European Union Risk Assessment Report

2-BUTOXYETHYL ACETATE

(EGBEA)

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

RISK ASSESSMENT

GENERAL NOTE

This document contains two different reports:

- **Volume 69 Part I Environment** (Publication: EUR 22475 EN) – pages 2-67
- **Part II Human Health** (Final approved version awaiting for publication) – pages 68-204

European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

Existing Substances

European Union Risk Assessment Report

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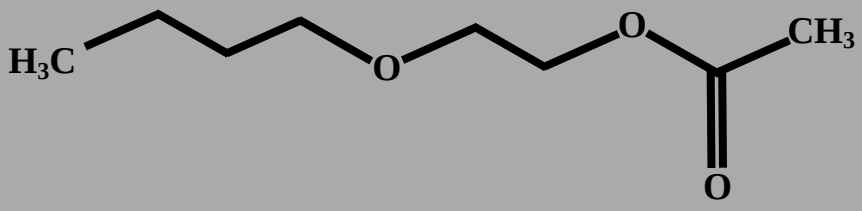
2-butoxyethanol acetate (EGBEA) Part I - environment



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European Union Risk Assessment Report
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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.

The Toxicology and Chemical Substances Unit (TCS), commonly known as the European Chemicals Bureau (ECB), provides scientific and technical input and know-how to the conception, development, implementation and monitoring of EU policies on dangerous chemicals including the co-ordination of EU Risk Assessments. The aim of the legislative activity of the ECB is to ensure a high level of protection for workers, consumers and the environment against dangerous chemicals and to ensure the efficient functioning of the internal market on chemicals under the current Community legislation. It plays a major role in the implementation of REACH through development of technical guidance for industry and new chemicals agency and tools for chemical dossier registration (IUCLID5). The TCS Unit ensures the development of methodologies and software tools to support a systematic and harmonised assessment of chemicals addressed in a number of European directives and regulation on chemicals. The research and support activities of the TCS are executed in close co-operation with the relevant authorities of the EU MS, Commission services (such as DG Environment and DG Enterprise), the chemical industry, the OECD and other international organisations.

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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RISK ASSESSMENT

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Part I – Environment

CAS No: 112-07-2

EINECS No: 203-933-3

RISK ASSESSMENT

Final Report, 2006

France

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**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

Roland Schenkel
Director General
DG Joint Research Centre

Mogens Peter Carl
Director General
DG Environment

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[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

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

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 EGBEA: 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.

CONTENTS

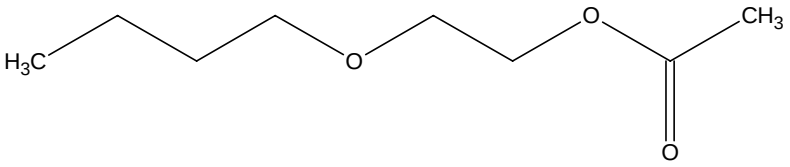
Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 112-07-2
EINECS Number: 203-933-3
IUPAC Name: 2-butoxyethanol acetate
Molecular formula: $C_8H_{16}O_3$
Structural formula: CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-O-C-O-CH_3



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

The median of all the different values above is 171°C. This value will be used for the risk evaluation.

1.3 PHYSICO-CHEMICAL PROPERTIES

Note: When the reliability of values do not enable a clear choice between one and another, a median value is chosen or calculated taking into consideration all figures supplied by the industry and only once the values found in handbooks or reports and which differ.

The physico-chemical properties are discussed below and summarised in **Table 1.1**.

Table 1.1 Summary of 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
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

1.3.1 Physical state

EGBEA is a colourless liquid with a sweet and fruity characteristic odour. An absolute perceptible limit in air of 0.1 ppm (50% recognition = 0.35 ppm and 100% recognition = 0.48 ppm) was referred to EGBEA (Verschueren, 2001).

1.3.2 Melting point

Values found in several handbooks range between -63 and -65°C with a majority at -64°C (Ullmann, 2000; Howard, 1989; Verschueren, 2001; Lewis, 1999; Kirk-Ohtmer, 1983). Technical product data sheets give similar values: (-63)-(-64)°C (Eastman, 2001; Merck, 1996) with only one giving a freezing point < -70°C (BP, 1998) measured at 100% concentration.

A melting point of –64°C is retained.

1.3.3 Boiling point

Boiling points are ranging between 184 and 198°C, at normal pressure conditions. 192.3°C is the most frequent boiling point reported in handbooks or studies (Staples et al., 1998; Lewis, 1999;

Howard, 1989). Rounded value of 192°C is also found in other books or works (Rowe and Wolf, 1982 cited in ECETOC, 1994; Kirk-Ohtmer, 1983).

A boiling point of 192.3°C is retained.

1.3.4 Relative density

At 20°C, the relative density of EGBEA is around 0.94: 0.94 (BP, 1998; Verschueren, 2001; Staples et al., 1998; BASF, 2002), 0.941 (Eastman, 2001), 0.9424 (Lewis, 1999; Kirk-Ohtmer, 1983), 0.945 (Ullmann, 2000).

The rounded value (0.94) will be used for the relative density of EGBEA.

1.3.5 Vapour pressure

Vapour pressures ranging from 0.31 to 0.77 hPa, at 20°C have been reported. Values come from handbooks: 0.4 hPa (Ullmann, 2000; Verschueren, 2001), studies: 0.4 hPa (Rowe and Wolf, 1982 cited in ECETOC, 1994), 0.5 hPa (Staples et al., 1998; Weber RC et al, 1981 cited in Howard, 1989), technical product data sheets: 0.32 hPa (BASF, 2002; Merck, 1996), 0.39 hPa (Eastman, 2001) or from calculation programs using QSAR: 0.716 hPa (US-EPA and Syracuse Research Corporation, 2001) and 0.77 hPa (ASTER, 1996). Another value, measured at 25°C, is also quoted: 0.39 hPa (Boatman and Knaak, 2000).

The median of all measured vapour pressures, 0.4 hPa at 20°C, is retained for the study (based on this value, a vapour pressure of 0.56 hPa has been recalculated at 25°C, by EUSES, EC, 2004).

1.3.6 Surface tension

Technical product data sheets give several values for a range of temperature: ~ 31.1 mN/m at 10°C (BP, 1998), ~ 30 mN/m (BP, 1998) and 30.3 mN/m (Eastman, 2001) at 20°C, ~ 27.79 mN/m at 30°C (BP, 1998).

The rounded value at 20°C (the temperature recommended in the OECD guideline No 115), 30 mN/m, is retained.

Surface active properties can be assumed for acetate esters of glycol ethers, and especially for ethylene glycol butyl ether acetate, because of its quite long carbon chain. The values reported in the literature for EGBEA tend to indicate that this substance is a surface active reagent even if no indication has been found about the concentration of the substance during the tests listed above. Indeed, OECD guideline n°115 suggests that surface tension measurements should be performed using a concentration of 1 g/L for soluble substances.

The fact that EGBEA shows surface active properties could thus lead to the disturbance of analytical method employed to measure some physico-chemical characteristics.

However, there is a difference between the surface activity of traditional surfactants and substances that can reduce the surface activity of solutions like EGBEA. What is observed during the surface tension measurements is the typical non ideal behaviour of a mixture of a water miscible solvent such as methanol and ethanol. The reason for the observed relationship between surface tension and concentration is the disruption of the hydrogen bonding of the water

causing non-linear behaviour of the surface tension against the concentration. In this case the substance is not migrating to the surface; it is not acting in the traditional surface active manner. Therefore it would not affect the measurements of the physical chemical properties. One should also notice that EGBEA do not form micelles. It is fully miscible with water and forms clear solutions.

Furthermore, considering the other properties of this substance (EGBEA is highly miscible in water, hydrosphere is the preferential target of EGBEA in the environment: > 90%, see Section 3.1.1.2), surface active properties of EGBEA will not be considered in this assessment.

1.3.7 Water solubility

In literature, water solubility for EGBEA is ranging from 10,000 mg/L to 15,000 mg/L. Most references give a solubility of 15,000 mg/L at 20°C (Boatman and Knaak, 2000; Verschueren, 2001; Rowe and Wolf, 1982 cited in ECETOC, 1994; Merck, 1996) and, at this temperature, a value of 13,400 mg/L is also mentioned (BASF, 2002). At 25°C, a solubility of 11,000 mg/L is quoted (Kirk-Ohtmer, 1983; Eastman, 2001) whereas other values are quoted without temperature mention: 10,000 mg/L (OSHA, 1990 cited in ATSDR, 1998) and 11,000 mg/L (Staples et al., 1998; Kirk-Ohtmer, 1983; HSDB, 1997 cited in ATSDR, 1998).

A solubility of EGBEA in water of 15,000 mg/L at 20°C will be chosen (based on this value, a solubility of 16,100 mg/L has been recalculated at 25°C, by EUSES, EC, 2004).

1.3.8 Partition coefficient n-octanol/water

Both measured and calculated octanol water partition coefficients are available. The different values found in literature are presented in **Table 1.2**.

Table 1.2 Range of octanol / water partition coefficients

Method	Value (log P_{ow})	References
Calculated	1.41	HSDB, 1997 cited in ATSDR, 1998
Measured	1.51	Verschueren, 2001 BASF AG, 1994
Calculated with SRC log K_{ow} interactive calculation program	1.57	Staples et al., 1998
Calculated (Assessment Tools for the Evaluation of Risk)	1.71	ASTER, 1996
Measured	1.79	Staples et al., 1998
Calculated (Assessment Tools for the Evaluation of Risk)	2.27	ASTER, 1996

The octanol/water partition coefficient test made by BASF was conducted in accordance with an international standard test guideline (OECD 107: partition coefficient (n-octanol/water), flask-shaking method). The value of 1.51 (mean of three measures) is retained for this study.

1.3.9 Granulometry

Not applicable: the substance is a liquid.

1.3.10 Flash point

Flash point values are ranging from 71°C to 88°C (closed cup): 71°C (National fire protection association, 1997; Eastman, 2001), 73.9°C (OSHA, 1990 cited in ATSDR, 1998), 75°C (Ullmann, 2000), 84°C (BP, 1998) and 88°C (Kirk-Ohtmer, 1983). Two other values were measured using the open cup method: 81°C (Eastman, 2001) and 87.8°C (OSHA, 1990 cited in ATSDR, 1998).

The median of the values measured using a closed cup is retained: 75°C.

1.3.11 Autoflammability

Four different autoflammability values are available: 300°C (BASF, 2002), 340°C (National fire protection association, 1997; OSHA, 1990 cited in ATSDR, 1998; Eastman, 2001), 355°C (Merck, 1996) and 375°C (Ullmann, 2000).

The more quoted value is retained: 340°C.

1.3.12 Flammability

It has been reported that EGBEA presents moderate fire hazard when exposed to heat, flame or oxidisers (HSDB, 1997 cited in ATSDR, 1998). Three flammability limits are quoted: 1-6.1% - volume (BASF, 2002), 1.7-8.4% - volume (Merck, 1996) and 0.88% (at 93°C) – 8.54% (at 135°C) – volume (Eastman, 2001; National fire protection association, 1997). The last one will be retained for this study.

1.3.13 Explosive properties

Not explosive.

1.3.14 Oxidising properties

No oxidising properties.

1.3.15 Viscosity

At 20°C, three different viscosity values for EGBEA are quoted: 1.75 mPa.s (BASF, 2002), 1.8 mPa.s (Ullmann, 2000; Merck, 1996; Eastman, 2001), ~ 1.94 mPa.s (BP, 19988), at 20°C. The value with the highest frequency (1.8 mPa.s) will be retained.

1.3.16 Henry's constant

Both measured and calculated Henry's constants are available. A measure, performed with a bag method for equilibrium partitioning gives a value of 0.13 $Pa.m^3/mol$, at 20°C whereas another measurement, performed with a batch stripping method, at 25°C, leads to a Henry's constant of 0.55 $Pa.m^3/mol$ (Kim et al., 2000).

Concerning calculated data, results are presented in **Table 1.3** below.

Table 1.3 Calculated Henry's law constant

Method	Value ($Pa.m^3$ / mole)	References
Group method, at 25°C	0.068	US EPA and Syracuse Research Corporation, 2001
SAR estimates developed by the US EPA – ECOSAR program	0.071	Staples et al., 1998
Calculated from experimental values for vapour pressure and water solubility	0.537	Syracuse Research Corporation cited in HSDB
Bond method, at 25°C	0.646	US EPA and Syracuse Research Corporation, 2001
Calculated from water solubility (11 g/L) and vapour pressure (0.5 hPa)	0.729	Howard, 1989
Assessment Tools for the Evaluation of Risk	1.581	ASTER, 1996
Calculated with the VP/Wsol ratio using EPI estimated values, at 25°C	3.696	US EPA and Syracuse Research Corporation, 2001

Henry's law constant can also be estimated from the ratio of the vapour pressure to the water solubility using selected values from this study: 56 Pa for vapour pressure and 16,100 mg/L for water solubility. Calculation gives a Henry's law constant of 0.557 $Pa.m^3/mol$.

At 25°C, several calculated Henry's law constants are matching quite well the measured value obtained at the same temperature. Moreover, direct measurement of the Henry's law constant is recommended for water miscible compounds (TGD - EC, 2003). A Henry's law constant of 0.55 $Pa.m^3/mol$ is retained.

1.4 CLASSIFICATION

1.4.1 Current classification

There is no classification for the environment.

1.4.2 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 (see **Table 2.1**). For comparison, the most recent data available show a total use of 2-butoxyethanol (EGBE) of about ~ 97 kt/year in Europe.

2.1.1 Production processes

No specific data on European production processes is available. Nevertheless, literature reports that EGBEA is predominantly produced by treatment of 2-butoxyethanol (EGBE) with acetic acid. Treatment with acetic acid anhydride or acetic acid chloride are secondary, minor methods of production (ATSDR, 1998).

2.1.2 Production capacity

The production or sales data for years 2001, 2002 and 2003 are given in **Table 2.1**.

Table 2.1 Overview of EGBEA production and sales in Europe for years 2001 to 2003 (data provided by CEFIC)

(in kilo tonnes)	2001	2002	2003	Figures retained
Production	13,600	12,000	13,400	12,800
Imports	0	2,500	2,800	1,700
Exports	700	1,800	2,400	1,700
Net into stock		200	500	
Sales in EU	12,900	12,500	13,300	12,800

The figures presented above show that both production and sales amounts for EGBEA are nearly constant since 2001. The last column of **Table 2.1** shows the figures retained for this assessment. They are mainly based on averages over the three years for which data are available.

A production volume of 12,800 tonnes/year will be retained for the risk assessment.

The production in the European Union is located at three different sites (see **Table 2.2**).

Table 2.2 EGBEA production sites in EU (larger than 1,000 tonnes/year)

Company	Location
BASF AG	Ludwigshaven, Germany
BP	Lavera, S. France
Sasol Gmbh*	Marl, Germany

* Huls sold to Condea in 1998 and then EGBEA business sold to Sasol in 2001

From **Table 2.2**, it appears that some production sites are located in the same area. Consequently the locations of both German sites have been checked so as to establish whether they could pertain to the same region (TGD definition EC, 2003). Distance between Marl and Ludwigshaven is 259 km. So, in the regional assessment, these sites will be considered in different regions.

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 by CEFIC (see **Table 2.3**). Values presented in this table are based both on volumes shown in **Table 2.1** and on the EGBE volumes declared by uses reported in 2001, 2002 and 2003. The analysis of this set of data has led to a choice which is meant to represent a reasonable worst case. The final data choice is based mainly on averages but some expert judgement has also been applied to adjust for market knowledge and the fact that supply via distributors adds some uncertainty to the numbers. This uncertainty explains the significant fluctuation in the annual tonnage figures for the smaller uses. Typically, 25-40% of volume goes via distributors. To reflect these uncertainties, the figures are quoted as rounded numbers. 2002 and 2003 data should be given more weight as some errors have possibly been made during assessment of the 2001 data in allocating users to the appropriate end use categories.

Moreover, some uses have been reported in the past that seem to no longer exist or errors could have occurred when allocating volumes to end-uses. For some of these uses, the percentage of total use has been set at 0 since no information has confirmed that EGBEA was still used in this sector. For some other uses figures reported does not seem to indicate a real annual use of the substance since stockpiles could be made during several years without using the product.

Table 2.3 Breakdown of EGBEA uses in Europe

End use	Stage of the life cycle	Industry category	Use category	2001¤	2002	2003	Retained proposal	
							Quantity used (Tonnes)	Percentage of total use
Paints and coatings (including estimation for indirect sales via distributors)	Formulation Processing Private use	14: paints, lacquers and varnishes industry	48: solvents	11,400	10,900	12,100	11,500	89.84
Metal cleaning	Formulation Processing	8 : metal extraction, refining and processing industry	9: cleaning, washing agents	0	500	350	400	3.13
Screen printing inks	Formulation Processing	12: pulp, paper and board industry	48: solvents	200	500	300	350	2.73
Detergents, cleaners	Formulation Private / public use	5: personal / domestic 6: public domain	9: cleaning, washing agents	100	300	300	250	1.95
Leather finishing	Processing	7: leather processing industry	48: solvents	100	300	0	150	1.17
Intermediates	Processing	3: chemicals used in synthesis	33: organic interme-diates	0	0	250	150	1.17
Total	-	-	-	12,900	12,500	13,300	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.

2.2.1 Paints and coatings

EGBEA is mostly used as a high-boiling, retarder solvent (i.e. an active, slow-evaporating solvent which ensures smooth film formation) for nitro-cellulose lacquers, acrylic enamels, epoxy resins and multicolour lacquers (ATSDR, 1998).

Sax and Lewis (1987) reported EGBEA concentrations of 1 to 5 percent in latex paints and lacquers where EGBEA is used as a slowly evaporating solvent and coalescing agent.

Use of EGBEA in products available to the consumers is believed to be very small. For example: in USA, 200 tonnes/year are used in consumer paints/solvents (typical concentration range 5-25%).

The French registered products database (SEPIA, personal communication), shows 17 preparations containing EGBEA in paints and varnishes categories. The EGBEA

concentrations are ranging from 0.5 to 20%. The calculation of a weighted average according to the number of preparations for each range of EGBEA concentrations gives a value of 5% which can be chosen to estimate the typical EGBEA concentration percentage in formulated products.

2.2.2 Other uses

Metal cleaning (3.13%): metal cleaning/degreasing is used in industries where the production process includes fabricating and/or assembling metal parts: mainly the automotive, aviation, appliance and railroad industries. During the various steps of the production process, metal parts must be cleaned of oils, fluxes and grease.

Screen printing inks (2.73%): Rastogi, 1991 has reported a range of EGBEA concentrations in printing inks between 0.7 and 24.8%. In this study, EGBEA was found in 3/29 samples. It has been found in printer's inks for screen printing on electric and electronic articles for example. It is also used in some ink and spot remover formulations. Nevertheless this application for EGBEA is believed to be a minor application.

Detergents, cleaners (1.95%): EGBEA is reported as having a minor use in detergents and cleaners. EGBE percentage in formulated products has been evaluated at 10% (OECD, 1996). Such a fraction could be used so as to estimate the amount of EGBEA in detergents for physical and chemical properties for EGBE and its acetate are quite similar.

Leather finishing (1.17%): EGBEA is quoted as being used in leather finishing operations, which is effectively a "coating" operation where a preparation is applied by air atomised spraying in a spray booth. Actual usage rates are quoted as up to 0.4 g/kg of dry finished leather, which, following the above assumptions, would lead to total GE consumption of up to 250 tonnes/year. There will in addition be wastage from over spray and emissions to water from the over spray control systems. However, since this is a coating operation, it is already covered by the existing painting scenario. Consequently, there will not be a separate risk characterisation for this use.

