to derive the PNEC for seawater. Thus the PNEC for marine organisms is determined from the lowest chronic test result to which an assessment factor of 500 is applied as proposed in the TGD. This gives a $PNEC_{saltwater}$ of 32.8 µg/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: $PNEC_{sed}$ = 713 µg/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 $PNEC_{marine\ sed}$ = 71.3 µg/kg wet weight of marine sediment.

Calculation of the PNEC for micro-organisms in STP

The determination of the $PNEC_{STP}$ for EGBEA is made using the result of the test conducted on *Pseudomonas putida*. The EC_{10} of 722 mg/L can be considered as a PNEC for micro-organisms in a STP.

$PNEC_{STP}$ = 722 mg/L

Calculation of the PNEC for the terrestrial compartment

Since there are no EGBEA 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: $PNEC_{soil}$ = 409 µg/kg (ww)

Calculation of the PNEC for the air compartment

No data are available in order to correctly assess the effect of EGBEA 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 studies performed with EGBEA, signs of haematotoxicity and associated lesions were seen on all species except guinea pigs. No other symptoms were observed. Studies available are old and are not reliable for risk assessment. The results obtained with EGBE studies can be taken into account. The results obtained in these studies are summarised below:

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 fore-stomach 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.

Calculation of the PNEC for secondary poisoning

No specific data available.

3.3 RISK CHARACTERISATION

Table 3.6 presents the calculated PEC/PNEC ratios for the aquatic compartment and for soil.

Table 3.6 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 (2.10^{-4})	0.004	0.005	0.203
Paints F	0 (4.10^{-4})	0.002	0.008	0.004
Paints P	0 (3.10^{-4})	0.074	0.582	0.157
Paints U	0 (8.10^{-6})	0.003	0.018	0.004
Metal F	0 (9.10^{-4})	0.078	0.612	0.135
Metal P	0 (6.10^{-5})	0.017	0.123	0.033
Printing F	0 (2.10^{-4})	0.036	0.285	0.063
Printing P	0 (2.10^{-5})	0.005	0.030	0.008
Detergents F	0 (8.10^{-6})	0.003	0.012	0.003
Detergents P	0 (2.10^{-5})	0.005	0.035	0.009
Detergents U	0 (8.10^{-6})	0.004	0.022	0.006
Leather P	This use is already covered by the painting scenario			
Intermediates P	0 (3.10^{-4})	0.020	0.610	0.135

P Processing
F Formulation
U Private use

According to **Table 3.6** 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 EGBEA in sediment nor ecotoxicity data for benthic organisms are available, no risk characterisation is conducted for this compartment. In addition, the partition coefficient between sediment and water for EGBEA 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 EGBEA, 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. These results come from the effect assessment of EGBE that have been retained for the EGBEA risk assessment since no reliable data are available for EGBEA.

The worst $PEC_{local\_air,ann}$ of 39.1 $\mu g/m^3$ has been calculated for the processing of paints containing EGBEA (Scenario Paints P).

The ratio between the threshold retained in the effect assessment and this worst case exposure is about a factor of 3,100. 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).

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

Secondary poisoning

Conclusion (ii).

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

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 EGBEA: 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 EGBEA: 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 EGBEA: 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 22477 EN **European Union Risk Assessment Report**
2-butoxyethanol acetate (EGBEA) – 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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2006 – III pp., 15 pp. – 17.0 x 24.0 cm

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The report provides the comprehensive summary of the risk assessment of the substance 2-butoxyethanol acetate (EGBEA). 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 acetate (EGBEA) 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.