Intermediates (1.17%): EGBEA is also employed as an intermediate for other chemicals manufacture.

Cosmetics/Personal care: EGBEA has been reported as having a minor use in cosmetic products. However, recent data tend to indicate that this use has been abandoned.

EGBEA is also reported as a film-coalescing aid for polyvinyl acetate latex (ATSDR, 1998).

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

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 discusses the behaviour of EGBEA and its releases into the environment.

3.1.1 Environmental fate

3.1.1.1 Degradation in the environment

Hydrolysis

Hydrolysis is not a major process of ultimate degradation for EGBEA. ASTER, 1996 reported a value of more than 1,000 days for the abiotic degradation of EGBEA in water.

Photodegradation

According to its vapour pressure, EGBEA is expected to exist almost entirely in vapour phase in the atmosphere where reaction with photochemically produced hydroxyl radicals may be important.

Two different calculated values are available to express the photodegradation capacity of EGBEA. The first one was only found once: $1.8.10^{-11}$ cm^3/molecule.second (Atkinson, 1988) whereas a value of $2.1.10^{-11}$ cm^3/molecule.second can be found in several studies: Atkinson (1987), Meylan and Howard (1993) and Staples et al. (1998) who based their value on SAR estimates developed by the US EPA and Syracuse Research Corporation (cited in HSDB). The more quoted calculated value is retained for this assessment.

By relating K_{OH} to the OH-radical concentration in the atmosphere, a pseudo first order rate constant for degradation in air can be calculated: $Kdeg_{air}$ = 0.9 d^{-1}. This rate constant gives a half-life value of ~ 18.5 hours for EGBEA in air.

Biodegradation

Biodegradation test characteristics are presented in **Table 3.1**.

Table 3.1 Biodegradation test results for EGBEA

Test #	Type of test	Detection	Result	Day	Method	Conc. Of TS	Conc. Of inoculum	Reference	Validity
1	Inherent biodeg. Test	DOC	> 90%	6.5	OECD 302B	Unknown	1 g/L[a,2]	Zahn and Wellens, 1980	Valid with restrictions
2	Ready biodeg. test	DOC	0 26 97 96	1 3 7 14	ISO 7827	20 mg/L (DOC)	0.5 mL/L[b]	BASF, 1989d	Valid with restrictions
3	Ready biodeg. Test	O_2 uptake	3 31 56 72 83 88 (BOD/ ThOD)	1 5 10 15 20 28	OECD 301F	100 mg/L	Unknown[b,1]	BASF, 1989b	Valid with restrictions

a) Industrial STP
b) Activated sludge from a municipal sewage treatment plant
1) Non-adapted
2) Due to origin of inoculum, pre adaptation is possible

The inherent biodegradability of EGBEA is proved by the test #1 conducted by Zahn and Wellens, 1980. The OECD guideline n°302 B was used and a measured degradation rate of 12%/day was found with no lag phase. The inoculum, originating from an industrial STP, was introduced at a concentration of 1 g/L. It was mentioned that the inoculum had not been adapted but due to its origin, pre adaptation could be considered.

The two other tests (#2 and 3) assess the ready biodegradability of EGBEA. Test #2, performed by BASF, 1989d was conducted according to the norm ISO 7827 (equivalent to the OECD guideline 301 A). The test threshold was reached before the end of the test: EGBEA was degraded at 97% after seven days. We can also notice that the inoculum is constituted with activated sludge from a municipal STP.

In test #3, conducted according to the OECD guideline n°301 F by BASF, 1989b, biodegradation reached 10% after 2 days and, at the end of the ten-day window (day 12), biodegradation was above 70% (graphically). Aniline was used as control substance and, with this compound; biodegradation reaches 65% at day 14. The inoculum was reported to be non-adapted and coming from a domestic sewage.

To sum up and according to standard tests, EGBEA can be regarded as readily biodegradable.

As no result from biodegradation simulation tests in STP, surface freshwater, surface saltwater and soil is available, the degradation rates have to be estimated based on the "ready biodegradability" classification and the partition behaviour of EGBEA according to the method described in the Technical Guidance Document for risk assessment of new and existing chemicals (TGD - EC, 2003). Results of these estimations are presented in **Table 3.2**.

Table 3.2 Estimated biodegradation rate constants for EGBEA in WWTP, surface water, soil and sediment

Compartment/medium	Biodegradation rate	Half-life
Activated sludge (WWTP)	K_{STP} = 1 h^{-1}	0.7 hour
Surface freshwater	$K_{freshwater}$ = 4.7.10^{-2} d^{-1}	15 days
Marine water	$K_{marine\ water}$ = 1.4.10^{-2} d^{-1}	50 days
Soil*	K_{soil} = 2.3.10^{-2} d^{-1}	30 days
Marine and freshwater sediments **	K_{sed} = 2.3.10^{-3} d^{-1}	300 days

* Biodegradation rates in sediment and soil take account of adsorption to solid matter (K_{oc}=63.9 L/kg, see below)

** Biodegradation rate in sediment takes account of the aerobic fraction of this compartment (0.1)

3.1.1.2 Distribution

Volatilisation

Based on the measured Henry's law constant of 0.55 Pa.m^3/mol at 25°C (Kim et al., 2000), the air-water partitioning coefficient ($K_{air\text{-}water}$) can be calculated. $K_{air\text{-}water}$ of 2.32.10^{-4} indicates that volatilisation of EGBEA from surface water and moist soil is expected to be very low.

Adsorption/desorption

Using the log K_{ow} of 1.51 and according to the TGD (EC, 2003) (QSAR for soil and sediment sorption for non-hydrophobic chemicals) a K_{oc} of 63.9 L/kg can be estimated. The solid/water partition coefficients in each compartment can be calculated as supplied in TGD (EC, 2003) (see **Table 3.3**).

Table 3.3 Estimated solids / water partition coefficients

Water/Compartment	OC fraction in solid phase (F_{OCcomp})	Solids / water partition coefficients	Total compartment water partition coefficients
Soil / water	0.02	K_{p_soil} = 1.28 L/kg	$K_{soil\text{-}water}$ = 2.12 m^3/m^3
Sediment / water	0.05	K_{p_sed} = 3.20 L/kg	$K_{sed\text{-}water}$ = 2.40 m^3/m^3
Suspended matter / water	0.1	K_{p_susp} = 6.39 L/kg	$K_{susp\text{-}water}$ = 2.50 m^3/m^3

Distribution in the environment

The following theoretical distribution in the environment has been calculated using the multimedia fugacity model EQC (MacKay level I) and the physico-chemical properties given in Section 1.

Table 3.4 Calculated distribution of EGBEA in the different compartments of the environment

Compartment	% EGBEA
Air	7.85
Water	89.5
Soil	2.57
Sediment	0.06

Regarding these results, the hydrosphere is the preferential target of the substance in the environment.

Distribution in STPs

Based on physical chemical properties discussed in this study (log H = -0.26 and log K_{ow} = 1.51) as well as the biodegradation rate of 1 h^{-1} in STP, the elimination through biodegradation can be estimated with the model SIMPLETREAT in **Table 3.5**.

Table 3.5 Estimated distribution in a STP (SIMPLETREAT)

Designation	%
Air	$2.18.10^{-1}$
Water	12.5
Sludge	$5.98.10^{-1}$
% degraded	86.7
% removal	87.5

3.1.1.3 Accumulation

No experimental data on bioaccumulation is available. Therefore, BCF-values for fish and earthworm are estimated using the log Kow of 1.51. The estimated BCF-values amount to 3.8 and 6.5 for fish and worm, respectively. Two other calculated values are available: a BCF of 3 has been estimated using a measured water solubility of 15,000 mg/L (Lyman et al., 1990) and the other one was estimated at 13.5 using the following equation [log BCF = 0.76.log Kow - 0.23] which gives a log Kow of 1.79 (Staples et al., 1998).

In view of these BCF, EGBEA is expected to have a low bioaccumulation potential.

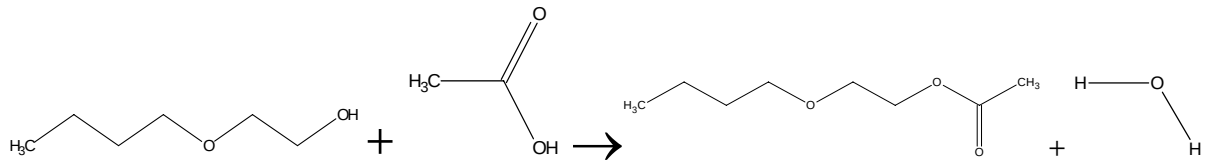
3.1.2 Environmental releases

The regional and continental releases include all relevant life cycle stages of EGBEA. For production, it is assumed that there is only one production site in the region. The exposure assessment is based on the EU Technical Guidance Documents (TGD - EC, 2003) applying the European Union System for the Evaluation of Substances, EUSES (EC, 2004).

3.1.2.1 Release from production

The general production process for EGBEA, reported by producers, consists in the reaction of EGBE with acetic acid in a closed system, continuously. During this reaction, a catalyst is used. After the reaction, the mixture is fractionated via distillation to recover unreacted material which is recycled for further reaction. Water formed during the reaction is removed.

Equation 3.1 EGBEA synthesis reaction



EGBE + *acetic acid* → *EGBEA* + *water*

Releases to water

Data of releases to water for EGBEA production sites in Europe (see **Table 2.2**) are presented in **Table 3.6** (Note: the site numbers in **Table 3.6** do not directly correspond to the order of companies in **Table 2.2**).

As there are only three EGBEA production sites in Europe, the regional production will not be set at 10% of total EGBEA production (TGD default) but at the maximum volume produced at one site. The amount remaining corresponds to the continental production. Fraction releases and number of days of emission are taken from Table A1.1 and Table B1.5 (TGD - EC, 2003; Chapter 3 – Appendix I), with Main Category equal to Ib (substances produced in a continuous production process) for EGBEA is produced in a continuous production process.

All EGBEA producers reported that releases to water enter a sewage treatment plant. During this step, 87.5% of EGBEA is expected to be removed by degradation and physico-chemical processes. When more precise data were available (EGBEA concentration in STP effluents) they were also used.

Relevant data for the calculation of Predicted Environmental Concentrations (PEC) in a STP and for the aquatic compartment are presented in **Table 3.6**. When such data was not available or as a comparison mean, the effluent concentration leaving the STP (PEC_{STP}) has been calculated according to **Equation 3.2**. This PEC_{STP} is divided by a dilution factor so as to obtain the local concentration in surface water - $Clocal_{aqua}$ (see **Equation 3.3**).

Equation 3.2 Calculation of PEC_{STP}

$$PEC_{STP} = \frac{Elocal_{water} \times F_{STPwater} \times 10^6}{EFFLUENT_{STP}}$$

$Elocal_{water}$	local release to waste water during episode	[kg/d]
$F_{STPwater}$	fraction of emission directed to water by STP	0.125
$EFFLUENT_{STP}$	effluent discharge rate of STP	[L/day]
PEC_{STP}	EGBEA concentration in the STP effluent	[mg/L]

Equation 3.3 Calculation of $Clocal_{aqua}$

$$Clocal_{aqua} = \frac{PEC_{STP}}{DILUTION}$$

PEC_{STP}	concentration of the substance in the STP effluent	[mg/L]
$Clocal_{aqua}$	local concentration in surface water during emission episode	[mg/L]
$DILUTION$	(STP flow + river flow) / STP flow	[-]

The calculation of $Clocal_{aqua}$ is reduced to this equation due to the low adsorption of EGBEA on suspended matter (Kp_{susp} = 6.39 L/kg).

Table 3.6 Aquatic emission data from production sites of EGBEA in EU

Site #	Emission in water
1	Reference years: 2001 and 2002 Release to wastewater treatment plant: 6.1* kg/day (35* days of production). Assuming 87.5% removal in STP: 0.8* kg/day in STP effluent. Before discharge to receiving waters, the effluent undergoes a dilution by a factor of 100 (mixing with seawater). Receiving water is the sea. The real dilution for marine environment is unknown. The releases of EGBEA occur in a region where the tidal influences are really low. For those particular seas it is proposed in the TGD to use only a dilution factor of 10 instead of 100. Flow of STP = 7,000* m3/day. PEC_{STP} = 0.11* mg/L and $Clocal_{aqua}$ = $1.1.10^{-4}$ mg/L
2	Reference year: 2000 Release to water: 25 kg/day in wastewater treatment plant influent. Emissions are calculated as a worst case using default release fractions, average STP flow and 365* days/year. Flow of STP = 5* m^3/s; 10^{th} percentile of receiving water flow = 734* m^3/s; dilution in receiving water = 150*. Assuming 87.5% removal in STP: PEC_{STP} = $7.2.10^{-3}$ mg/L ; $Clocal_{aqua}$ = $4.8.10^{-5}$ mg/L
3	Reference year: 2000 Release to water: 90 kg/day in STP influent. Emissions are calculated as a worst case using default release fractions and a production frequency of 150* days/year. Assuming 87.5% removal in STP: 11.3 kg/day in STP effluent. Flow of STP = 0.83* m^3/s; 10^{th} percentile of receiving water flow = 18.4* m^3/s; dilution in receiving water = 23*. PEC_{STP} = $1.6.10^{-2}$ mg/L ; $Clocal_{aqua}$ = $7.0.10^{-4}$ mg/L

* Original data provided by industry or calculated with original data. Other data is calculated using default TGD values

Releases to air

Release data to air for EGBEA production sites in EU are presented in **Table 3.7**.

Table 3.7 Atmospheric emissions of EGBEA from European producers

Site #	Release to air (kg/d)	$Clocal_{air,ann}$* (mg/m^3)	Year
1	0.15 (35 days/year)	$4.00.10^{-6}$	2002
2	5.10^{-3} (365 days/year)	$1.39.10^{-6}$	1996 (production and processing volumes in 2000 were however comparable)
3	0.13 (150 days/year)	$1.49.10^{-5}$	2000

* EGBEA concentration in air calculated at a 100 m distance from the source (annual average)

Releases to soil

Release data to soil for EGBEA production sites in EU are presented in **Table 3.8**.

Table 3.8 Emissions of EGBEA to soil, from European producers

Site #	Total deposition flux during emission episode ($\mu g.m^{-2}.j^{-1}$)	Annual average deposition flux ($\mu g.m^{-2}.j^{-1}$)	Local concentration in agricultural soil after 30 days (µg/kg ww)	Local concentration in agricultural soil after 180 days (µg/kg ww)	Local concentration in grassland after 180 days (µg/kg ww)
1	0.06	0.01	48.00	15.20	5.73
2*	0 (2.10^{-3})	0 (2.10^{-3})	0.24	0.24	0.45
3*	0.05	0.02	0 (3.10^{-3})	0 (3.10^{-3})	0 (5.10^{-3})

* At this production site STP sludge is incinerated

3.1.2.2 Release from formulation, processing and private use

Generic exposure scenarios are used to estimate the releases from formulation, processing and private use of EGBEA, as no actual data are available. The scenarios are based on the different use categories of EGBEA (see Section 2.2). An overview of the various environmental exposure scenarios for formulation, processing and private use of EGBEA is given in **Table 3.9**.

Table 3.9 Environmental exposure scenarios for formulation, processing and private uses of EGBEA

Scenario names	Designation	Life cycle step
Paints F, P, U ¤	Paints and coatings	Formulation / Processing / Private use
Metal F, P ¤	Metal cleaning	Formulation / Processing
Printing F, P ¤	Screen printing inks	Formulation / Processing
Detergents F, P, U	Detergents and cleaners	Formulation / Processing / Private use
Leather P*	Leather finishing	Processing
Intermediates P	Intermediates for chemical synthesis	Processing

¤ For these end uses there is a possibility that formulation and processing steps take place at a same site. These cases will be treated during risk characterisation.
* This use is already covered by the painting scenario (see Section 2.2.2)
P Processing
F Formulation
U Private use

3.1.2.2.1 Continental and regional releases

The total continental and regional EGBEA emissions from formulation, processing and private uses are given in **Table 3.10**.

Table 3.10 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

3.1.2.2.2 Local releases

Note: Tables used for local release estimates refer to TGD (EC, 2003), Tables A and B, Chapter 3, Appendix I; other tables, Chapter 7.

The local release estimates for formulation, processing and use of EGBEA are given in **Table** 3.11 to **Table 3.13**.

EGBEA used in paints

The EGBEA tonnage for use in consumer paints will be set at 5% of the total use in paints. This fraction is based on several statements which lead to believe that private use of paints containing EGBEA might be very low. In fact, in USA such a use represents approximately 200 tonnes/year. Moreover, a study performed by CEPE (personal communication) asserts that the main fraction of EGBEA is sold to industrial users. 100% (30 answers) of questioned paints and inks manufacturing industries report only sales to industrial users except for 2/9 answers reporting sales to private consumers. Due to the lack of information on the part of EGBEA used in consumer paints, the tonnage obtained with the fraction of 0.05 will not be deducted from the volume affected to the industrial use of paints.

EGBEA used for metal cleaning operations (processing)

During the various steps of the production process, metal parts must be cleaned of oils, fluxes and grease. Due to the properties of EGBEA it is used in cleaning formulations as a wetting agent and dispersant. Typical cleaning formulations contained 4% of this kind of additives (cleaning formulations used for soak). In the calculation of EGBEA daily releases to wastewater it will be assumed that the metal parts are cleaned by a static soak process. During this step of the process, losses of substance will be by drag out into the rinse bath and subsequent release of the rinse water. Here, as a worst case, the following assumptions are made:

- it is considered that there is no return of the rinse water ($F_{recycle} = 0$)
- the amount of solution removed from treatment bath due to drag out is taken as 0.3 L/m² as a worst case
- is a same way, the surface area of metal processed is taken at 40 m²/hr

If we consider a fraction of 0.04 for EGBEA in the cleaning formulation, then, using a typical concentration of the formulation in the cleaning bath of 25-75 g/L, the concentration of substance in the treatment bath (C_{bath}) can be calculated as follow: 4% · 75 g/L = 3 g/L.

Equation 3.4 is used to calculate the daily emission to wastewater:

Equation 3.4 Daily emission to wastewater during metal cleaning operations

$$Elocal_{process,water} = Q_{dragout,type} \cdot AREA_{process,metal} \cdot C_{bath} \cdot 10^{-3} \cdot (1 - F_{recycle}) \cdot T_{process}$$

$$Elocal_{process,water} = 0.3 \cdot 40 \cdot 3 \cdot 10^{-3} \cdot (1 - 0) \cdot 22 = 0.792 kg / d$$

$Elocal_{process,water}$	emission from process to water per day	[kg/d]
$Q_{dragout,type}$	amount of solution removed from treatment bath per unit area	[0.3 L/m²]
$AREA_{process,metal}$	surface area of metal processed per hour	[40 m²/hr]
C_{bath}	concentration of substance in treatment bath	[3 g/L]
10^{-3}	conversion factor for g to kg	[kg/g]
$F_{recycle}$	fraction of drag out returned to treatment bath	[0]
$T_{process}$	number of hours worked per day	[22, worst case]

In addition, it will be considered that the cleaning bath is disposed of every 4-8 weeks. Assuming a bath capacity of 1,000 L, the amount of substance released will be 3 g/L · 1,000 L = 3 kg – source OECD, 2004. This release will be considered an intermittent emission.

Results are shown in **Table 3.11** to **Table 3.13**.

Table 3.11 Local releases of EGBEA

Scenario	Paints F	Paints P	Paints U	Metal F	Metal P
Main category	Multi-purpose equipment	Non-dispersive use	Wide dispersive use	Multi-purpose equipment	Non-dispersive use
Total fraction and connected tonnage	0.898/ 11,500 tonnes	0.898/ 11,500 tonnes	0.043/550 tonnes	0.031/400 tonnes	0.031/400 tonnes
Regional tonnage	1,150 tonnes	1,150 tonnes	55 tonnes	40 tonnes	40 tonnes
Typical max. % of EGBEA	5	5	25	4	4
Number of days/ Fraction of main source	(Table B2.10) 300 / 0.4	(Table B3.13) 300 / 0.05	(Table B4.4 only for waste water) 150 / 0.002	(Table B2.4) 150 / 0.75	(Table B3.6) 150 / 0.8
Release estimates (fraction) - air - waste water - soil	Specific scenario 0.00643* 0.00003** No direct release to industrial soil	(Table A3.15 solvent based) 0.9*** 0.02 0.001	(Table A4.5 water based) 0.8 0.15 0.01	(Table A2.1) 0.005 0.02 0.0001	(Table A3.7) 0.25 Specific scenario (see Section 3.1.2.2.2) 0.05

Table 3.11 continued overleaf

Table 3.11 continued Local releases of EGBEA

Scenario	Paints F	Paints P	Paints U	Metal F	Metal P
Amount released (kg/day) - air - waste water - soil	9.9 0.05 -	172.5 3.8 0.2	- 0.1 -	1 4 0.02	53.3 0.8 (3 kg – intermittent release) 10.7

* Worst case for high boiling point substances, issued from Environment Agency, 2003, emissions to air from the manufacture of organic solvent-borne coatings, p. 39.

** Issued from Environment Agency, 2003, emissions to wastewater from the manufacture of organic solvent-borne coatings, p. 41.

*** This emission fraction should be considered a really worst case. Indeed, most of paint processing plants are now equipped with air treatment systems, lowering substance emissions to the atmosphere (Environment Agency, 2003).

Table 3.12 Local releases of EGBEA (continued)

Scenario	Printing F	Printing P	Detergents F	Detergents P	Detergents U
Main category	Multi-purpose equipment	Non-dispersive use	Multi-purpose equipment	Non-dispersive use	Wide dispersive use
Total fraction and connected tonnage	0.027 / 350 tonnes	0.027 / 350 tonnes	0.020 / 250 tonnes	0.020 / 250 tonnes	0.020 / 250 tonnes
Regional tonnage	35 tonnes	35 tonnes	25 tonnes	25 tonnes	25 tonnes
Typical max. % of EGBEA	25	25	10	10	10
Number of days / Fraction of main source	(Table B2.1) 300 / 0.8	(Table B3.10 – large companies) 300 / 0.333	(Table B2.1) 300 / 1	(Table B3.3 – only for waste water) 200 / 0.002	(Table B4.1 – only for waste water) 365 / 0.002
Release estimates (fraction) - air - waste water - soil	(Table A2.1) 0.005 0.02 0.0001	(Table A3.12 – for printing and allied process) 0.05 0.005 0.0015	(Table A2#) 0.00002 0.0009 0.0032	(Table A3.5) 0.0025 0.9 0.05	(Table A4.1) 0 0.99 0.01
Amount released (kg/d) - air - waste water - soil	0.5 1.9 0 (9.10^{-3})	1.9 0.2 0.1	0 (2.10^{-3}) 0.1 0.3	- 0.2 -	- 0.1 -

Table 3.13 Local releases of EGBEA (continued)

Scenario	Leather P	Intermediates P
Main category	Non-dispersive use	Dedicated equipment
Total fraction and connected tonnage	0.0012 / 150 tonnes	0.012 / 150 tonnes
Regional tonnage	15 tonnes	15 tonnes
Typical max. % of EGBEA	5	100 (default value)
Number of days / Fraction of main source	(Table B3.4 except for waste water release) 180 / 0.6	(Table B3.2) 10 / 0.65
Release estimates (fraction) - air - waste water - soil	This use is already covered by the painting scenario (see Section 2.2.2)	(Table A3.3) 0.00001 0.02 0.0001
Amount released (kg/d) - air - waste water - soil		0 (1.10^{-2}) 19.5 0.1

3.1.3 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 (EC, 2003) are used. **Table 3.14** shows the calculated continental and regional PECs for air, water and soil using EUSES (EC, 2004).

Table 3.14 Regional PECs in air, water and soil (calculations made by EUSES – SIMPLEBOX model)

Compartment	PEC continental	PEC regional
Air	$3.40.10^{-6}$ mg/m^3	$3.31.10^{-5}$ mg/m^3
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)

3.1.4 Local predicted environmental concentrations (PEC_{local})

3.1.4.1 Aquatic compartment

3.1.4.1.1 PEC_{local} for production

PEC_{STP}

At production level, the local Predicted Environmental Concentration for micro-organisms in STP ranges from 7.2 to 110 µg/L.

PEC_{aqua}

Emissions at production result in a PEC for surface water ranging from 0.14 to 1 µg/L (including the PEC regional for the aquatic compartment). The PEC_{aqua} for the different production sites are presented in **Table 3.15**.

Table 3.15 Local PEC in water at production

Production sites	#1 ($PEClocal_{marine}$)	#2	#3
$PEClocal_{aqua}$ (µg/L)	0.14	0.35	1.00

3.1.4.1.2 Calculation of PEC_{local} for formulation, processing and private use

Concentrations of EGBEA in water for formulation, processing and private use in the EU are estimated with a generic scenario which was carried out based on default values (TGD - EC, 2003) because no site specific data were available.

It is assumed that the amounts released to water will enter a sewage treatment plant. During sewage treatment, 87.5% of EGBEA is expected to be removed (see **Table 3.5**). The default flow rate of the treatment plant is 2,000 m^3/day.

The effluent concentration leaving the STP (Predicted Environmental Concentration in a STP or PEC_{STP}) is calculated according to **Equation 3.2**. This PEC_{STP} is divided by a dilution factor (10: default value) to obtain the local PEC in surface water (see **Equation 3.3**). The daily amounts released for the generic scenarios are the basis for the calculation of the PECs. **Table** 3.16 gives the PECs for the aquatic compartment. $PECs_{seawater}$ have been calculated with EUSES 2.0 (EC, 2004).

Table 3.16 Local PEC_{STP} and PEC_{aqua} for EGBEA

Scenario	Daily release to waste water (kg/day)	PEC_{STP} (µg/L)	Local PEC_{aqua} (µg/L)	Total local PEC_{aqua}* (µg/L)	Total local $PEC_{seawater}$¤ (µg/L)
Paints F	0.05	2.9	0.3	0.6	0.26
Paints P	3.8	238	23.8	24.1	19.1
Paints U	0.1	6.9	0.7	1.0	0.6

Table 3.16 continued overleaf

Table 3.16 continued Local PEC_{STP} and PEC_{aqua} for EGBEA

Scenario	Daily release to waste water (kg/day)	PEC_{STP} (µg/L)	Local PEC_{aqua} (µg/L)	Total local PEC_{aqua}* (µg/L)	Total local $PEC_{seawater}$¤ (µg/L)
Metal F	4	251	25.1	25.4	20.1
Metal P	0.8	50	5.0	5.3	4.0
Metal P (intermittent release)	(3 kg/event)	1,500	18.8	19.1	15.0
Printing F	1.9	117	11.7	12.0	9.4
Printing P	0.2	11.8	1.2	1.5	1.0
Detergents F	0.1	4.7	0.5	0.8	0.4
Detergents P	0.2	13.9	1.4	1.7	1.1
Detergents U	0.1	8.4	0.8	1.1	0.7
Leather P	This use is already covered by the painting scenario (see Section 2.2.2)				
Intermediates P**	19.5	250	6.3	6.6	20.0

* Total local PEC_{aqua} = Local PEC_{aqua} + regional PEC_{aqua}
¤ Total local $PEC_{seawater}$ = Local $PEC_{seawater}$ + regional $PEC_{seawater}$
** Dilution factor = 40 and $EFFLUENT_{STP}$ = 10,000 m^3/day (see scenario for IC3 chemicals used in synthesis)
P Processing
F Formulation
U Private use

3.1.4.2 Terrestrial compartment

Different PECs can be determined to assess the exposure level in terrestrial compartment. The local PEC in soil is calculated according to the following equation:

Equation 3.5 Calculation of $PEClocal_{soil}$

$$PEClocal_{soil} = Clocal_{soil} + PECregional_{natural\_soil}$$

3.1.4.2.1 PEC_{local} for production

The different PEC_{local} in soil at production level are presented in **Table 3.17**.

Table 3.17 $PEClocal_{soil}$ at production and *in situ* processing (according to EUSES)

Site #	Local PEC in agricultural soil averaged over 30 days (µg/kg ww)	Local PEC in agricultural soil averaged over 180 days (µg/kg ww)	Local PEC in grassland averaged over 180 days (µg/kg ww)
1	48.10	15.30	5.84
2*	0.11	0.11	0.11
3*	0.11	0.11	0.11

* At this production site STP sludge is incinerated

3.1.4.2.2 Calculation of PEC_{local} for formulation, processing and private use

The EUSES models (EC, 2004) take into account both the application of STP sludge on agricultural soil and deposition from air for the calculation of EGBEA concentrations in the terrestrial compartment. **Table 3.198** gives the terrestrial PECs at local scale for the various generic scenarios.

Table 3.18 Local PEC_{soil} for EGBEA (according to EUSES)

Scenario	PECsoil - average concentration in agricultural soil over 30 days (µg/kg ww)	PECsoil - average concentration in agricultural soil over 180 days (µg/kg ww)	PECsoil - average concentration in grassland over 180 days (µg/kg ww)
Paints F	1.0	0.7	1.0
Paints P	37.0	16.4	16.5
Paints U	1.1	0.5	0.3
Metal F	31.8	10.2	4.0
Metal P	7.6	3.3	3.0
Printing F	14.9	4.9	2.0
Printing P	1.8	0.8	0.6
Detergents F	0.8	0.4	0.3
Detergents P	2.0	0.8	0.5
Detergents U	1.3	0.6	0.4
Leather P	This use is already covered by the painting scenario (see Section 2.2.2)		
Intermediates P	31.7	10.2	4.0

- $PECregional_{natural\_soil}$ = 0.24 µg/kg (ww)

P Processing
F Formulation
U Private use

3.1.4.3 Atmosphere

3.1.4.3.1 PEC_{local} for production

Emissions of EGBEA in air at production result in an average annual concentration in air ($Clocal_{air,ann}$) of $1.49.10^{-5}$ mg/m^3 in the worst case (site specific information for site #3). This results in a $PEClocal_{air,ann}$[4] of $4.92.10^{-5}$ mg/m^3.

3.1.4.3.2 Calculation of PEC_{local} for formulation, processing and private use

The calculated annual average EGBEA concentrations in air are presented in **Table 3.19** for the different use patterns.

[4] $PEClocal_{air,ann} = Clocal_{air,ann} + PECregional_{air}$

Table 3.19 Local PEC_{air} for EGBEA

Scenario	Concentration during emission ($\mu g/m^3$)	$C_{local\_air,ann}$ 100m from source ($\mu g/m^3$)	Annual deposition ($\mu g.m^{-2}.d^{-1}$)	$PEC_{local\_air,ann}$* ($\mu g/m^3$)
Paints F	2.74	2.25	3.24	2.29
Paints P	47.50	39.10	56.20	39.10
Paints U	$7.14.10^{-5}$	$2.93.10^{-5}$	$4.22.10^{-5}$	0.03
Metal F	0.28	0.11	0.17	0.15
Metal P	14.80	6.09	8.76	6.12
Printing F	0.13	0.11	0.16	0.14
Printing P	0.53	0.43	0.62	0.47
Detergents F	$4.63.10^{-4}$	$3.80.10^{-4}$	$6.05.10^{-4}$	0.03
Detergents P	$1.73.10^{-4}$	$9.47.10^{-5}$	$2.51.10^{-4}$	0.03
Detergents U	$8.74.10^{-5}$	$8.74.10^{-5}$	$1.26.10^{-4}$	0.03
Leather P	This use is already covered by the painting scenario (see Section 2.2.2)			
Intermediates P	0.01	$3.54.10^{-4}$	$6.19.10^{-4}$	0.03

* $PEC_{local\_air,ann} = C_{local\_air,ann}$ + regional PEC_{air}
P Processing
F Formulation
U Private use

3.1.4.4 Secondary poisoning

The bioconcentration factor for fish is very low, so it is not expected that there is a significant exposure for humans or predators via the local environment. Moreover, as EGBEA is not classified as Very Toxic (T+), Toxic (T) or Harmful (Xn and R48), it is assumed that there is a low potential for the substance to cause toxic effects if accumulated in higher organisms.

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

Studies are classified as valid if they fully describe the test material used, the test organism, the test method and conditions and if the endpoint concentration is based upon measured levels. Where only some of these criteria are described the tests may be used with care or considered not valid. Moreover for some studies or results, some data are lacking i.e. the original paper is not available but only a citation.

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Fish

Acute toxicity

EGBEA short term toxicity studies for fish are summarised in **Table 3.20**.

Table 3.20 Short term fish toxicity data for EGBEA

Test #	Species	Duration	Endpoint	Result (mg/L)	Method	References	Validity
1	*Oncorhynchus mykiss*	96 hours	LC_{50}	20-40*	OECD n°203	DeVillers et al., 2002	Valid
2	*Leuciscus idus*	48 hours	LC_{50}	80	DIN 38412 part. 15	Huels, 1994	Lack of data

* It was impossible to calculate an accurate LC50 value because the mortality rate changed from 0% to 100% in two successive concentrations

Test #1 was performed by DeVillers et al., 2002 on the fish species *Oncorhyncus mykiss* to determine the acute toxicity of EGBEA. The OECD guideline No 203 "Fish, acute toxicity test" has been followed. A LC_{50} can be obtained from the two successive concentrations which caused 0% (20 mg/L) and 100% (40 mg/L) mortality by calculating the geometrical mean: 28.3 mg/L. Groups of seven young fish were disposed in 15L of reconstituted water and exposed to a serial dilution of eight concentrations of the test substance and controls (in duplicate). Other test conditions were as follow: pH = 8 +/- 0.3, water hardness = 250 +/- 25 mg/L $CaCO_3$, T = 16 +/- 1°C with a 12-hour light/dark photo period. The number of dead animals was registered after 24, 48, 72 and 96 hours. We can also notice that $K_2Cr_2O_7$ was used as the toxic reference chemical. Moreover, chemical analyses were made to verify that real concentrations corresponded with the nominal concentrations.

The test report for test #2 performed by Huels, 1994 is not available. The data showed in **Table** 3.20 are only quoted.

3.2.1.2 Aquatic invertebrates

Acute toxicity

Short term toxicity tests for EGBEA are presented in **Table 3.21**.

Table 3.21 Short term invertebrate toxicity data for EGBEA

Test #	Species	Duration	Endpoint	Result (mg/L)	Method	References	Validity
1	*Daphnia magna*	24 hours	EC_0 EC_{50} EC_{100}	58 145 320	DIN 38412/11	BASF, 1989a	Valid with restrictions
		48 hours	EC_0 EC_{50} EC_{100}	10 37 320			
2	*Daphnia magna*	48 hours	EC_{50}	67.5	ISO 6341 15	DeVillers et al., 2002	Valid
3	*Daphnia magna*	24 hours	EC_{50}	81.9	DIN 38412/11	Huels	Lack of data

BASF, 1989a has tested the toxicity of EGBEA on Daphnia magna according to the norm DIN 38412/11 – test #1. Test conditions were as follow: pH between 5.8 and 8.1 and O_2 between 2.9 and 8.1 mg/L, T = 21°C, four replicates were performed for each concentration (0, 10, 18, 32, 58, 100, 180, 320 mg/L). Three different endpoints were calculated after 24 and 48 hours: EC_0, EC_{50} and EC_{100}. After 48h, an EC_0 of 10 mg/L and an EC_{50} of 37 mg/L (95% confidence interval = 29-48 mg/L) were obtained.

Test #2 has been conducted by DeVillers et al. (2002) according to the norm ISO 6341 15: "Water quality – determination of the inhibition of the mobility of Daphnia magna Straus". During this assay groups of neonates were exposed in darkness to a serial dilution of EGBEA. Four replicates of five animals were used for each concentration. Other test conditions included a pH of 7.8 +/- 0.2, a water hardness of 250 +/- 20 mg/L ($CaCO_3$) and a temperature of 20+/- 2°C. $K_2Cr_2O_7$ has been used as the toxic material of reference. A 48-hour EC_{50} of 67.5 mg/L was calculated by probit analysis. Chemical analyses were made to verify that the actual concentrations corresponded with the nominal ones.

Test #3, performed by Huels on Daphnia magna gave a 24-hour EC_{50} of 81.9 mg/L. The assay was conducted according to the norm DIN 38412/11. As the test report is not available, it should be considered as invalid.

Long-term toxicity

Chronic toxicity tests for EGBEA are presented in **Table 3.22**.

Table 3.22 Long term invertebrate toxicity data for EGBEA

Test #	Species	Duration	Endpoint	Result (mg/L)	Method	References	Validity
1	*Brachionus calyciflorus*	48 hours	EC_{10} EC_{20} EC_{50}	6.9 13.7 303	AFNOR NF T 90-377	DeVillers et al., 2002	Not useable for PNEC derivation
2	*Ceriodaphnia dubia*	7 days	NOEC EC_{10} EC_{20}	16.4 30.4 30.7	Draft AFNOR NF T 90-376	DeVillers et al., 2003	Valid

The chronic toxicity of EGBEA on the rotifer *Brachionus calyciflorus* has been determined by DeVillers et al. (2002) according to the French norm AFNOR NF T 90-377 – test #1. Cyst hatching was initiated in moderately hard water about 20 hours before the beginning of the test (at 25°C under a light intensity of 3,000 lux.) pH was adjusted to 7.5. After 18 hours of incubation cysts were regularly checked to ensure the removal of test organisms within two hours of hatching. The assay was performed in a 48-well microplate (five concentrations plus

one control with eight replicates). Test media consisted in synthetic fresh water solution with a suspension of the green alga *Chlorella vulgaris* as food source. One rotifer was disposed per well (newly hatched rotifer) and the incubation occurred at 25°C in darkness, in a covered microplate. After 48 hours, the total number of rotifers per well was counted and EC_{10}, EC_{20} and EC_{50} were determined by non-linear regression using a log logistic model. The respective confidence intervals for these endpoints were as follow: EC_{10} = 5.4-23.2 mg/L, EC_{20} = 9.9-16.4 mg/L and EC_{50} = 229-343 mg/L. No analytical monitoring was performed during the test.

Several points can be highlighted so as to assess the validity of this test performed on *Brachionus calyciflorus* and showing the highest sensitivity. The pros and cons for the validation of the test are compiled in **Table 3.23**.