EUROPEAN COMMISSION
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European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

2-butoxyethanol acetate (EGBEA)
Part I – environment

CAS No: 112-07-2 EINECS No: 203-933-3

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2-BUTOXYETHANOL ACETATE

Part II – Human Health

CAS-No.: 112-07-2

EINECS-No.: 203-933-3

SUMMARY RISK ASSESSMENT REPORT

FINAL APPROVED VERSION

Final report, 2008

France

Rapporteur for the risk assessment of 2-butoxyethanol acetate 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

Exposure and human health effect assessment and risk characterisation for workers

Institut National de recherche et Sécurité (INRS)

Département Risques Chimiques et Biologiques

30, rue Olivier Noyer

75680 Paris cedex 14

And

BERPC

60-62 rue d'Hauteville
75010 Paris
FRANCE

Exposure and Risk characterisation for consumers

Centre Anti-Poison de Lille
5, Avenue Oscar Lambret
59037 Lille cedex France
FRANCE

And

BERPC
60-62 rue d'Hauteville
75010 Paris
FRANCE

Exposure and Risk characterisation for Man via the environment

National Institute for Industrial Environment and Risks (INERIS)
Direction of chronic risks
Parc Technologique Alata
BP n°2
60550 Verneuil-en-Halatte
FRANCE

Date of Last Literature Search : **[2007]**
Review of report by MS Technical Experts finalised: **[05-2008]**
Final report: **[2008]**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 2-butoxyethanol acetate 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.

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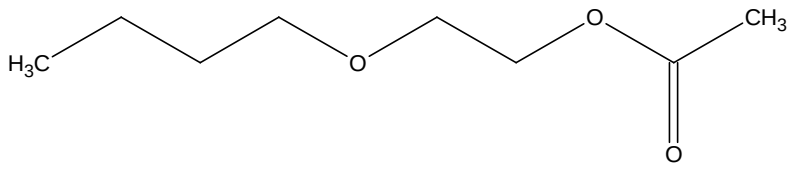
EINECS Number: 203-933-3

IUPAC Name: 2-butoxyethanol acetate

Molecular formula: $C_8H_{16}O_3$



Structural formula: CH3-CH2-CH2-CH2-O-CH2-CH2-O-C-O-CH3

Molecular weight: 160.21 $g.mol^{-1}$

Synonyms: The synonym (EGBEA) will be used in the present study to refer to the chemical Ethylene glycol butyl ether acetate. Other synonyms: Butyl Glycol Acetate (BGA); 2-butoxyethyl acetate; butoxyethyl acetate; butyl ethoxol acetate; Embkanol AEG; ethylene glycol monobutyl ether acetate; glycol monobutyl ether acetate.

Commercial trade names: Butyl Cellosolve Acetate; Butyl Ethoxyl Acetate; Butyl Oxitol Acetate; Eastman EB acetate.

Annex I entry: 607-038-00-2

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: the purities were all ≥ 98% w/w

Impurities: - ethylene di (acetate) (CAS 111-55-7) < 1% w/w

- water ~ 0.1% w/w

- 2-butoxyethanol (CAS 111-76-2) ~ 0.05% w/w

- the remaining 2% or less is very dependent on the purity of the alcohol source and will contain a mixture of alcohols and acetates of homologues. It is thought that there is not any one which is predominant.

Additives: It is reported that a food approved antioxidant has been added at a level below that requiring to be declared.

1.3 PHYSICO-CHEMICAL PROPERTIES

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

Table 1: Summary of physical and chemical properties of EGBEA

Property	Value
Physical state	Liquid
Melting point	-64°C
Boiling point	192.3°C
Relative density	0.94, at 20°C
Vapour pressure	0.4 hPa, at 20°C
Surface tension	30 mN/m, at 20°C
Water solubility	15000 mg/L, at 20°C
Partition coefficient n-octanol/water (log value)	1.51
Granulometry	n.a.
Flash point	75°C, closed cup
Autoflammability	340°C
Flammability	0.88 % (at 93°C) – 8.54 % (at 135°C) – volume
Explosive properties	Not explosive
Oxidising properties	No oxidising properties
Viscosity	1.8 mPa.s
Henry's constant	0.55 Pa.m^3/mol at 25°C
Conversion factors (101 kPa, 20°C)	1 ppm = 6.65 mg/m^3 1 mg/m^3 = 0.15 ppm

1.4 CLASSIFICATION

1.4.1 CLASSIFICATION

Human health effects (adopted classification)

Classification: Xn; R 21/22 (adopted during TC C&L of September 2007).

CLP: Acute Tox. 4*; H332, H312

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

General information on exposure

Humans may be exposed to EGBEA at workplace, via consumer products and indirectly via the environment. The highest potential exposure is likely to occur during occupational exposure.

Workers and consumers are primarily exposed via inhalation and dermal routes. EGBEA 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, dermal absorption may be predominant or may contribute significantly to overall exposure.

Exposure may occur during manufacture and during formulation and use of products. EGBEA is a solvent used in industrial activities or consumer applications. The main use is by far in paints or surface coatings (solvent-based or water-based), other minor uses are printing inks, detergents and cleaners, cosmetics and leather finishing agents

Occupational exposure

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

The worst-case estimates generated in this exposure assessment are considered to be feasible 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.

There are very limited data on measured levels of EGBEA in occupational settings particularly for dermal exposure. When available, they are presented in this section and compared with that predicted from the EASE (Estimation and Assessment of Substance Exposure) model.

EGBEA is not a wide spread solvent compared to 2-butoxyethanol (EGBE). Many of their physico-chemical properties are in the same order. In view of the similarity between these values and also between the specific uses of each substance, a read-across approach to the exposure data available on EGBE is proposed for EGBEA where few data are available on this substance.

Since no measured data are available to predict occupational dermal exposure to EGBEA, modelling and conclusions of the dermal exposure of EGBE will be used. Many of the references related to glycol ether derivatives stress the importance of dermal exposure, particularly during use of products. All sections on dermal exposure deal with liquid exposure.

Occupational exposure assessment will be carried out through three main categories of scenarios:

(a) the manufacture of EGBEA;

(b) the formulation of products containing EGBEA;

(c) the use of products containing EGBEA.

The third category focus 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 20 ppm in the EU.

Manufacture and use as intermediate

This scenario includes all activities concerning the production of EGBEA in the chemical industry. A few people are exposed during these activities. There are three sites producing EGBEA in the EU.

EGBEA is produced in closed systems under strict control. There is a potential for exposure during transfer to tankers or drums. Accidental exposure may occur when the process is breached or when spills occur. Exposure may also occur during sampling, maintenance and cleaning activities.

Inhalation exposure is based on measured reasonable worst-case data. For dermal exposure no data were available, so EASE is used.

Formulation of products containing EGBE

During the formulation of products containing EGBEA, 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.

While during preweighing and transfer to the mixing tank, workers are potentially exposed to pure EGBEA, 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.

For inhalation exposure, measurement data on EGBEA are used. These data are consistent with EASE estimates and with EGBE inhalation exposure data.

Since no measured data are available to predict occupational dermal exposure to EGBEA, modelling on EGBEA and conclusions of the dermal exposure of EGBE are used. Considering the read-across approach to the exposure results available on EGBE, a skin exposure of 2,000 mg/day is proposed for EGBEA and the scenario “formulation of products containing EGBEA”. This estimate is based on measured data from RISKOFDERM (DEGBE) and biomonitoring studies on EGBE.

Use of products containing EGBE

EGBEA is mainly used in paints and to a lesser extent in printing inks. Therefore the two following scenarios are considered as representative:

- use of paints

- use of printing inks

- Scenario 3-1 Painting/Surface coatings

Taking into account paint formulation industry data together with the information collected in European product registers, a maximum content of 20 % EGBEA in paints will be assumed in this assessment for industrial paints and 5 % for decorative paints.

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…

As for the scenario 2 "formulation of products containing EGBEA, dermal exposure", there are no available measured dermal data for EGBEA, so dermal exposure value for EGBE paint application is used.

- Scenario 3-2 Printing

EGBEA is a solvent in a range of specialist inks particularly silk-screen inks used by professional trades.

Recent data provided by one of the main producer of screen printing show that typical percentages range from 2 to 35 %. Typical maximum contents of 35 % EGBEA in silk-screen inks and 20 % in others is assumed in this assessment.