Table 3.23 Pros and cons for the validation of the test performed with *Brachionus calyciflorus*

Issue	Pros	Cons
Analytical monitoring	The test compound is considered stable in similar testing conditions, during 48 hours. Under static conditions, the monitoring of test concentrations during test #2 for invertebrates (DeVillers et al., 2002) has revealed that measured and nominal concentrations were comparable, after 48 hours. In order to prevent evaporation of the solvent or the test substance during the test (EGBE evaporates more slowly than water), the microplate was covered. Indeed, the French norm recommends that the incubation is carried out in a water saturated atmosphere in order to avoid losses of test solution by evaporation; for example, the microplate can be arranged in a closed dish at the bottom of which a film of water has been previously deposited. Furthermore, an interlaboratory test has been successfully performed with copper sulphate and no evaporation problem has been encountered.	No analytical monitoring has been performed during the test. Consequently, neither a loss of test substance nor a loss of solvent (water), during the test duration, could have been followed.
Concentration / effect relationship	Glycol ethers often show non-conventional concentration/effect relationships. Such non-conventional curves have already been reported for *Xenopus* exposed to 2-methoxyethanol (Daston et al., 1991) or for *Hydra attenuata* exposed to EGBE (Bowden et al., 1995). DeVillers et al., 2002b has also reported the same difficulty in finding clear relationships between the tested concentrations and the endpoints studied for their tests with EGME/EGMA performed on algae, rotifers, molluscs, daphnids and fish (some of these tests where repeated two or more times so as to ensure that they reached their respective conditions of acceptance). The authors also report that similar conclusions can be drawn from an analysis of published papers in which the ranges of tested concentrations of EGME are given. These tests were performed with *Pimephales promelas* and *Drosophila melanogaster* (Daston et al., 1991), *D. melanogaster* again in Lynch and Toraason, 1996.	The test results show a non-conventional concentration/effect relationship (a factor of 44 can be calculated between EC50 and EC10). The studies from Daston et al. (1991) and Bowden et al. (1995) also show a conventional response for methoxyethanol with *Hydra* and, whilst the EGBE response is flat, it is still of conventional shape, which is not the case with the *Brachionus*. Even if there are indications that the non conventional dose-response curves may be a general reaction to glycol ethers, no explanation has been found to this phenomenon.

Table 3.23 continued overleaf

Table 3.23 continued Pros and cons for the validation of the test performed with *Brachionus calyciflorus*

Issue	Pros	Cons
Normalisation	The test has been carried out following a French norm (NF T 90-377). An ISO norm is also in preparation.	The methodology used for the test with rotifers is not as well normalised as the one for standard tests usually used for effect assessments of chemicals.
Higher sensitivity		For EGBEA, the *Brachionus* test shows the highest sensitivity among all species tested. A ratio of 4.4 can be calculated between the ECs10 for *Ceriodaphnia dubia* and *Brachionus* indicating a greater sensitivity of *Brachionus* compared to *Ceriodaphnia dubia*. This is not in accordance with the trend generally observed when sensitivities of both species are compared, giving a ration of 2 between *Brachionus* and *Daphnia* indicating that *Daphnia* would be twice as sensitive as *Brachionus* (RIVM, 2004).
Oxygenation of the test media	*Daphnia* 48-hour test can be taken for comparison with the 48-hour *Brachionus* test. It can be expected that a sufficient DO level was maintained during the rotifer test too. Although test solution volumes are lower in the rotifer test, both tests show similar conditions and the same duration	Since no aeration took place and the test wells were covered during the test phase, it should have been reported how appropriate oxygen concentration was maintained during the whole test phase. This was not done. In fact, because EGBEA is readily biodegradable, oxygen depletion is possible, which would mean that the low NOECs of the *Brachionus calyciflorus* studies were not caused by the toxic properties of EGBEA. This may not occur to a significant degree over the timescale of the study but, with no oxygen data, it is not possible to be certain.

Considering all the elements from **Table 3.23** no clear reason can be found to fully invalidate the test. However, considering all the elements highlighted that have triggered off some concerns for the validation of this test, this study will be excluded from the PNEC derivation. This decision is also supported by the availability of standard toxicity test results such as the one performed with *Ceriodaphnia dubia* (test #2).

DeVillers et al. (2003) – test #2 - have tested the toxicity of EGBEA on *Ceriodaphnia dubia* according to the draft of the method AFNOR NF T90-376 (equivalent to the OECD guideline No 211). An EC_{10} of 30.4 mg/L has been determined after seven days. One daphnid was disposed per container, in ten replicates. The parental mortality and the number of offspring per living parent were used as endpoints. Other test conditions are shown here: eight concentrations plus control were tested at a temperature of 23 +/- 1°C and pH = 8-9, DO = 8.1-8.3 mg/L and water hardness was 200 +/- 40 mg/L ($CaCO_3$). An analytical monitoring was performed but results were expressed based on nominal concentrations. The 95% confidence interval for the EC_{10} ranged between 9.89 and 37.73 mg/L. A NOEC (16.4 mg/L) and an EC_{20} (30.7 mg/L) have also been calculated in another report (INERIS, 2001) but methods used for calculation tend to give a preference to the EC_{10} value.

3.2.1.3 Algae

Toxicity tests for EGBEA are summarised in **Table 3.24**.

Table 3.24 Algae toxicity data for EGBEA

Test #	Species	Duration	Endpoint	Result (mg/L)	Method	References	Validity
1	*Scenedesmus subspicatus*	72 hours	EC_{10}	> 500	DIN 38412/9	BASF, 1989c	Valid with restrictions
2	*Pseudokirchneriella subcapitata*	72 hours biomass	NOEC EC_{50}	300 520	ISO 8692	DeVillers et al., 2002	Valid
		72 hours growth rate	NOEC EC_{50}	300 1,570			

Test #1 has been performed by BASF, 1989c on the algae *Scenedesmus subspicatus*. The norm DIN 38412/9 was followed. The effects of five concentrations (25, 50, 100, 250 and 500 mg/L) plus one control were measured after 72 and 96 hours. Temperature and pH were respectively 24.8°C and 7.6-8. No effect was detected at any concentration tested.

A NOEC of 300 mg/L was determined in test #2 (DeVillers et al., 2002). This test was performed according to the norm ISO 8692: "Water quality – fresh water and algal growth inhibition test with *Scenedesmus subspicatus* and *Selenestrum capricornutum*". Test conditions were as follow: incubation occurred on a shaking table under constant temperature (approximately 23°C) and light. Each test was performed on three replicate batches at each concentration and at each control batch. The cell densities were determined using an electronic particle counter after 24, 48 and 72 hours and the inhibition of growth was estimated as the average growth rate expressed as a percentage of the control growth rate. EC_{50} was calculated by means of probit analysis and NOEC was determined by using a software (TOXSTAT). It can also be noticed that although the solutions were analysed, toxicity results were based on nominal concentrations.

3.2.1.4 Micro-organisms

EGBEA toxicity studies with micro-organisms are presented in **Table 3.25**.

Table 3.25 Micro-organisms toxicity data for EGBEA

Test #	Species	Duration	Endpoint	Result (mg/L)	Method	References	Validity
1	*Pseudomonas putida*	17 hours	EC_{10} EC_{50} EC_{90}	722 964 1,026	DIN 38412/8	BASF, 1990b	Valid with restrictions
2	Domestic, activated sludge	30 min.	EC_{20}	900	OECD n°209	BASF, 1990a	Not valid
		180 min.		>1,000			

The toxicity of EGBEA has been tested on an individual bacteria species, *Pseudomonas putida*, by BASF, 1990b – test #1. The method DIN 38412/8 (European reference method: EN ISO 10712:1995) has been followed and three different endpoints have been measured after 17 hours: EC_{10} = 722 mg/L, EC_{50} = 964 mg/L and EC_{90} = 1,206 mg/L. The assay was conducted at 24 +/- 1°C and measures were performed at 20 +/- 1°C. Nine concentrations were tested: 39, 78, 156, 312, 625, 1,250, 2,500, 5,000 and 10,000 mg/L plus one control. Cell multiplication in samples with the tested substance was compared to the control test.

The test #2 was conducted on activated sludge from a domestic waste water treatment plant by BASF, 1990a according to the OECD guideline No 209. The EC_{20} were calculated after 30 and 180 minutes: 900 and >1,000 mg/L respectively. A substance was used as the toxic chemical of reference (3,5-dichlorophenol) and the corresponding EC_{50} after 30 minutes was 22 mg/L. Although test conditions were similar, results obtained from the test performed during 180 minutes do not confirm those from the 30-minute test. Moreover, an effect was only detected at the highest concentration tested: 1 g/L in the 30-minute test. This test has to be considered as invalid.

3.2.1.5 PNEC for the aquatic 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 3.26**.

Table 3.26 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	-	-	-	-	*Oncorhynchus mykiss* LC_{50} after 96 hours = 28.3 mg/L (DeVillers et al., 2002)
Invertebrates: *Ceriodaphnia dubia*	7 days	NOEC	16.4	DeVillers et al., 2003	*Daphnia magna* EC_{50} after 48 hours = 37 mg/L (BASF, 1989a)
Algae: *Pseudokirchneriella subcapitata*	72 hours	NOEC	300	DeVillers et al., 2002	*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.

3.2.1.6 Calculation of the intermittent PNEC for freshwater

For substances subject to intermittent release, long-term effects are not likely to occur. Consequently, the effect assessment for substances with intermittent release is based on the acute toxicity data set (see **Table 3.26**).

Usually an assessment factor of 100 applies to the lowest result of acute toxicity tests performed on three trophic levels. Indeed, the derivation of a PNEC for substances with intermittent release aims to consider only short-term effects (see “the likelihood of long-term effects arising from [intermittent] exposure is low”). This would result in a $PNEC_{aqua,inter}$ = 28.3 (mg/L) / 100 = 283 µg/L thus lower than the chronic PNEC. For this assessment, the $PNEC_{aqua,inter}$ will be set equal to the $PNEC_{aqua}$.

$$PNEC_{aqua,inter} = PNEC_{aqua} = 328\ \mu g/L$$

3.2.1.7 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 TGD (EC, 2003), 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.

3.2.1.8 Calculation of the intermittent PNEC for seawater

In a same way than what has been done for the derivation of a PNEC for intermittent release for freshwater, an assessment factor of 1,000 should be applied on the lowest acute toxicity test result. This would result in a $PNEC_{saltwater,inter}$ = 28.3 (mg/L) / 1,000 = 28.3 µg/L thus lower than the chronic $PNEC_{seawater}$. For this assessment, the $PNEC_{seawater,inter}$ will be set equal to the $PNEC_{seawater}$.

$$PNEC_{seawater,inter} = PNEC_{seawater} = 32.8\ \mu g/L$$

3.2.1.9 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.

Equation 3.6 Formula for the calculation of $PNEC_{sed}$ using the equilibrium partitioning approach

$$PNEC_{sed} = \frac{K_{susp-water}}{RHO_{susp}} \times PNEC_{aqua} \times 1000$$

$PNEC_{sed}$	Predicted No Effect Concentration in sediment	[mg/kg, wet weight]
$K_{susp\text{-}water}$	partition coefficient suspended matter / water	[~2.50 m^3/m^3]
RHO_{susp}	bulk density of wet suspended matter	[~1150 kg/m^3]
$PNEC_{aqua}$	Predicted No Effect Concentration in water	[328 µg/L]

This results in: $PNEC_{sed}$ = 713 µg/kg (ww)

3.2.1.10 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.

3.2.1.11 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* (BASF, 1990b). The EC_{10} of 722 mg/L can be considered as a PNEC for micro-organisms in a STP.

$PNEC_{STP}$ = 722 mg/L

3.2.2 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.

Equation 3.7 Formula for the calculation of $PNEC_{soil}$ using the equilibrium partitioning approach

$$PNEC_{soil} = \frac{K_{soil-water}}{RHO_{soil}} \times PNEC_{aqua} \times 1000$$

$PNEC_{soil}$	Predicted No Effect Concentration in soil	[mg/kg, wet weight]
$K_{soil\text{-}water}$	partition coefficient soil water	[~2.12 m^3/m^3]
RHO_{soil}	bulk density of wet soil	[~1700 kg/m^3]
$PNEC_{aqua}$	Predicted No Effect Concentration in water	[328 µg/L]

This results in: $PNEC_{soil}$ = 409 µg/kg (ww)

3.2.3 Atmosphere

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.

3.2.4 Secondary poisoning

No specific data available.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

STP and surface water (including seawater)

Table 3.27 presents the calculated PEC / PNEC ratios for the aquatic compartment. PECs for STP and surface water appear in Section 3.1.4.1 of this study whereas the corresponding PNECs are determined in Section 3.2.1: 722 mg/L for the $PNEC_{STP}$ and 328 µg/L for $PNEC_{aqua}$ (32.8 µg/L for $PNEC_{saltwater}$).

Table 3.27 Risk characterisation for micro-organisms in STP and aquatic organisms

Scenario	RCR_{STP}	RCR_{aqua}	$RCR_{seawater}$
Production site #1	0 (2.10^{-4})	n. a.	0.005
Production site #2	0 (1.10^{-5})	0.001	n. a.
Production site #3	0 (2.10^{-5})	0.004	n. a.
Paints F	0 (4.10^{-4})	0.002	0.008
Paints P	0 (3.10^{-4})	0.074	0.582
Paints U	0 (8.10^{-6})	0.003	0.018
Metal F	0 (9.10^{-4})	0.078	0.612
Metal P	0 (6.10^{-5})	0.017	0.123
Metal P (intermittent release)	0.002	0.058	0.457
Printing F	0 (2.10^{-4})	0.036	0.285
Printing P	0 (2.10^{-5})	0.005	0.030
Detergents F	0 (8.10^{-6})	0.003	0.012
Detergents P	0 (2.10^{-5})	0.005	0.035
Detergents U	0 (8.10^{-6})	0.004	0.022
Leather P	This use is already covered by the painting scenario (see Section 2.2.2)		
Intermediates P	0 (3.10^{-4})	0.020	0.610
Intermittent releases $		0.012	0.354

$ The generic scenario takes into account 10 days of processing per year. With this low number of days, intermittent releases could also be considered in the assessment. Both calculations considering or not intermittent releases are consequently incorporated to this report.

P Processing
F Formulation
U Private use

For the risk characterisation at production it can be noticed that no risk is expected even when the worst case is considered.

For some end uses, formulation and processing steps can be achieved at a same site. So, in order to characterise the total risk at such sites it is necessary to add the calculated risks for each step. For the freshwater compartment, according to **Table 3.27**, no risk is identified for all end uses

even when both formulation and processing can be considered at a same site (dimmed lines of **Table 3.27**).

EGBEA is readily biodegradable and has a low potential for accumulation in biota. Consequently, this substance will not remain in the environment and secondary poisoning is not expected. Based on the risk assessment performed for freshwater and on the lack of specific hazard identified for the marine environment, no risk is expected in the marine compartment.

Sediment (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

Conclusion (ii).

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

3.3.2 Terrestrial compartment

Risk characterisation for the terrestrial compartment has been performed calculating PEC/PNEC ratios. PECs for soil have been estimated in Section 3.1.4.2 and the corresponding PNEC has been determined in Section 3.2.2 (409 µg/kg, wet weight). Results are shown in **Table 3.28**.

Table 3.28 Risk characterisation for the terrestrial compartment

Scenario	$RCR_{agricultural\_soil\_over\_30\_days}$	$RCR_{grassland\_over\_180\_days}$
Production site #1	0.203	0.025
Production site #2	0 (4.10^{-4})	0 (4.10^{-4})
Production site #3	0 (4.10^{-4})	0 (4.10^{-4})
Paints ^{F}	0.004	0.004
Paints ^{P}	0.157	0.070
Paints ^{U}	0.004	0.002
Metal ^{F}	0.135	0.016
Metal ^{P}	0.033	0.012
Printing ^{F}	0.063	0.009
Printing ^{P}	0.008	0.003
Detergents ^{F}	0.003	0.002
Detergents ^{P}	0.009	0.002
Detergents ^{U}	0.006	0.002

Table 3.28 continued overleaf

Table 3.28 continued Risk characterisation for the terrestrial compartment

Scenario	$RCR_{agricultural\_soil\_over\_30\_days}$	$RCR_{grassland\_over\_180\_days}$
Leather P	This use is already covered by the painting scenario (see Section 2.2.2)	
Intermediates P	0.135	0.016

P Processing
F Formulation
U Private use

It can be noticed that no risk is expected at the production level.

For some end uses, formulation and processing steps can be achieved at a same site (see dimmed lines in **Table 3.28**). So, in order to characterise the total risk at such sites it is necessary to add the calculated risks for each step. According to (**Table 3.28**) no risk is identified for all end uses even when both formulation and processing are considered.

Conclusions to the risk assessment for the terrestrial compartment

Conclusion (ii).

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

3.3.3 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 for all levels of the life cycle of EGBEA: production, formulation, processing and private use.

3.3.4 Secondary poisoning

Conclusions to the risk assessment for secondary poisoning

Conclusion (ii).

Conclusion (ii) is applied for all levels of the life cycle of EGBEA: 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 EGBEA: 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).

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling

PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SCHER	Scientific Committee on Health and Envionment Risks
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations

UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

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

EUR 22475 EN **European Union Risk Assessment Report 2-butoxyethanol acetate (EGBEA) – Part I – Environment, Volume 69**

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The report provides the comprehensive 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.

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2-butoxyethanol acetate (EGBEA)
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European Union Risk Assessment Report

2-BUTOXYETHANOL ACETATE

Part II – Human Health

CAS No: 112-07-2

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RISK ASSESSMENT

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Part II – Human Health

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RISK ASSESSMENT

FINAL APPROVED VERSION

August 2008

France

Rapporteur for the risk assessment of 2-butoxyethanol acetate is BERPC

Contact point:

BERPC

60-62 rue d'hauteville

75009 Paris

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Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

Contact Details of the Rapporteur(s)

Rapporteur: France

Human Health: BERPC
60/62 rue d'Hauteville
75010 Paris
France

Tel: + 33 1 55 07 89 89
Fax: + 33 1 47 70 63 13

The scientific work on the human health sections has been elaborated by:

Effects assessment, Exposure and Risk Characterisation for Workers: Institut National de Recherche et de Sécurité (INRS)
Expertise and Technical Advice Division - RCB
30 rue Olivier Noyer
75680 Paris Cedex 14
France

And

BERPC
60/62 rue d'Hauteville
75010 Paris
France

Exposure and Risk Characterisation for Man via the environment: Institut National de l'Environnement Industriel et des Risques (INERIS)
Département TEC
Parc Technologique ALATA
BP n° 2
60550 Verneuil-en-Halatte
France

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

0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number: 112-07-2
EINECS Number: 203-933-3
IUPAC Name: 2-butoxyethanol acetate

Environment

Human health

Human health (toxicity)

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.

Conclusion (ii) applies for all end points and for all scenarios

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.

Conclusion (ii) applies for all end points and for all scenarios

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.

4 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.

Human health (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.

CONTENTS

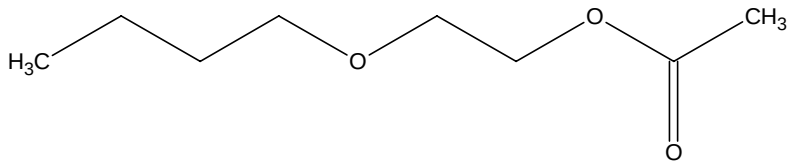
EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 112-07-2
EINECS Number: 203-933-3
IUPAC Name: 2-butoxyethanol acetate
Molecular formula: $C_8H_{16}O_3$
Structural formula: CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-O-C-O-CH_3



Molecular weight: 160.21 $g.mol^{-1}$
Synonyms: (EGBEA) (this 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

Note: When the reliability of values do not enable a clear choice between one and another, a median value is chosen or calculated taking into consideration all figures supplied by the industry and only once the values found in handbooks or reports and which differ.

The physico-chemical properties are discussed below and summarised in Table 1.1.

Table 1.1: summary of 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	0.4 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

1.3.1 Physical state

EGBEAis a colourless liquid with a sweet and fruity characteristic odour. An absolute perceptible limit of 0.1 ppm (50% recognition = 0.35 ppm and 100% recognition = 0.48 ppm) was referred to EGBEA(Verschueren, 2001).

1.3.2 Melting point

Values found in several handbooks range between -63 and -65°C with a majority at -64°C (Ullmann, 2000 ; Howard, 1989 ; Verschueren, 2001 ; Lewis, 1999 ; Kirk-Othmer, 1983). Technical product data sheets give similar values: (-63)-(-64)°C (Eastman, 2001 ; Merck, 1996) with only one giving a freezing point < -70°C (BP, 1998) measured at 100% concentration.

A melting point of –64°C is retained.

1.3.3 Boiling point

Boiling points are ranging between 184 and 198°C, at normal pressure conditions. 192.3°C is the most frequent boiling point reported in handbooks or studies (Staples *et al.*, 1998 ; Lewis, 1999 ; Howard, 1989). Rounded value of 192°C is also found in other books or works (Rowe and Wolf, 1982 ; Kirk-Othmer, 1983).

A boiling point of 192.3°C is retained.

1.3.4 Relative density

At 20°C, the relative density of EGBEA is around 0.94: 0.94 (BP, 1998 ; Verschueren, 2001 ; Staples *et al.*, 1998 ; BASF, 2002), 0.941 (Eastman, 2001), 0.9424 (Lewis, 1999 ; Kirk-Othmer, 1983), 0.945 (Ullmann, 2000).

The rounded value (0.94) will be used for the relative density of EGBEA.

1.3.5 Vapour pressure

Vapour pressures ranging from 0.31 to 0.77 hPa, at 20°C have been reported. Values come from handbooks: 0.4 hPa (Ullmann, 2000 ; Verschueren, 2001), studies: 0.4 hPa (Rowe and Wolf, 1982), 0.5 hPa (Staples *et al.*, 1998 ; Weber *et al.*, 1981), technical product data sheets: 0.32 hPa (BASF, 2002 ; Merck, 1996), 0.39 hPa (Eastman, 2001) or from calculation programs using QSAR: 0.716 hPa (US EPA and SRC, 2001) and 0.77 hPa (ASTER, 1995). Another value, measured at 25°C, is also quoted: 0.39 hPa (Boatman *et al.*, 2000).

The median of all measured vapour pressures, 0.4 hPa at 20°C, is retained for the study.

1.3.6 Surface tension

Technical product data sheets give several values for a range of temperature: ~31.1 mN/m at 10°C (BP, 1998), ~30 mN/m (BP, 1998) and 30.3 mN/m (Eastman, 2001) at 20°C, ~27.79 mN/m at 30°C (BP, 1998).

The rounded value at 20°C (the temperature recommended in the OECD guideline No 115), 30 mN/m, is retained.

1.3.7 Water solubility

In literature, water solubility for EGBEA is ranging from 10000 mg/L to 15000 mg/L. Most references give a solubility of 15000 mg/L at 20°C (Boatman *et al.*, 2000 ; Verschueren, 2001 ; Rowe and Wolf, 1982 ; Merck, 1996) and, at this temperature, a value of 13400 mg/L is also mentioned (BASF, 2002). At 25°C, a solubility of 11000 mg/L is quoted (Kirk-Othmer, 1983 ; Eastman, 2001) whereas other values are quoted without temperature mention: 10000 mg/L (OSHA, 1990) and 11000 mg/L (Staples *et al.*, 1998 ; Parrish, 1983 ; HSDB, 1997).

A solubility of EGBEA in water of 15000 mg/L at 20°C will be chosen.

1.3.8 Partition coefficient n-octanol/water

Both measured and calculated octanol water partition coefficients are available. The different values found in literature are presented in Table 1.2.

Table 1.2: range of octanol / water partition coefficients

Method	Value (log P_{ow})	References
Calculated	1.41	HSDB, 1997
Measured	1.51	Verschueren, 2001 BASF AG
Calculated with SRC log K_{ow} interactive calculation program	1.57	Staples *et al.*, 1998
Calculated (Assessment Tools for the Evaluation of Risk)	1.71	ASTER, 1995
Measured	1.79	Staples *et al.*, 1998
Calculated (Assessment Tools for the Evaluation of Risk)	2.27	ASTER, 1995

The octanol / water partition coefficient test made by BASF was conducted in accordance with an international standard test guideline (OECD 107: partition coefficient (n-octanol/water), flask-shaking method). The value of 1.51 (mean of three measures) is retained for this study.

1.3.9 Granulometry

Not applicable: the substance is a liquid.

1.3.10 Flash point

Flash point values are ranging from 71°C to 88°C (closed cup): 71°C (National Fire Protection Association, 1997 ; Eastman, 2001), 73.9°C (OSHA, 1990), 75°C (Ullmann, 2000), 84°C (BP, 1998) and 88°C (Kirk-Othmer, 1983). Two other values were measured using the open cup method: 81°C (Eastman, 2001) and 87.8°C (OSHA, 1990).

The median of the values measured using a closed cup is retained: 75°C.

1.3.11 Autoflammability

Four different autoflammability values are available: 300°C (BASF, 2002), 340°C (National Fire Protection Association, 1997 ; OSHA, 1990 ; Eastman, 2001), 355°C (Merck, 1996) and 375°C (Ullmann, 2000).

The more quoted value is retained: 340°C.

1.3.12 Flammability

It has been reported that EGBEA presents moderate fire hazard when exposed to heat, flame or oxidisers (HSDB, 1997). Three flammability limits are quoted: 1-6.1 % - volume (BASF, 2002), 1.7-8.4 % - volume (Merck, 1996) and 0.88 % (at 93°C) – 8.54 % (at 135°C) – volume (Eastman, 2001 ; National Fire Protection Association, 1997). The last one will be retained for this study.

1.3.13 Explosive properties

Not explosive.

1.3.14 Oxidising properties

No oxidising properties.

1.3.15 Viscosity

At 20°C, three different viscosity values for EGBEA are quoted: 1.75 mPa.s (BASF, 2002), 1.8 mPa.s (Ullmann, 2000 ; Merck, 1996 ; Eastman, 2001), ~1.94 mPa.s (BP, 1998), at 20°C. The value with the highest frequency (1.8 mPa.s) will be retained.

1.3.16 Henry's constant

Both measured and calculated Henry's constants are available. A measure, performed with a bag method for equilibrium partitioning gives a value of 0.13 $Pa.m^3$/mol, at 20°C whereas another measurement, performed with a batch stripping method, at 25°C, leads to a Henry's constant of 0.55 $Pa.m^3$/mol (Kim *et al.*, 2000).

Concerning calculated data, results are presented in Table 1.3 below.

Table 1.3: calculated Henry's law constant

Method	Value ($Pa.m^3$ / mole)	References
Group method, at 25°C	0.068	US EPA and Syracuse Research Corporation, 2001
SAR estimates developed by the US EPA – ECOSAR program	0.071	Staples *et al.*, 1998
Calculated from experimental values for vapour pressure and water solubility	0.537	Syracuse Research Corporation cited in HSDB
Bond method, at 25°C	0.646	US EPA and Syracuse Research Corporation, 2001
Calculated from water solubility (11 g/L) and vapour pressure (0.5 hPa)	0.729	Howard, 1989
Assessment Tools for the Evaluation of Risk	1.581	ASTER, 1995
Calculated with the VP/Wsol ratio using EPI estimated values, at 25°C	3.696	US EPA and Syracuse Research Corporation, 2001

Henry's law constant can also be estimated from the ratio of the vapour pressure to the water solubility using selected values from this study: 40 Pa for vapour pressure and 15000 mg/L for water solubility. Calculation gives a Henry's law constant of 0.427 $Pa.m^3/mol$.

At 25°C, several calculated Henry's law constants are matching quite well the measured value obtained at the same temperature. Moreover, direct measurement of the Henry's law constant is recommended for water miscible compounds (TGD - EC, 2003). A Henry's law constant of 0.55 $Pa.m^3/mol$ is retained.

1.4 CLASSIFICATION

1.4.1 Current classification

Classification: Xn, R20/21

1.4.2 Proposed classification

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

CLP: Acute Tox. 4*; H332, H312

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

[click here to insert text]

2.1.2 Production capacity

[click here to insert text]

Table 2.1 [Production volume or appropriate text]

[Country or appropriate text]	[Volume or appropriate text]
[Total or appropriate text]	

[click here to insert table note or Table X.X continued overleaf or delete if not appropriate]

2.2 USES

2.2.1 Introduction

[click here to insert text]

Table 2.2 [click here to enter appropriate text]

Industry category	Use category	Quantity used [click here to add unit]	Percentage of total use
Total			

[click here to insert table note or Table X.X continued overleaf or delete if not appropriate]

2.2.2 Scenarios

[click here to insert text]

2.3 TRENDS

[click here to insert text]

2.4 LEGISLATIVE CONTROLS

[click here to insert text]

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

[click here to insert text]

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

[Please consider using overview tables to summarise the test results for the different species]

3.3 RISK CHARACTERISATION [5]

[click here to insert text; consider using overview tables with PEC and PNEC ratios]

[5] 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.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

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 (OSPA, 2002).

In the Swedish product register (KEMI, 2002), 227 products containing EGBEA have been identified, of which 214 were paints, inks or related products (hardeners, diluents …). 14 were consumer products.

In the Danish product register (Arbejdstilsynet, 2001), 256 products containing EGBEA have been identified. The most common uses were paints and varnishes (79 products), solvents (67 products), process regulators (54 products), adhesives/binding agents (12 products), reprographic agents (27 products). The distribution of concentration intervals in the main type of products is presented in the table 4.1.

Other data extracted from the French product register SEPIA (INRS, 2003) showed that 63 products out of the 14 137 products registered between 1997 and 2003 contained EGBEA. The use category is mainly related to paints, varnishes and inks. Concentrations of EGBEA reported for 55 preparations were always < 50 % and distributed as:

- 12 preparations between 0 and 1 %
- 25 preparations between 1 and 5 %
- 7 preparations between 5 and 10 %
- 8 preparations between 10 and 20 %
- 2 preparations between 20 and 50 %.

In an enquiry recently conducted by CEPE (European council of the paint, printing and artists' colours industry), 32 companies using EGBEA answered and mentioned the following branch or trade for the downstream users:

- automotive OEM: 5 times
- can coating: 5 times
- protective coatings: 5 times
- industrial coatings: 4 times

- vehicle refinishing: 4 times
- wood coating: 3 times
- coil coatings: 2 times
- decorative coating: 2 times
- marine coatings: 1 time
- printing inks: 1 time

Table 4.1 - Concentration of EGBEA in the main use categories in the Danish product register (2001)

Content %	Total Nb	Paints, lacquers and varnishes	Solvents	Process regulators	Adhesives, binding agents	Reprographic agents
[0-1]	14	12				
]1-5]	71	40	11	8	8	19
]5-10]	48	18	13	11	4	
]10-20]	64	9	15	16		
]20-50]	45		15	19		8
]50-80]	3		3			
]80-100]	11		10			

4.1.1.2 Occupational exposure

Definitions and sources

In this document, unless otherwise stated, the term exposure is used to denote external personal exposure as measured or otherwise, assessed without taking into account the attenuating effect of any personal protective equipment (PPE) which might have been worn. This definition permits the effects of controls, other than PPE, to be assessed and avoids the considerable uncertainty associated with attempting to precisely quantify the attenuation of exposure brought about by the proper use of PPE. Furthermore, inappropriate use of gloves may even increase dermal uptake.

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. When available, they are presented in this section and compared with that predicted from the EASE (Estimation and Assessment of Substance Exposure) model. EASE is a general purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data is limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

EGBEA is not a wide spread solvent compared to 2-butoxyethanol (EGBE). Many of their physico-chemical properties are in the same order (see the table 4.2).

Table 4.2 - summary of physico-chemical properties of EGBEA and EGBE

Property	Value for EGBEA	Value for EGBE
Physical state	Liquid	Liquid
Melting point	-64°C	-73.4°C
Boiling point	192.3°C	170.5°C
Relative density	0.94, at 20°C	0.9 at 20°C
Vapour pressure	0.4 hPa, at 20°C	1 hPa at 20°C
Surface tension	30 mN/m, at 20°C	26.6 mN/m, at 20°C
Water solubility	15000 mg/L, at 20°C	Miscible
Partition coefficient n-octanol/water (log value)	1.51	0.8
Granulometry	n.a.	n.a.
Flash point	75°C, closed cup	63.2°C
Autoflammability	340°C	244.5°C
Flammability	0.88 % (at 93°C) – 8.54 % (at 135°C) – volume	1.1 % - 12.7 % - volume
Explosive properties	Not explosive	Not explosive
Oxidising properties	No oxidising properties	No oxidising properties
Viscosity	1.8 mPa.s	3.28_ mPa at 20°C
Henry's constant	0.55 Pa.m^3/mol at 25°C	0.08 Pa.m^3/mol at 25°C
Conversion factors (101 kPa, 20°C)	1 ppm = 6.66 mg/m^3 1 mg/m^3 = 0.15 ppm	1 ppm = 4.9 mg/m^3 1 mg/m^3 = 0.204 ppm

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.

Although its vapour pressure (EGBEA) is somewhat lower than EGBE (but in the same order of magnitude), inhalation exposure to EGBEA can also be extrapolated from the data available for EGBE. For this purpose, the exposure assessment recently performed for EGBE will be used in this report (draft of the EU 2-butoxyethanol risk assessment, November 2007). When data on EGBEA are sufficient, conclusions in the RAR on inhalation exposure will be based on data from EGBEA. If not, data on EGBE will be used.

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.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data; it predicts inhalation exposure as ranges for concentrations for continuous exposure at the process under consideration. Dermal exposure is provided by EASE as the quantity of a product adhering to the skin due to a task.

In the present assessment all inhalation exposures are expressed in parts per million (ppm), although the figures in the original publication are sometimes given as mg/m^3. All mg/m^3 have been converted to ppm using the following approximation:

$$ppm = mg\ EGBEA/m^3 \times 24.05/160.2 = mg\ EGBEA/m^3 \times 0.15$$

$$mg\ EGBEA/m^3 = ppm \times 160.2/24.05 = ppm \times 6.66$$

Routes of exposure and relevant scenarios

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.

Workers may be significantly exposed during the production of EGBEA, its processing as an intermediate or during the formulation and use of EGBEA containing products.

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 will focus on particular sub-scenarios for exposure in the most frequent type of use or particular pattern of use, when relevant.

Number of workers exposed

Due to the use categories of products containing EGBEA, it is assumed that there are a large number of workers in many professional sectors who may be exposed daily or occasionally.

Data from the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1980 to 1983 indicate that an estimated 150 892 workers in 236 industry/occupation categories were potentially exposed to EGBEA in the United States from 1981 to 1983. These numbers do not include workers potentially exposed to trade-name compounds that contain EGBEA (ATSDR, 1998).

Other data specific to some activities are reported further in this section.

Occupational exposure limits (OELs)

OELs apply to workplace air concentrations of chemicals. They are normally intended to protect workers against short-term adverse effects (irritation, acute CNS effects) or long-term effects (e.g. on liver, lungs, kidneys, or chronic CNS effects) after months or years of exposure. When applicable, a "short-term exposure limit" (STEL) may be proposed or imposed for the first ones, and/or a "time-weighted average" (TWA) for the second. The first value ordinarily refers to a 15 minutes or so duration, the second to a shift (generally considered as an 8-hour shift).

The table 4.3 details the OELs recommended for EGBEA in various countries. They are provided for information and are not an indication of the level of control of exposure achieved in practice in workplaces. Most of them add a "skin" notation.

Table 4.3 - OEL values (BGIA, 2007)

	8-hour TWA		STEL, 15 min	
Country	mg/m^3	ppm	mg/m^3	ppm
EU*	133	20	333	50
Austria	133	20	270	40
Denmark	130	20	260	40
Finland	130	20	330	50
France	13.3	2	199.8	30
Germany	130	20	520	80
Netherlands	135	20	333	50
Norway	65	10	-	-
Spain	133	20	333	50
Sweden	70	10	140	20
Switzerland	135	20	540	80
United Kingdom	147	20	367	50
USA (ACGIH)	-	20	-	-
USA (NIOSH)	33	5		

*Directive 2000/39/CE of 8 June 2000

Biological exposure levels (BELs) proposed to characterize occupational exposure to EGBE and EGBEA by measuring BAA (Butoxy Acetic Acid) urinary concentration are presented in table 4.4.

Table 4.4 - Biological exposure levels (BELs)

Country	Determinant	Sampling time	BEL	Reference
Germany	BAA in urine	Post-shift at the end of the working week	100 mg/l	DFG 2002
USA	BAA in urine	Post-shift	60 mg/g creatinine	NIOSH 1990

Nota:1 mmol/mol creatinine = 1.17 mg/g creatinine = 0.83 mg/l

4.1.1.2.1 Scenario 1: Manufacture

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

Measured data

Airborne measurements were provided in the framework of this assessment by one EU producer. Analysis of 62 personal air sampling (exposure duration > 1 hour) carried out in 30 enterprises during the period 1995-2000 leads to a 90th percentile of 0.07 ppm (0.48 mg/m^3). Measurement strategy is based on Technical Rule for Hazardous Substances TRGS 402 "determination and assessment of the concentrations of hazardous substances in the atmosphere in work areas".

There is no other measured data.

Modelling

Therefore the EASE model is used to predict exposure during production. Considering a closed system with full containment, the model provides an exposure estimation of 0 - 0.1 ppm (0 - 0.7 mg/m^3). If the system is breached in some activities (like maintenance, sampling, cleaning, filling), concentrations could be in the range of 0.5 - 3 ppm (3.3 – 20.0 mg/m^3) (non dispersive use, low tendency to become airborne, presence of LEV).

Analogous data

For EGBE, a value of 2.4 ppm (11.8 mg/m^3) was retained as a reasonable worst-case TWA atmospheric concentration in production activities, based on results of monitoring data (draft of the EU 2-butoxyethanol risk assessment, November 2007). In most situation, exposure was < 0.5 ppm (2.5 mg/m^3) (using personal sampling).

Statement of the exposure level

It is proposed to adopt the specific value of 0.07 ppm (0.48 mg/m^3) obtained for EGBEA as a reasonable worst-case TWA atmospheric concentration in production activities.

Dermal exposure

Measured data

There are no available measured data.

Modelling

Due to the enclosure of the process and control measures taken to minimize skin contact, for example, during transfer to tankers, dermal exposure at the plant is incidental and therefore likely to be low. The main source of potential exposure is during maintenance activities.

The EASE model estimated a dermal exposure in the range of 0 - 0.1 mg/cm^2/day (non dispersive use with direct handling and incidental contact). Assuming exposed skin surface area is 420 cm^2 (palms of hands for consistency with other EU occupational risk assessments), maximum external dermal exposure would be 42 mg/day. This exposure will be mitigated by the use of suitable gloves.

Statement of the exposure level

The retained value for the dermal exposure is 42 mg/day.

4.1.1.2.2 Scenario 2: Formulation of products containing EGBEA

General

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.

Quite a high number of workers are likely to be exposed during formulation of products. An enquiry was recently conducted by CEPE on the industrial uses of 4 glycol ethers in paints or inks, one of which is EGBEA: 109 answers were received from all over Europe, 32 users (two times less than the numbers of users of EGBE) and 77 non-users. They comprise both multinationals and small or medium size enterprises from most of the EU countries. The number of workers exposed was indicated by 17 user companies out of the 32, the answers were in the range of 5 to 183 and represent a total number of 607 workers (CEPE, 2002).