EGBEA measured data are available only for inhalation exposure. Dermal exposure for silk screening is based on EGBE data and as no data are available for general printing EASE model is used.

Summary of exposure data

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

Table 2: Summary of proposed reasonable worst case occupational exposures

Scenario	8-hour TWA inhalation mg/m^3 (ppm)	Remarks on 8-hour TWA inhalation	Dermal mg/day	Remarks on dermal exposure data
1 - Manufacture	0.48 (0.07)	Measured data	42	EASE
2 – Formulation	23 (3.45)	Measured data	2000	Analogous data
3 - Use of products				
3.1 Coating/Painting				
- Industrial:				
- spraying	13.3 (2.0)	Measured data	2000	Analogous data
- other work	13.3 (2.0)	Measured data	430	Analogous data
- Decorative	13.3 (2.0)	Measured data	117	Analogous data
3.2 Printing				
- silk screening	11 (1.65)	Measured data	23	Analogous data
- general printing	30 (4.5)	Measured data	168	EASE

Consumer exposure

Paint application is considered as the representative use for consumer exposure. It covers large concentration of EGBA (up to 20%) and it leads to manipulation of high quantity of product with direct contact. Consumers do not seem to be exposed to EGBEA through other products.

Exposure from uses

- Scenario Painting

As a worst case, it was considered the consumer apply paint containing 20% of EGBA during 6 hours.

No data about exposure of the consumer by paints being available. As all models give an overestimation of consumer exposures by inhalation comparing to professional exposure value, we have chosen to consider professional exposure value for consumer exposure assessment by inhalation. Dermal exposure value has been obtained by using EASE model.

It leads to an external exposure of 1.11 mg/kg/d by inhalation and an external exposure of 10.5 mg/kg/d by the dermal route.

For the risk characterisation, the internal doses are calculated to take into account the absorption rates.

Humans exposed via the environment

Generic exposure scenarios are used to estimate the releases from formulation, processing and private use of EGBEA, 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.

The highest indirect exposure is estimated for processing operations performed in unknown uses: $9.33.10^{-2}$ $mg.kg^{-1}.day^{-1}$. 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 $2.57.10^{-5}$ $mg.kg^{-1}.day^{-1}$.

4.1.2 EFFECTS ASSESSMENT

The molecule of 2-butoxyethanol acetate is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate. It can therefore be anticipated that EGBEA made systemically available will be metabolised in EGBE (2-butoxyethanol) and acetate. Based on the structural similarities between EGBE and EGBEA and the high likely metabolism of EGBEA to EGBE at least in the systemic circulation, it is reasonable to assume that a read-across from EGBE data to EGBEA could be conducted when no specific or valid data on systemic toxicity are available on EGBEA.

<u>Toxicokinetics, metabolism and distribution</u>

If extrapolation is needed from 2-butoxyethanol (EGBE), the following rule applies for oral and dermal exposures: 1 mg/kg EGBE will give 160/118 (1.356) mg/kg EGBEA (160 molecular weight of EGBEA and 118 molecular weight of EGBE). For inhalation exposures, the values in ppm are the same for EGBE and EGBEA.

According to *in vitro* data, EGBEA is rapidly hydrolysed in plasma in acetate and EGBE presumably by esterases. It can therefore, be anticipated that EGBEA made systemically available will be metabolised in EGBE and acetate. Based on the structural similarities between EGBE and EGBEA and the high likely metabolism of EGBEA to EGBE at least in the systemic circulation, it can be anticipated as a reasonable approach that EGBEA have absorption, distribution, metabolism and excretion properties close to EGBE considering that an extrapolation from EGBE to EGBEA can be conducted.

EGBE data:

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 use 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.

In the risk characterisation section, the following absorption rates for EGBEA will be used:

- 100% via oral route;

- 60% via inhalation route;

- 30 % of dermal penetration of liquid EGBEA and about 39 % of vapour EGBEA.