Exposure strongly depends on the process, which may be enclosed or relatively open. When the transfer of EGBEA 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.

Exposure will also strongly depend on the quantities handled, the concentration in the products and the duration and frequency of exposure.

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.

In the recent enquiry conducted by CEPE, a few informations were collected about frequency and duration of exposure (table 4.5).

Table 4.5 – Exposure frequency and duration in the EU paints and inks manufacturing industry (CEPE, 2002)

	Exposure in days/year (9 answers)	Exposure in hours/day (19 answers)
Arithmetic mean	156	4.8
Median	214	6.0
Range	2-250	1-8

Inhalation exposure

Measured data

From 1996 to 2000, 791 measurements were collected in the MEGA database of the BG Institute for Occupational Safety (BGAA, 2002). 59 measurements with a duration > 1 hour were obtained in connection of paint production during mixing and filling of EGBEA in 13 companies. The measurement procedure is in accordance to (DIN) EN 659 “Workplace atmospheres – guidance for the assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy”, (DIN) EN 482 “Workplace atmospheres – general requirements for the performance of procedures for the measurement of chemical agents and TRGS 402. When possible, a distinction is made on the basis of whether or not control measures (LEV) were taken. In this regard, the results present an apparent paradox that the workplaces with LEV frequently do not exhibit lower exposures than those without LEV and the exposures may even be higher.

Technical measures are mostly taken in place where the situation may result in a higher release of vapours, for instance when large quantities of substance are handled or when process occurs at high temperature. By contrast, the release is comparatively low during use of small quantities or processing at ambient temperature. In most cases, control measures create a situation where the exposure level of workplaces with large release approximately reaches the level of workplaces with only low release but without control measures. Results are presented in table 4.6.

Table 4.6 - Measurements results in the MEGA database for paint production during mixing and filling (BGAA, 2002)

Type of company/ working area	No of measurements	No of companies	95 % value ppm (mg/m^3)
Paint production	59	13	3.46 (23.05)
without LEV	10	7	2.02 (13.5)
with LEV	49	8	3.38 (22.55)

No other measured data are available.

Modelling

Using the EASE model (non dispersive use, with a low tendency to become airborne), the exposure estimate would be in the range of 0.5-1 ppm (3.3 – 6.7 mg/m^3) with LEV and 10-20 ppm (66.6 – 133.2 mg/m^3) in case of direct handling with dilution ventilation.

Analogous data

For EGBE, results during formulation show that airborne concentrations are generally low. Recent data provided by industry indicate that exposure would not be higher than 5 ppm (24.6 mg/m^3) but very little information is available to the context of this measurement. Based on the 90th percentile of the MEGA database values for EGBE (BGAA, 2001), the following reasonable worst case inhalation exposure during formulation of products containing EGBE was retained: 3.2 ppm (15.7 mg/m^3).

Statement of the exposure level

Typical exposure levels are probably much lower (<1 ppm or 6.7 mg/m^3).

It is proposed to adopt the specific value of 3.46 ppm (23.0 mg/m^3) obtained for EGBEA as a reasonable worst-case TWA atmospheric concentration in formulation activities; this value is extracted from the MEGA database (BGAA, 2002).

It is consistent with the EASE exposure estimates and also closed to the value of 3.2 ppm (15.7 mg/m^3) used in the RAR EGBE for the scenario “formulation of products containing EGBE”. A continuous exposure for full shift (8 hours a day) is assumed.

Dermal exposure

Measured data

There are no available measured dermal data for EGBEA.

Modelling

The EASE model estimates a dermal exposure in the range of 0.1-1 mg/cm^2/day (non dispersive use with direct handling and intermittent contact). Assuming exposed skin surface area is 420 cm^2 (palms of hands for consistency with other EU occupational risk assessments), maximum external dermal exposure would be :

- 42-420 mg/day for loading pure substance
- 21-210 mg/day for filling (assuming 50% EGBEA in the product).

Dermal exposure may be lower if suitable gloves are worn.

Read-across approach to the exposure results available on EGBE

For EGBE, it was proposed to take available data of DEGBE (RISKOFDERM, 2002 ; Gijsbers *et al.*, 2004) as a basis and to adapt them to EGBE using biomonitoring data of EGBE when applicable.

On the basis of results obtained with DEGBE, a rounded value of 10,000 mg EGBE /day was determined for the loading step of the formulation process. The filling of packages with products leads to substantially lower exposure levels. Assuming a product with 50% EGBE and a 90th percentile exposure level for the product of 3,300 mg/day led to a reasonable worst case exposure level of approximately 1,600 mg EGBE/day.

Conservatively, it might be assumed that both tasks are done by the same workers, leading to a total exposure of approximately 11 600 mg. Due to the higher vapour pressure of EGBE compared to DEGBE, this exposure level is considered to be overestimated.

On the other hand, limited biomonitoring data were available for EGBE itself, also in real conditions of use, with the advantage of not requiring any extrapolation of uncertain validity from another chemical substance. Its main weakness lies in the important penetration of EGBE through the inhalation route, which must then be assessed with sufficient reliability. These limited biomonitoring data led to the following dermal exposure: about 500 mg/day.
Since neither of these sources (RISKOFDERM data and biomonitoring data on EGBE) could be ignored, a final assessment had to be based on both. The difficulty to do so lay here in assessments that differ by a factor of 23 (11,600 mg/day for RISKOFDERM, 500 mg/day for biomonitoring). This factor is in fact relatively small considering the extreme variability evidenced in assessments made by RISKOFDERM in a variety of situations. Moreover, there are good reasons to think that data obtained with DEGBE may be overestimates when transposed to EGBE. Based on extensive data from this RISKOFDERM project (Marquart *et al.*, 2006) consider that 550 mg is more a typical exposure value than a reasonable worst-case. According to them, “individual mean dermal exposure levels were on average within a 4-fold range”. In this context, it is proposed to re-evaluate the assessment of the limited data based on biomonitoring by a factor of 4. This eventually led to propose a skin exposure of 2,000 mg EGBE/day for this scenario.

Statement of the exposure level

Since no measured data are available to predict occupational dermal exposure to EGBEA, modelling on EGBEA and conclusions of the dermal exposure of EGBE will be used.

Considering the read-across approach to the exposure results available on EGBE, the skin exposure of 2,000 mg/day is proposed for EGBEA and the scenario "formulation of products containing EGBEA".

The estimates based on measured data from RISKOFDERM (DEGBE) and biomonitoring studies on EGBE should be preferred to the EASE estimates on EGBEA as they represent real exposure situation and EASE is known to be a weak model for this purpose.

4.1.1.2.3 Occupational exposure from end uses

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

Measured exposure levels in general

Exposures to EGBEA were found in a 1983 survey of 336 Belgian businesses (Veulemans *et al*., 1987). In this study, one or more glycol ethers were detected in 262 air samples collected in a wide variety of industry. EGBEA was the less frequently detected glycol ether : it was found in 4 of 94 air samples from sites using printing pastes and 3 of 67 samples from various other industrial sites where materials such as varnishes, sterilization agents and cleaning agents were used. The geometric mean atmospheric concentrations and ranges of EGBEA were 1.9 ppm (12.7 mg/m^3) at these sites using printing pastes and 1.6 ppm (10.6 mg/m^3) at other sites corresponding to range of 0.7 - 4 ppm (4.6 - 26.5 mg/m^3) and 1.3 - 1.7 ppm (8.9 - 11.7 mg/m^3) respectively.

From 1987 to 1998, the French COLCHIC database collected 10,593 personal sampling results of glycol ethers for 602 facilities (Vincent, 1999). EGBEA was found 373 times; the arithmetic atmospheric mean value of the 60 to 480 minutes samplings (106 results) was 0.48 ppm (3.2 mg/m^3), median 0.3 ppm (2.0 mg/m^3); range 0.015-5.25 ppm (0.1-35.0 mg/m^3), 95th percentile 1.87 ppm (12.5 mg/m^3). The distribution of the results for the type of industry is presented in table 4.7.

Table 4.7 - Personal exposure for measurements 60-480 minutes, years 1987-1998, in ppm (mg/m3) (Vincent, 1999)

Activities	No of results	Arithmetic mean	Range	Median	95th percentile
Printing industry	41	0.85 (5.7)	0.07-5.25 (0.5-35)	0.3 (2)	4.5 (30)
Chemical industry	4	<0.01 (< 0.1)			
Rubber and plastics	28	0.3 (2.3)	0.01-1 (0.1-7)	0.2 (1.4)	1 (6.9)
Metal finishing	19	0.2 (1.4)	0.07-0.9 (0.5-6)	0.07 (0.5)	0.9 (6)
Electrical industry	2	<0.01 (< 0.1)			
Manufacture of radio and television equipment	8	0.2 (1.7)			

Results related to specific activities are presented in table 4.8.

Table 4.8 - Personal exposure in specific activities for measurements 60-480 minutes, years 1987-1998, in ppm (mg/m³) (Vincent, 1999)

Activity	No of sampling	Median	Arithmetic mean. ppm(mg/m^3)	Range ppm (mg/m^3)	95th percentile ppm (mg/m^3)
Pneumatic coating of paint or varnish	4		0.18 (1.2)	0.015-0.46 (0.1-3.1)	
Varnishing (curtain)	5		0.75 (5)	0.75-0.75 (0.5-0.5)	
Silk screening	61	2	0.54 (3.6)	0.07-5.25 (0.5-35)	1.65 (11)
Screen washing	3	-	0.10 (0.7))	0.07- 0.15 (0.5-1)	-
Offset printing	8	-	0.16 (1.1)	0.07-0.40 (0.5-2.7)	-
Flexography	2		<0.01(<0.1)	<0.01(<0.1)	-

For the years 1999 to 2002, the COLCHIC database collected 58 results of 60 to 480 minutes personal atmospheric samplings. The arithmetic mean value of samplings was found 0.09 ppm (0.6 mg/m^3) with a median of 0.06 ppm (0.4 mg/m^3), a range of 0.015-0.99 (0.1 - 6.6 mg/m^3) and a 95th percentile 0.73 ppm (4.9 mg/m^3) (Vincent, 2003).

From 1996 to 2000, 791 measurements were collected in the MEGA database of the BG Institute for Occupational Safety in about 313 companies (BGAA, 2002). The 527 measurements with duration > 1 hour obtained in connection with the use of products containing EGBEA is presented in table 4.9. All short duration measurement values (< 1 hour) were below the analytical determination limit.

Table 4.9 - Measurements results in the MEGA database (BGAA, 2002)

Type of company/ working area	No of measurements	No of companies	95% value ppm (mg/m^3)
Cleaning, manual, mechanical	42	15	2.9 (19.3)
without LEV	17	6	Note A
with LEV	24	10	4.7 (31.2)
Painting, brush and roller, filling work	23	14	Note A
without LEV	12	8	Note A
with LEV	8	6	Note A
Spraying	189	81	1.7 (11.55)
without LEV	33	13	1.8 (12.10)
with LEV	150	67	1.7 (11.50)
Printing	79	42	Note A
without LEV	47	26	3.2 (21.30)
with LEV	29	18	1.6 (10.55)
Surface coating, mechanical	129	70	Note A
without LEV	71	37	Note A
with LEV	50	33	Note A
Surface coating, general	65	35	Note A
without LEV	25	16	1.6 (11.00)
with LEV	33	18	Note A

Note A : measurement value < analytical determination limit

The sum of the measurements with and without technical measures (ventilation) may be lower than the number of measurements for the particular type of company / work area since information on technical measures (ventilation) is not included in the data in all cases.

- **Scenario 3-1: Painting**

EGBEA is used as a solvent in paints. Analysis of the answers collected in the paint formulating industry by CEPE (2002) shows that the concentrations of EGBEA range from 0.5 to 20 % with an arithmetic mean up to 5.8 % (see table 4.10). Taking into account this data together with the information collected in European product registers (see 4.1.1.1), a maximum content of 20 % EGBEA in paints will be assumed in this assessment for industrial paints and 5 % for decorative paints.

Table 4.10 - Contents of EGBEA in paints (CEPE, 2002)

	Industrial paints		Decorative paints	
	Water-based	Solvent-based	Water-based	Solvent-based
Number of answers	7	24	3	1
Arithmetic mean	5.8 %	4.9 %		
Median	0.9 %	4.5 %		
Range	0.54-20 %	0.5-17 %	1.2-1.5 %	3 %

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…Application techniques inventoried in the CEPE enquiry are presented in table 4.11 (CEPE, 2002).

Table 4.11 - Relative frequencies of application techniques in painting/surface coating (CEPE, 2002)

Application technique	Number of mentions
Spray	22
Roll	7
Brush	5
Dipping	3
Roller coaters	2
Flow coat	1

Inhalation exposure

Measured data

A study was performed by INRS (Vincent *et al*., 1996) from 1988 to 1993 to assess glycol ethers exposure. Among others, exposure measurements were made in 26 firms using paints or varnishes containing glycol ethers. In the formulations used, concentration of glycol ethers varied greatly and ranged from 1% to 100% by volume in case of thinners for example.

EGBEA was the glycol ether the less detected in the products. Exposure of 372 workers using paints and varnishes was measured by 8-hour personal atmospheric sampling (783 samples). Exposure to EGBEA was identified for 138 workers (288 samples). EGBEA atmospheric concentrations for different painting activities are presented in table 4.12.

Table 4.12 - Measured inhalation data (TWA) during painting (Vincent et al, 1996)

Activity	No of sampling	Mean ppm (mg/m^3)	Max or range ppm (mg/m^3)
Coil coating	39 (20 w, 1 f)	0.1 (0.7)	<0.1-0.5 (0.7-3.3)
Painting of metal frame	50 (23 w, 2 f)	<0.1 (0.7)	<0.1-0.7 (0.7-4.7)
Painting of building	63 (63 w, 11 f)	<0.1 (0.7)	<0.1-0.5 (0.7-3.3)
Varnishing of printed circuit boards	57 (13 w, 2 f)	0.2 (1.3)	<0.1-0.4 (0.7-2.66)
Painting of plastics	79 (19 w, 2 f)	<0.1 (0.7)	<0.1-0.6 (0.7-4)

w: workers, f: facilities.

From 1996 to 2000, 791 measurements were collected in the MEGA database of the BG Institute for Occupational Safety (BGAA, 2002). 406 measurements with a duration > 1 hour was obtained during paint application in 200 companies. The measurement procedure is in accordance to (DIN) EN 659 “Workplace atmospheres – guidance for the assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy”, (DIN) EN 482 “Workplace atmospheres – general requirements for the performance of procedures for the measurement of chemical agents and TRGS 402. When possible, a distinction is made on the basis of whether or not control measures (LEV) were taken. In this regard, the results present an apparent paradox that the workplaces with LEV frequently do not exhibit lower exposures than those without LEV and the exposures may even be higher. EGBEA atmospheric concentrations for different painting activities are presented in table 4.12 bis.

Table 4.12 bis- Measurements results in the MEGA database for paint application (BGAA, 2002)

Type of company/ working area	No of measurements	No of companies	95% value ppm (mg/m^3)
Painting, brush and roller, filling work	23	14	Note A
without LEV	12	8	Note A
with LEV	8	6	Note A
Spraying	189	81	1.7 (11.55)
without LEV	33	13	1.8 (12.10)
with LEV	150	67	1.7 (11.50)
Surface coating, mechanical	129	70	Note A
- without LEV	71	37	Note A
with LEV	50	33	Note A
Surface coating, general	65	35	Note A
without LEV	25	16	1.6 (11.00)
with LEV	33	18	Note A

Note A : measurement value < analytical determination limit

The sum of the measurements with and without technical measures (ventilation) may be lower than the number of measurements for the particular type of company / work area since information on technical measures (ventilation) is not included in the data in all cases.

Modelling

Exposure to vapours during the use of paints is estimated by EASE to be in the following range:

- 0.5 - 1 ppm (3.3 – 6.7 mg/m^3) for non dispersive use, low tendency to become airborne, with LEV (industrial painting)
- 100 - 140 ppm (666.1 – 932.6 mg/m^3) for wide dispersive, low tendency to become airborne, direct handling and dilution ventilation (industrial or decorative painting).

The model overestimates exposure levels, particularly because of non-consideration of the content of EGBEA in the mixtures. The estimates cannot be corrected for the partial vapour pressure because the composition of the formulations is not known. A simple approach based on a reduction of the exposure by a factor equivalent to the EGBEA concentration in the mixture would lead to exposure levels of:

- 0.1 – 0.2 ppm (0.67 – 1.33 mg/m^3) (with LEV) or 20 - 28 ppm (133.2 – 186.5 mg/m^3) (without LEV) for use of industrial paints containing up to 20 % EGBEA
- 5 - 7 ppm for use without LEV of decorative paints containing up to 5 % EGBEA.

However the validity of these estimates is rather questionable.

Exposure to EGBEA during painting may be extremely variable, due to differences in frequency and duration of use, concentration of EGBEA in the paint, method of application and precautions taken during use.

Analogous data

For EGBE, exposure during painting may be also extremely variable for the same reason as above. To some extent, this variation is reflected in the atmospheric monitoring data available for EGBE during painting and surface treatment.

(SIDS, 1996) proposed a maximum atmospheric concentration of 10 ppm (49.1 mg/m^3) for use of a paint/surface coating containing 10 % EGBE, the justification for this estimation is not clear. On the basis of the available data, results of air monitoring are generally much lower except during spraying.

For spraying (EGBE), the available measured data are mainly extracted from the COLCHIC (Vincent, 1999) and the MEGA databases (BGAA, 2001). The 90th percentile of the MEGA database values (11.6 ppm or 57 mg/m^3) seems to be the most representative worst-case inhalation exposure.

For other application techniques (EGBE), inhalation exposure is likely to be lower. The 95th percentile of the COLCHIC and MEGA databases results are lower than 4 ppm (19.6 mg/m^3). The highest result from the largest study (Vincent, 1996) is 6.2 ppm (30.5 mg/m^3). This value will be used for risk characterisation to ensure that highly exposed workers are represented.

In conclusion, the following worst case inhalation exposures were adopted in the RAR EGBE:

- 11.6 ppm (57.01 mg/m^3) for spray application of paint
- 6.2 ppm (30.47 mg/m^3) for other application techniques

Statement of the level exposure

Although limited, the measured exposure data related to painting and collected for EGBEA in databases or reported in the study of Vincent are always lower than 2 ppm (13.3 mg/m^3). In the MEGA database, the highest 95th percentile value for painting, 1.8 ppm (12.1 mg/m^3), was obtained for spraying without LEV. For Coating/painting (other work as surface coating (mechanical or general)), the highest 95th percentile value is 1.6 ppm (11 mg/m^3).The EASE estimates seem to high compared to real situations.

In conclusion, the value of 2 ppm (13.3 mg/m^3) will be regarded as valid to represent the reasonable worst case exposure to EGBEA during painting for spraying, other work or decorative scenario; this value is somewhat lower (but in the same order of magnitude) than the values retained in the RAR EGBE for the scenario “Painting/surface coatings”(see above the values 11.6 ppm and 6.2 ppm).

Dermal exposure

Measured data

As for the scenario 2 "formulation of products containing EGBEA, dermal exposure", there are no available measured dermal data for EGBEA; because of the similarity between the EGBEA and EGBE physicochemical properties and also between their specific uses, a read-across approach to the exposure results available on EGBE is proposed for EGBEA. Since no measured data are available to predict occupational dermal exposure to EGBEA, modelling on EGBEA and conclusions of the dermal exposure of EGBE will be used.

Skin contact due to manual transfer of liquids, spray application and brushing, rolling and cleaning is to be expected. In several of the available references, the importance of skin exposure is stressed.

Modelling

SIDS (1996) retained continuous skin contact over the work period (8 hours) and a 1000 cm^2 skin area exposed (a hand and a forearm). Intermittent contact seems more appropriate for tasks as brushing and rolling in this scenario. For spray application, extensive contact is assumed. For wide dispersive use, the EASE model estimates a dermal exposure in the range of 1-5 mg of product/cm^2/day for intermittent contact and 5-15 mg of product/cm^2/day for extensive contact. The estimation is made from a formulation containing up to 20 % of EGBEA (industrial paint) and a formulation containing up to 5 % of EGBEA (decorative paint) and an exposed skin surface area of 840 cm^2 (two hands for consistency with other EU occupational risk assessments).

Daily dermal exposure= EASE estimation*EGBEA concentration*exposed skin surface area

This leads to estimated external dermal exposures of:

- 168-840 mg/day for industrial painting (excluding spray application) with intermittent contact,
- 840-2520 mg/day for industrial spray painting with extensive contact,
- 42-210 mg/day for decorative painting with intermittent contact.

Dermal exposure may be lower if suitable gloves are worn. However, personal protective equipments are rarely worn during painting.

Read-across approach to the exposure results available on EGBE

For the scenario "industrial coating/painting (spraying application), the dermal exposure to EGBE was determined as following:

- the exposure levels from industrial spray application apparently depend on the scale of application, as well as on control measures in use. Without further information, it is assumed that large scale application with limited exposure control can be done with paints containing up to 20% EGBE. The measured values over short periods cannot be extrapolated towards longer periods, because this would lead to over saturation of the skin. Therefore, a reasonable

worst case exposure level of 10,000 mg product per day is assumed, based on the levels mentioned in the TGD and the measurements by Hughson *et al.* (2004). This leads to an estimated exposure to EGBE of 2000 mg on 840 cm^2. Because EGBE is much more volatile than the measured substances, this may be an overestimation. Also, if less large scale tasks are done, the exposure levels may be substantially lower. These uncertainties should be taken into account in the evaluation of the MOS.

This estimation was made from a formulation containing up to 20% EGBE which is the same concentration as for EGBEA : considering the read-across approach to the exposure results available on EGBE, the skin exposure of 2,000 mg/day is proposed for EGBEA and the scenario "industrial coating/painting (spraying application)".

For the scenario "industrial coating/painting (other works as brushing and rolling)" and the scenario "industrial decorative coating/painting", the dermal exposures to EGBE were obtained from biomonitoring data (Delest and Desjeux, 1995 ; Haufroid, 1997 ; Vincent *et al.*, 1996):

- 430 mg/day of EGBE (industrial coating/painting (other works as brushing and rolling)) for formulations containing 20% EGBE
- 70 mg/day of EGBE (industrial decorative coating/painting) for formulations containing 3% EGBE

Statement of the level exposure

For EGBEA, it is proposed to use EGBE dermal exposure values taking into account that the used concentration of EGBEA for industrial decorative coating/painting is 5% and not 3% as for EGBE and that the reasonable worst case exposure level of the product containing EGBEA could be estimated at about 430:0.2 = 2150 mg/day.

Calculations lead to the following dermal exposures for EGBEA:

- 2150*20% = 430 mg/day of EGBEA for industrial coating/painting (other works as brushing and rolling)

- 70*5%/3% = 117 mg/day of EGBEA for industrial decorative coating/painting

And EGBE exposure value for of 2000 mg /day will be used for EGBEA industrial spraying application.

- **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 % (BP, 2002). Typical maximum contents of 35 % EGBEA in silk-screen inks and 20 % in others will be assumed in this assessment.

Inhalation exposure

Measured data

A maximum exposure to EGBEA of 0.75 ppm (4.9 mg/m^3) was reported for workers in a screen printing operation in the United States (Clapp *et al*., 1984 reported in ATSDR, 1998).

EGBEA was found in personal air samples from 5 of 19 workers in 4 Swedish silk-screen printing facilities (Johanson *et al*., 1989), at an average time-weighted concentration of 2.9 mg/m^3 (0.44 ppm) (range 0.1-10 mg/m^3 [0.015 - 1.5 ppm]). BAA was found in the urine of 12 of the 19 workers at an average concentration of 8 mol/L (1.2 mg/L) (range 4 - 29 mol/L or 0.6 – 4.2 mg/L).

More recent but limited exposure measurements made in 2001 and provided by one of the main producer of screen printing inks in the EU have been presented by industry (BP, 2002). "Print shop" includes screen printing only. "Reclaim" concerns screens reclaimed for use. It involves ink removal with a solvent blend, addition of an oxidising agent to remove the photostencil from the mesh and considerable quantities of water. "Other" includes litho and digital inkprinting.

Table 4.13 - Personal breathing zone monitoring to EGBEA in the screen printing industry (BP, 2002)

Activity	No of sampling	Average ppm (mg/m3)	Maximum ppm (mg/m3)	5-95 % percentile ppm (mg/m3)
Print shop	41	0.33 (2.2)	2.14 (14.3)	0.03-0.94 (0.2-6.3)
Reclaim	6	0.12 (0.8)	0.34 (2.3)	0.04-0.28 (0.3-1.9)
Other	2	2.94 (19.6)	3.33 (22.2)	

From 1987 to 1998, the French COLCHIC database collected 10,593 personal sampling results of glycol ethers for 602 facilities (Vincent, 1999). Exposure to EGBEA was measured for general printing activities (41 samples) and silk screening activities (61 samples). Exposure duration ranged from 60 to 480 minutes. The distribution of the results is presented in table 4.13 bis.

Table 4.13 bis - Personal exposure for general printing industry and silk screening activities, years 1987-1998, in ppm (mg/m^3) (Vincent, 1999)

Activity	No of sampling	Median	Arithmetic mean. ppm(mg/m^3)	Range ppm (mg/m^3)	95th percentile ppm (mg/m^3)
Printing industry	41	0.85 (5.7)	0.07-5.25 (0.5-35)	0.3 (2)	4.5 (30)
Silk screening	61	2	0.54 (3.6)	0.07-5.25 (0.5-35)	1.65 (11)

Modelling

Exposure to vapours during printing is estimated by EASE to be in the following range:

- 0.5 - 1 ppm (3.3 – 6.7 mg/m^3) for non dispersive use with LEV and low tendency to become airborne,
- 100 - 140 ppm (666.1- 932.6 mg/m^3) for wide dispersive, direct handling and dilution ventilation and low tendency to become airborne.

The model overestimates exposure levels, particularly because of non-consideration of the content of EGBEA in the products. The estimates cannot be corrected for the partial vapour pressure because the composition of the formulations is not known. A simple approach based on a reduction of the exposure by a factor equivalent to the EGBEA concentration in the mixture (35% for screen inks and 20% for others) would lead to exposure levels of:

- for silk screening (formulation at 35%) 0.18-0.35 ppm (1.2 – 2.3 mg/m^3) or 35-49 ppm (233.1 – 326.4)
- for general printing (formulation at 20%) 0.1-0.2 ppm (0.7 – 1.3 mg/m^3) or 20-28 ppm (133.2-186.51).

However the validity of these estimates is rather questionable.

Read-across approach to the exposure results available on EGBE

Mainly based on the data from the French database COLCHIC, the reasonable worst-case exposures proposed for EGBE was the following:

- silk screening (including washing): 4 ppm (20 mg/m^3)

- general printing: 1 ppm (5 mg/m^3).

Statement of the level exposure

Although limited, the measured data related to printing collected for EGBEA in the databases or in studies are in the same order of magnitude as for EGBE. The highest 95th percentile values extracted from the study (Vincent, 1999) and related to the printing industry and silk screening are respectively 4.5 ppm (30 mg/m^3) and 1.65 ppm (11 mg/m^3). The EASE estimates seem to high compared to real situations.

In conclusion, the following values will be regarded as valid to represent the worst-case exposure during printing:

- silk screening (including washing): 1.65 ppm (11 mg/m^3)

- general printing: 4.5 ppm (30 mg/m^3).

Dermal exposure

Measured data

They are no available measured dermal data for EGBEA.

Modelling

Dermal exposure may occur during mixing, application and cleaning activities. Assuming direct handling and intermittent contact, the EASE model estimates a dermal exposure in the range of 0.1-1 mg of product/cm^2/day for non-dispersive use. The estimation is made from a formulation containing up to 35% (screen inks) or 20% (others) of EGBEA and an exposed skin surface area of 840 cm^2 (two hands for consistency with other EU occupational risk assessments). This leads to an estimated external dermal exposure of:

- 29 - 294 mg/day for silk screening (35%)
- 17 - 168 mg/day for general printing (20%).

Dermal exposure may be lower if suitable gloves are worn.

Analogous data from EGBE

As for the scenario 2 “formulation of products containing EGBEA, dermal exposure”, there are no available measured dermal data for EGBEA; because of the similarity between the EGBEA and EGBE physicochemical properties and also between their specific uses, a read-across approach to the exposure results available on EGBE is proposed for EGBEA.

For silkscreen printing, a set of 16 potential full shift hand exposure data extracted from a study performed in Finland by Kuopio Regional Institute of Occupational Health (KRIOH) (RISKOFDERM, 2003) is available and a 90^{th} percentile exposure level of 65 mg/day of product containing EGBE is reported. These measured values are based on a more than 12 measurements and come from different workplaces, they can be considered sufficiently representative for use in risk characterisation.

Statement of the level exposure

- Concerning general printing, no relevant exposure data are available. The EASE estimate therefore has to be used for risk characterisation: the retained value is 168 mg EGBEA/day.

- Concerning silkscreen printing, EGBE values of 65 mg/day will be used to derive an exposure value for EGBA. Assuming that the concentration of EGBEA in screen printing inks can be up to 35%, the reasonable worst case exposure level for EGBEA in this process would be approximately 65*35% = 23 mg/day.

In conclusion, the following range are proposed for dermal exposure during printing:

- 168 mg/day of EGBEA for general printing and 20% EGBEA concentration.

- 23 mg/day of EGBEA for silk screening.

4.1.1.2.4 Summary of occupational exposure

Proposed reasonable worst case occupational exposures

Table 4.14 - Summary of proposed reasonable worst case 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

4.1.1.3 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.

4.1.1.3.1 Exposure from uses

Scenario: Paints

EGBEA is used as a solvent in paints. Analysis of the information collected in the paint formulating industry by CEPE (2002) shows that the concentrations of EGBEA range from 0.5 to 20 % with an arithmetic mean up to 5.8 % (see table 4.10 in 4.1.1.2.3.1). Taking into account this data together with the information collected in European product registers (see 4.1.1.1), a maximum content of 20 % EGBEA in paints will be assumed in this assessment for industrial paints and 5 % for decorative paints.

As a conservative approach consumers will be considered using industrial paint containing 20% of EGBA.

No data was found about dermal and inhalation exposure of consumers by paints during their use or after their application.

Inhalation exposure

Measured data

Measured data exists for professional application of paint. A value of 2 ppm (13.3 mg/m^3) has been regarded as valid for professional exposure assessment. These data are based on (Vincent, 1996) study and MEGA database (BGAA, 2002). Vincent's (1996) study considers a concentration of glycol ether ranged from 1% to 100% in formulation used. For same applications, values from MEGA database are higher than values from Vincent's study. It could be estimated that concentration of formulation used in MEGA database are at least equal or higher than those of Vincent's study.
So use of 20% paint formulation by consumer is covered by professional exposure values.

Modelling

Modelling provides very high value of exposure:

- EASE: 133-266 mg/m^3 (20-40 ppm) (for wide dispersive, low tendency to become airborne, direct handling and taking into account a concentration about 20%.
- CONSEXPO leads to an event concentration of 972 mg/m^3 (146 ppm) by evaporation, a mean concentration on day of 243 mg/m^3 (36.5 ppm) and a concentration year average of 6.65 mg/m^3 (1.0 ppm) considering 10 event a year (see appendix A for modelling report).

Statement of the level of exposure

As all models give an overestimation of consumer exposures comparing to professional exposure value, we have chosen to consider that consumer's exposure will be lower than professional exposure. So the professional exposure value of 13.3 mg/m^3 will be used for consumer exposure assessment by inhalation.

Assuming an application time of 6 hours, a respiratory rate of 20 m^3/day and a bodyweight of 60 kg, the total inhalation exposure by paints is :

$$C_{tot} = \frac{20 \times 6 \times 13.3}{24 \times 60} = 1.11 \text{ mg/kg/d}$$

Dermal exposure

For dermal exposure, the transfer from paints to the skin of hands will be based on data used for the occupational exposure assuming a 5 mg paint/cm^2 of skin for a eight hours day of work. The duration of the event is 6 hours for a consumer, the surface of skin is 840 cm^2 (two hands) and the bodyweight of a consumer is 60 kg. The concentration of EGBEA in the paint is 20 % (CEPE, 2002).

So the exposure of skin to EGBEA from paints will be :

$$\frac{20 \times 5 \times 6 \times 840}{100 \times 8 \times 60} = 10.5 \text{ mg/kg/d}$$

4.1.1.3.2 Summary of consumer exposure

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 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 will be calculated to take into account the absorption rates.

4.1.1.4 Humans exposed via the environment

The information relating to the estimation of the indirect exposure of humans via the environment are presented in table 4.15. The concentrations calculated in intake media (drinking water, fish, plant roots and leaves, milk, meat, air) and the subsequent estimation of human intakes via different routes are shown hereafter with the corresponding total daily intakes. Both local and regional levels are taken into consideration and the estimation of local environmental exposures has been performed for all scenarios listed in chapter 3.1.2.2. Concerning the production step, only the worst case has been reported.

Table 4.15 - concentrations for indirect exposure of humans via the environment and subsequent total daily intakes (highest values for each exposure route appear in bold)

	Conc. in drinking water (mg.L^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in wet fish (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in plant roots (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in plant leaves (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in milk (mg.kg^{-1} ww) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in meat (mg.kg^{-1} ww) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in air (mg.m^{-3}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Total daily intake (mg.kg^{-1}.d^{-1})
Production (site-specific, worst case)	1.23.10^{-2} / 3.50.10^{-4}	4.45.10^{-4} / 7.30.10^{-7}	1.61.10^{-2} / 8.86.10^{-5}	3.39.10^{-4} / 5.82.10^{-6}	5.55.10^{-6} / 4.45.10^{-8}	5.68.10^{-7} / 2.44.10^{-9}	3.83.10^{-5} / 8.20.10^{-6}	4.54.10^{-4}
Paints F	2.39.10^{-2} / 6.82.10^{-4}	9.15.10^{-2} / 1.50.10^{-4}	1.24.10^{-2} / 6.81.10^{-5}	1.01.10^{-2} / 1.74.10^{-4}	1.76.10^{-5} / 1.41.10^{-7}	1.80.10^{-6} / 7.74.10^{-9}	1.77.10^{-3} / 3.80.10^{-4}	1.45.10^{-3}
Paints P	1.98.10^{-2} / 5.66.10^{-4}	7.59.10^{-2} / 1.25.10^{-4}	1.71.10^{-2} / 9.40.10^{-5}	**2.22.10^{-1} / 3.80.10^{-3}**	1.66.10^{-4} / 1.33.10^{-6}	1.70.10^{-5} / 7.29.10^{-8}	**3.91.10^{-2} / 8.38.10^{-3}**	1.30.10^{-2}
Paints U	7.15.10^{-4} / 2.04.10^{-5}	2.74.10^{-3} / 4.50.10^{-6}	2.36.10^{-4} / 1.30.10^{-6}	1.96.10^{-4} / 3.36.10^{-6}	4.51.10^{-7} / 3.62.10^{-9}	4.62.10^{-8} / 1.99.10^{-10}	3.43.10^{-5} / 7.35.10^{-6}	3.69.10^{-5}
Unknown F	5.56.10^{-3} / 1.59.10^{-4}	2.13.10^{-2} / 3.50.10^{-5}	2.81.10^{-3} / 1.54.10^{-5}	2.38.10^{-3} / 4.07.10^{-5}	4.11.10^{-6} / 3.29.10^{-8}	4.20.10^{-7} / 1.81.10^{-9}	4.15.10^{-4} / 8.89.10^{-5}	3.39.10^{-4}
Unknown P	**2.47 / 7.07.10^{-2}**	**2.61 / 4.28.10^{-3}**	**3.26 / 1.79.10^{-2}**	2.53.10^{-6} / 4.34.10^{-4}	**1.09.10^{-3} / 8.74.10^{-6}**	**1.12.10^{-4} / 4.80.10^{-7}**	1.05.10^{-4} / 2.24.10^{-5}	**9.33.10^{-2}**
Printing F	5.91.10^{-3} / 1.69.10^{-4}	2.26.10^{-2} / 3.72.10^{-5}	2.93.10^{-3} / 1.61.10^{-5}	5.62.10^{-4} / 9.63.10^{-6}	2.97.10^{-6} / 2.38.10^{-8}	3.04.10^{-7} / 1.31.10^{-9}	9.52.10^{-5} / 2.04.10^{-5}	2.52.10^{-4}
Printing P	9.78.10^{-4} / 2.80.10^{-5}	3.75.10^{-3} / 6.16.10^{-6}	4.43.10^{-4} / 2.43.10^{-6}	1.60.10^{-3} / 2.74.10^{-5}	1.56.10^{-6} / 1.25.10^{-8}	1.60.10^{-7} / 6.86.10^{-10}	2.82.10^{-4} / 6.03.10^{-5}	1.24.10^{-4}
Detergents F	3.85.10^{-3} / 1.10.10^{-4}	1.48.10^{-2} / 2.42.10^{-5}	1.87.10^{-3} / 1.03.10^{-5}	4.24.10^{-4} / 7.28.10^{-6}	1.98.10^{-6} / 1.59.10^{-8}	2.02.10^{-7} / 8.70.10^{-10}	7.23.10^{-5} / 1.55.10^{-5}	1.67.10^{-4}
Detergents P	7.23.10^{-4} / 2.06.10^{-5}	2.77.10^{-3} / 4.55.10^{-6}	3.44.10^{-4} / 1.89.10^{-6}	1.97.10^{-4} / 3.38.10^{-6}	4.55.10^{-7} / 3.65.10^{-9}	4.65.10^{-8} / 2.00.10^{-10}	3.43.10^{-5} / 7.35.10^{-6}	3.78.10^{-5}
Detergents U	7.53.10^{-4} / 2.15.10^{-5}	2.88.10^{-3} / 4.74.10^{-6}	2.52.10^{-4} / 1.38.10^{-6}	1.96.10^{-4} / 3.37.10^{-6}	4.68.10^{-7} / 3.75.10^{-9}	4.79.10^{-8} / 2.06.10^{-10}	3.43.10^{-5} / 7.35.10^{-6}	3.83.10^{-5}
Leather P	1.50.10^{-2} / 4.30.10^{-4}	9.50.10^{-3} / 1.56.10^{-5}	1.98.10^{-2} / 1.09.10^{-4}	3.46.10^{-4} / 5.93.10^{-6}	6.77.10^{-6} / 5.43.10^{-8}	6.93.10^{-7} / 2.98.10^{-9}	3.45.10^{-5} / 7.39.10^{-6}	5.68.10^{-4}
Cosmetics F	3.85.10^{-3} / 1.10.10^{-4}	1.48.10^{-2} / 2.42.10^{-5}	1.87.10^{-3} / 1.03.10^{-5}	4.24.10^{-4} / 7.28.10^{-6}	1.98.10^{-6} / 1.59.10^{-8}	2.02.10^{-7} / 8.70.10^{-10}	7.23.10^{-5} / 1.55.10^{-5}	1.67.10^{-4}
Cosmetics U	6.89.10^{-4} / 1.97.10^{-5}	2.64.10^{-3} / 4.34.10^{-6}	2.26.10^{-4} / 1.24.10^{-6}	1.96.10^{-4} / 3.36.10^{-6}	4.40.10^{-7} / 3.53.10^{-9}	4.50.10^{-8} / 1.94.10^{-10}	3.43.10^{-5} / 7.35.10^{-6}	3.60.10^{-5}
Regional	4.22.10^{-4} / 1.21.10^{-5}	1.62.10^{-3} / 2.66.10^{-6}	5.68.10^{-5} / 3.12.10^{-7}	1.95.10^{-4} / 3.34.10^{-6}	3.22.10^{-7} / 2.58.10^{-9}	3.22.10^{-8} / 1.42.10^{-10}	3.43.10^{-5} / 7.34.10^{-6}	2.57.10^{-5}

The highest indirect exposure is estimated for processing operations performed in unknown uses (Unknown P): $9.33.10^{-2}$ $mg.kg^{-1}.day^{-1}$. 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 $2.57.10^{-5}$ $mg.kg^{-1}.day^{-1}$. These two figures will be taken forward into the risk characterisation.