Acute toxicity

Although the studies are old and some have methodological deficiencies, data on EGBEA consistently show symptoms of haematotoxicity similar to those observed with EGBE at a low order of acute toxicity by inhalation. The existing classification Xn; R20 was removed. EGBEA shows by dermal route a LD_{50} of about 1,500 mg/kg bw with haemolysis and associated lesions as main toxicity symptoms and by oral route a LD_{50} around 940 mg/kg in rabbits, the most sensitive species. A classification Xn; R21/R22 is applied.

EGBE data:

A number of human case studies are available from attempted suicides with EGBE which suggest that the human LOAEL is in the region of 400 mg/kg bw. In the reported cases, patients

exhibited CNS depression and metabolic acidosis. Signs of haemolysis were seen in some cases but this finding was not systematic. As human data is preferred if exists, this LOAEL of 400 mg/kg bw corresponding to 542 mg/kg of EGBEA is used for risk characterisation.

Summary haematotoxicity

EGBE data:

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, 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

Only very slight irritation signs were observed in animals or in *in vitro* tests. According to EC classification criteria, EGBEA does not warrant classification for skin and eye irritation. Overall, considering that EGBEA is not a skin or eye irritant, it would therefore not be predicted to act as a respiratory tract irritant, and hence this endpoint is of no concern.

Sensitisation

In an adequate Buehler test, no signs of dermal sensitisation were seen. No classification is needed for this end point.

Repeated dose toxicity

Data available on EGBEA are rather old and of limited quality not performed according to guidelines. However, these studies show as main effect signs of haematotoxicity and associated lesions.

EGBE data:

Based on the structural similarities between EGBE and EGBEA and the high likely metabolism of EGBEA to EGBE at least in the systemic circulation, it is reasonable to assume that a read-across from EGBE data to EGBEA could be conducted when no specific or valid data are available on EGBEA. The assessment of the repeated dose toxicity of EGBEA could then be reinforced with the use of EGBE data.

Humans are far less sensitive than other species (except Guinea Pig) to the haemolytical properties of EGBE. 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. 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. For the risk characterisation, haemotoxicity will be the end point chosen. Since all key effects are induced by haemolysis in rodents, a NOAEL based on haemotoxicity will be used in the risk characterisation, keeping in mind the interspecies differences (human/rodents).

Overall, the most reliable inhalation data is the LOAEC of 31 ppm derived from a 6 month satellite group in a two-year study in rats conducted with EGBE. For oral route, a LOAEL of 69 and 82 mg/kg/day for male and female rats respectively was derived for EGBE (haemolytical effects) from a 13 week oral study in rats corresponding to a LOAEL of 94 and 111 mg/kg/day for male and female rats expressed in EGBEA. 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 with EGBE, which corresponds to a NOAEL of 203 mg/kg bw/d expressed in EGBEA.

Mutagenicity

Due to the rapid hydrolysis of EGBEA in EGBE and acetate in the systemic circulation and due to the chemical similarities between EGEA and EGBE, the mutagenicity properties of EGBEA could be assessed via a read-across from EGBE data.

EGBE data:

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 were 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.

For EGBEA, assessment of the mutagenic properties is based on EGBE data. Based on these information, genotoxicity does not present a concern for EGBEA. No classification for mutagenicity is needed.

Reproductive toxicity

No studies is available on EGBEA. The assessment of the reproductive toxicity of EGBEA could be assessed via a read-across from EGBE data.

EGBE data:

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 and to EGBEA as well 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 converted on a molar basis, to 976 mg/kg bw/d and will be used in the risk characterisation.

Carcinogenicity

For EGBEA, assessment of the carcinogenic properties is based on EGBE data.

EGBE data:

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 haematoxicity, 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. The same conclusion is drawn for EGBEA.

4.1.3 RISK CHARACTERISATION

The human population may be exposed to EGBEA at the workplace or from use of consumer products and indirectly via the environment. Based on the structural similarities between EGBE and EGBEA and the high likely metabolism of EGBEA to EGBE at least in the systemic circulation, it is reasonable to assume that a read-across from EGBE data to EGBEA could be conducted when no specific or valid data on systemic toxicity are available on EGBEA. From the EGBE data, it can be assumed that oral absorption is complete and that dermal absorption of liquid EGBEA can be assumed as 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, that humans is less sensitive to BAA than rats (or mice), the selection of an appropriate interspecies chemical safety assessment factor must take into account this lower sensitivity of humans. 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 EGBEA. 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, risk at the workplace are considered specifically for each toxicological endpoint. A summary table 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 EGBEA is given in Table 3. Conclusion (ii): no concern is drawn for all the end-points and the identified scenarios.

Table 3: Overview of the MOSs and conclusions with respect to occupational risk characterisation for EGBEA

		Acute toxicity		Sensitisation	Repeated dose toxicity Systemic			Mutagenicity	Carcinogenicity	Fertility		
		Inhalation	Dermal	*Dermal*	Inhalation	Dermal	Combined			Inhalation	Dermal	Combined
1 - Manufacture	**MOS**	8021	3011		1344	338	363			13942	5422	3904
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
2 - Formulation	**MOS**	167	63		28	7	7.7			302	113	82
	Concl.	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**	289	63		48	7	8.6			522	113	93
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
-other works	**MOS**	289	296		48	33	24.5			522	542	264
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.12 - decorative	**MOS**	289	1063		48	119	37.8			522	1952	406
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.2 Printing												
3.21 Silk screening	**MOS**	350	6023		59	4676	56.7			633	9760	610
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
3.22 General printing	**MOS**	128	753		21	84	18.5			232	1394	199
	Concl.	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

Paint application is considered as the representative use for consumer exposure. It covers large concentration of EGBA (up to 20%) and it leads to manipulation of high quantity of product with direct contact. Consumers do not seem to be exposed to EGBEA through other products. For repeated dose toxicity, two frequencies of use have been considered for paint application. First, a typical use of paint by consumers corresponds to 10 application per year. Then as a very worst case approach a daily use has been considered to make sure that this scenario covers all consumers' applications.

Conclusion (ii): no concern is drawn for all the end-points and identified scenarios (see Table 4 below).

Table 4 : Overview of the MOSs and conclusions with respect to consumer risk characterisation for EGBEA

		Acute toxicity			***Sensitisation***	**Repeated dose toxicity Systemic**			**Mutagenicity**	**Carcinogenicity**	**Fertility**		
		Inhalation	Dermal	Combined	*Dermal*	Inhalation	Dermal	Combined			Inhalation	Dermal	Combined
3 – Painting	**MOS**	815	172	127							1467.67	309.84	230
	Concl.	ii	ii	ii	ii				ii	ii	ii	ii	ii
3– Painting average over the year (10 events/year)	**MOS**					7166	705	585					
	Concl.				ii	ii	ii	ii	ii	ii			
3 – Painting daily use (365 events/year)	**MOS**					192	19	14.4					
	Concl.				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 no concern. Comparison of the total internal dose of 90.7 mg/kg (corresponding to the LOAEC of 31 ppm for repeated dose toxicity via inhalation route corrected with PbPk modelling to obtain human internal dose of 90.7 mg/kg/d for EGBEA with the highest estimated exposure at regional ($3.22.10^{-4}$ $mg.kg^{-1}.day^{-1}$for EGBE, $4.4.10^{-4}$ $mg.kg^{-1}.day^{-1}$for EGBEA) and local ($3.73.\ 10^{-2}$ $mg.kg^{-1}.day^{-1}$for EGBE, $5.1.10^{-2}$ $mg.kg^{-1}.day^{-1}$for EGBEA) levels leads to margins of safety of, respectively, $2.1.10^{5}$ and $1.8.10^{3}$ which do not lead to concern. **Conclusion (ii)** is drawn.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

EGBEA has a low vapour pressure and is moderately flammable (flash point is 75°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. 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.