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

The molecule of 2-butoxyethanol acetate is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate (see 4.1.2.1). 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 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 (refer also to EGBE EU Risk Assessment Report Publication).

4.1.2.1 Toxicokinetics, metabolism and distribution

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.

4.1.2.1.1 *In vitro* studies

There is few toxicokinetic studies available on 2-butoxyethanol acetate. In the *in vitro* study available, the half life of 2-butoxyethylacetate in rat plasma was determined and is approximately 1 minute (0.96 minute). The molecule is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate. For that reason the systemic toxicity of EGBEA is practically equivalent to that of EGBE. The effective doses and adverse effects levels may be regarded as nearly identical on a molar basis (BASF, 1984 and Hoffman and Jackh, 1985).

Ester hydrolysis has been studied very well and is a key issue in the safety evaluation of flavouring substances (http://europa.eu.int/comm/food/fs/sc/scf/out158_en.pdf). The esters of primary alcohols and branched-chain carboxylic acids from chemical groups 1 and 2 reviewed by the Scientific Committee on Food in 2003, were expected to be hydrolysed enzymatically to carboxylic acids and alcohols via carboxylesterases found in most tissues throughout the body, the most important of which are the beta-esterases. Results of *in-vitro* studies indicate that the affinity of the esterases for their substrates increases as the chain length of the ester increases and that the rate of hydrolyses of the straight-chain esters is approximately 100 times faster than the rate of hydrolysis of the branched-chain esters (Arndt and Krisch, 1973 ; Junge and Heymann, 1979). It was finally assumed in this review that the examined esters will undergo hydrolysis either before or after absorption from the gastrointestinal tract, to yield their corresponding aliphatic alcohols and branched-chain carboxylic acids.

Overall, 2-butoxyethanol acetate is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate. Moreover, ester hydrolysis has been studied very well in the safety evaluation of flavouring substances and it was considered that the examined esters as flavouring agents will undergo hydrolysis either before or after absorption from the gastrointestinal tract, to yield their corresponding aliphatic alcohols and branched-chain carboxylic acids. It can therefore be anticipated that 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. Moreover as a reasonable estimate, it can be assumed that EGBEA have distribution, metabolism and excretion properties close to EGBE.

4.1.2.1.2 *Other data*

Comparison of the logKow of EGBEA to EGBE shows that EGBEA has a LogKow of 1.51 whereas EGBE has a LogKow of 0.8. This higher LogKow can increase dermal penetration but the higher molecular weight of EGBEA could also decrease dermal penetration in comparison to EGBE.
A comparison of the LD50 values obtained in the acute studies is summarised below.

For the dermal route with EGBEA, the results of the two of the three acute studies performed on rabbits (see 4.1.2.2.1), consistently showed a LD_{50} lesser than 2,000 mg/kg bw. Overall, a LD_{50} of about 1,500 mg/kg bw can be taken into account for EGBEA. For EGBE, depending on the application (occlusive or not), the LD_{50} was 500 mg/kg bw or > 2000 mg/kg bw respectively. The calculated LD_{50} for EGBEA on a molar basis would be 678 mg/kg bw or > 2,712 mg/kg bw, respectively whereas the identified LD50 with EGBEA was about of 1,500 mg/kg. It tends to indicate that absorption of EGBEA by dermal route is slightly lower than absorption of EGBE. But in the other hand the values obtained with EGBEA are obtained from quite old studies.

For other glycol ethers such as PGMA (acetate of methoxypropanol), it was found that dermal absorption was approximately 30% of that of PGME (1-methoxypropan-2-ol) in rats based on experimental data. But this ratio of 3 cannot be use in the EGBEA assessment due to insufficient information for a read-across from the PGME (1-methoxypropan-2-ol) data to the EGBE.

So finally in a weight basis, a reasonable estimation of the dermal absorption would be based as a start on the established figure for EGBE.

For the inhalation route, the LC50 identified for EGBEA were higher than 400 ppm (see 4.1.2.2.1), whereas for EGBE, LC50 of 450 ppm - 486 ppm were identified. However, it does not seem accurate to refine quantitatively the absorption rate determined with EGBE. So a reasonable estimation of the inhalation rate absorption of EGBEA will be based on EGBE value.

For the oral route, the LD50 values obtained with EGBEA (see 4.1.2.2.1), are quite in the same range as the LD50 values obtained with EGBE. So it seems accurate to consider that the oral absorption rate of EGBEA is in the same range as EGBE and that the EGBE oral rate absorption value should be kept.

Summary of absorption data on EGBE:

Three studies were reported in which human volunteers were exposed to EGBE by inhalation route (Johanson and Fernström,1988 ; Johanson and Johnsson, 1991 ; Kumagai *et al*., 1999). Theoretical absorption (calculated) of EGBE via inhalation route was found to be 80 %. However, measurements performed showed a real absorption of 55 to 60 %. This difference is explained by a "wash in / wash out" mechanism: due to its hydrophilic properties, EGBE is adsorbed to the surface of the respiratory tract during inspiration and it desorbed during exhalation leading to a decrease in the real uptake of substance. In the risk characterisation section, a 60 % of absorption for EGBE inhalation is used.

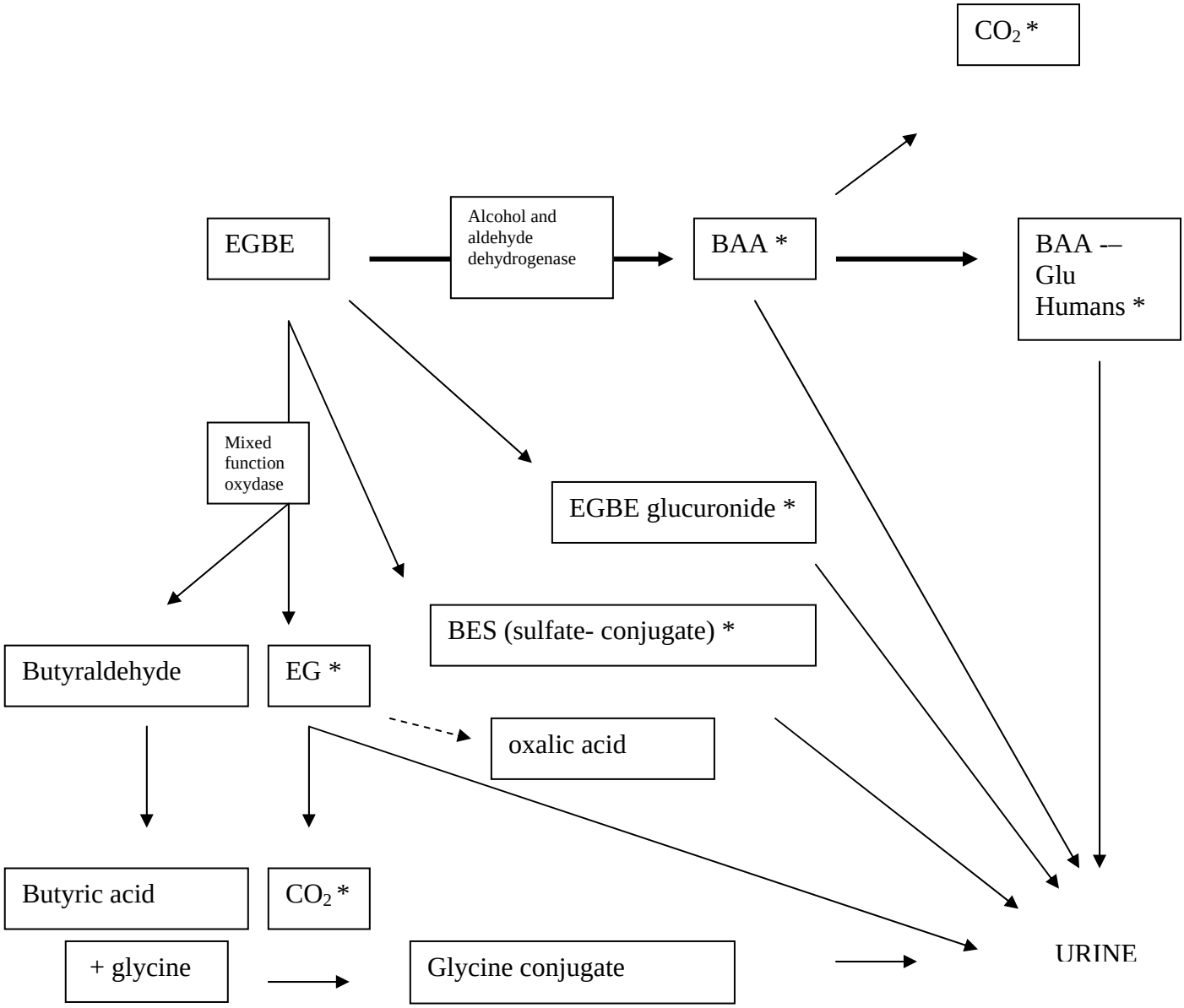
Via dermal route, uptake of liquid EGBE depends on the administration mode, the species and the concentration of EGBE in the final product. An occlusive administration will be responsible of a great percutaneous uptake whereas a non-occlusive administration will minimize absorption due to the volatility of EGBE. Rat skin seems to be readily permeable compared to pig or human skin (2 or 3 fold more) (Bartnik *et al*., 1987). Percutaneous uptake also depends on the EGBE concentration in the tested product : for 40 and 80 % aqueous solutions of EGBE, absorption was demonstrated to be maximum (Johanson and Fernström, 1988). In two rat studies, dermal absorption of liquid EGBE was estimated to be between 20 and 30 % (Bartnik *et al*., 1987).

In one *in vivo* study, percutaneous absorption of vapour EGBE was assessed (Jones, 2003). Depending on the external conditions during exposure, the internal dose of EGBE due to percutaneous absorption varies between 11 % and 39 %. The percentage of 11 % was found for "normal" conditions of use (temperature, humidity) and 39 % for the worst case of industrial use (high temperature, high humidity and overalls wearing). This worst-case percentage is use in the risk assessment section to estimate the internal dose of EGBE due to dermal absorption of vapour EGBE.
Absorption of EGBE orally administered was rapid and essentially complete (assumed to be 100 %) (Ghanayem *et al*., 1987).

Summary of distribution, metabolism and excretion data on EGBE:

- EGBE reaches a maximum blood concentration rapidly after exposure whichever the route of exposure. EGBE is rapidly metabolised (with a plasmatic half life of about an hour).
- After absorption, the substance is distributed by the blood way to all organs. The blood peak is reached in the 2 hours after a skin or inhalation absorption whatever the species considered
- The main metabolism pathway leads to the formation of butoxyacetic acid (BAA) 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. Minor metabolites of EGBE are also reported depending on the species used (see figure 4.1).

Figure 4.1: Metabolism of EGBE (Patty, 2001)



Materials identified with an asterisk (*) have been identified in either rodents or humans.

Elimination is rapid and mainly via urinary route (80 to 90 % of the metabolites). The plasmatic half-life of metabolites is about 4 hours. A small amount is eliminated as CO_2 by the respiration (10 to 20 %). Normal renal excretion is conditioned by physiological state of the kidneys: females excreted less rapidly BAA than males and aged animals have a trend to eliminate metabolites with more difficulties than young animals. Any renal injury will enhance BAA toxicity by increasing its blood persistence.

However if renal integrity is respected, a repeated administration of EGBE lead to an adaptation of the metabolism. 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.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

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 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. Moreover, 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.

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

- 100% via oral route;
- 60% via inhalation route;
- for dermal route, extrapolation is likely to be equal or less than EGBE (see 4.1.2.1.2). It can be assumed that dermal penetration of liquid EGBEA would be of about 30 % and vapour EGBEA of about 39 %.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Inhalation

In an old study (Smyth *et al*., 1962), the maximum period of time of exposure to concentrated vapour with no death was estimated. Six Female albino rats (no precisions on strains) survived to an 8-hour period at a concentrated vapour concentration “not precised”. Groups of rats were exposed to EGBEA at a highly saturated vapour-air mixture generated at two different temperatures (20° C and 120° C) and during variable periods of time (BASF, 1963 in IUCLID). The number of rats varies between the experiments.

Mortality and evidences of haemoglobinuria are summarised in the table 4.16.

Various animals (3 cats, 3 rabbits, 10 guinea-pigs, 10 rats and 20 mice) were exposed to a saturated vapour concentration of EGBEA (ca. 460 ppm) at 20°C (BASF, 1965 in IUCLID) during 6 hours. With the exception of the rats, the other animals were used two times under the same conditions for the investigation of acute inhalation toxicity. Between each investigations, there was a period of 6 days without any treatment.

All animals survived to the treatment. Cats showed symptoms of irritation to the mucus membranes and the rats showed severe haemoglobinuria.

The reliability of this study is questionable because of methodological deficiencies (all animals were exposed together in one inhalation chamber).

In a series of studies, (Truhaut *et al*., 1979) have studied the acute and chronic toxicological properties of EGBEA. In each study, the following parameters were assessed:

- Urinalysis: blood, pH, proteins, glucose, ketone bodies and nitrites
- Haematology: red blood cells and white blood cells counts, blood haemoglobin
- Pathology: brain, lungs, heart, liver, spleen, pancreas, kidneys, bladder, adrenals and testes or ovaries were checked for gross pathological examination and fixed, sectioned and stained for histological examinations.

For the acute inhalation study, groups of 10 rats (male and female) and 4 rabbits (2 males and 2 females) were exposed during 4 hours to saturated EGBEA air-vapour mixture (approximately 400 ppm). Animals were kept under observation for 14 days after exposure.

All animals survived to the treatment, a slight and transient haemoglobinuria and/or haematuria were observed in rabbits (not lasting over 24 to 48 hours). After sacrifice, no gross pathological lesions were noted. Histologically, all animals exhibited renal lesions, mainly lesions of tubular nephrosis, the severity increasing with the dose. According to the authors, all the lesions observed were probably due to the haemolysis.

Table 4.16 - Summary of EGBEA animal studies for acute inhalation exposure

Species	Exposure time (h)	LC_{50} (mg/L)	Observations and Remarks	Reference
Rats (females)	8 h	> concentrated vapour conc.	No death in 6 females exposed to "concentrated vapour concentration".	Smyth *et al.*, 1962
Rats		> saturated vapour conc.	Animals were exposed to highly saturated vapour-air mixture in various conditions: - 20°C, 3h: mortality: 0/6, haemoglobinuria: 5/6 - 20°C, 8h: mortality: 2/18, haemoglobinuria: 18/18 - 120°C, 30 min: mortality: 0/6, haemoglobinuria: 1/6 - 120°C, 3h: mortality: 0/12, haemoglobinuria: 12/12	BASF, 1963
Cats, rabbits, guinea pigs, rats and mice	6 h	> 3.06 mg/L	No mortality at the saturated vapour concentration at 20°C (ca. 460 ppm or 3.06 mg/L). Cats showed symptoms of irritation to the mucus membranes and the rats showed severe haemoglobinuria. The reliability of this study is questionable because of methodological deficiencies (all animals were exposed together in one inhalation chamber).	BASF, 1965
Rats (n=10) and rabbits (n=4)	4 h	> 2.66 mg/L	No mortality at the saturated vapour concentration (ca. 400 ppm or 2.66 mg/L). A slight and transient haemoglobinuria and/or haematuria were observed in rabbits (not lasting over 24 to 48 hours). No gross pathological lesions were noted.	Truhaut *et al.*, 1979

Summary inhalation route:

Quite old studies are available to assess acute toxicity by inhalation route. Low concentrations were tested and it can only be inferred that LC_{50} is probably above 3 mg/l. Symptoms of haemolysis were observed. It should be noted that this value corresponded to a value greater than the saturated vapour value and therefore would correspond to an aerosol exposure.

Symptoms of haematotoxicity are similar to those observed with EGBE with a LC_{50} for EGBE between 450 and 486 ppm (approximately 3.0 to 3.23 mg/l) estimated for inhalation exposure. An extrapolation from EGBE data will be contradictory with the results from the studies available on EGBEA. It may indicate that absorption of EGBEA in the respiratory tract is lower than absorption of EGBE. Although the studies are old and some have

methodological deficiencies, data on EGBEA consistently indicate a low order of acute toxicity by inhalation and the existing classification Xn; R20 was removed.

Dermal

In a series of studies, LD50 was calculated using male New Zealand rabbits (4/group) dosed by dermal route occlusively during a 24-hour period (Smyth *et al*., 1962).

After a 14-day observation period, the estimated LD50 was 1.58 ml/kg (1,485 mg/kg bw).

A LD_{50} of 4,700 mg/kg bw was calculated in guinea-pigs (Eastman Kodak, 1971).

Acute dermal toxicity was studied in rabbits with a modified Draize protocol (Truhaut *et al*., 1979). Six rabbits were used per dose level. EGBEA was applied during 24 hours occlusively. Animals were observed during 14 days after application. An approximation of the LD50 was performed at the end of the study. In the series of studies performed by Truhaut, some parameters were analysed after termination of the studies (see 4.1.2.2.1 inhalation for the details of the urinalysis, haematology and pathology performed).

The LD_{50} was approximately 1,500 mg/kg bw. Animals generally died between 24 and 48 hours after application, and no later than 4 days. Haemoglobinuria and haematuria was observed in some animals. When animals did not die from intoxication, the lowest red blood cells counts and haemoglobin values were reached after 48 to 72 hours and then progressively returned to normal after 8 to 14 days. Necropsy revealed bloody kidneys and the presence of a high quantity of blood in the bladder. Histologically, all animals exhibited renal lesions, mainly lesions of tubular nephrosis, the severity increasing with the dose. According to the authors, all the lesions observed were probably due to the haemolysis.

Table 4.17 - Summary of EGBEA animal studies for acute dermal exposure

Species	Exposure time (h)	LD_{50} (mg/kg)	Observations and Remarks	Reference
New Zealand rabbits (male)	24h (occlusive)	1,485 mg/kg		Smyth *et al*., 1962
Guinea pigs		4,700 mg/kg		Eastman Kodak, 1971
Rabbits (n=6)	24h (occlusive)	1,500 mg/kg	Animals generally died between 24 and 48 h after application, and no later than 4 days. Haemoglobinuria and haematuria was observed in some animals.	Truhaut *et al*., 1979

Summary dermal exposure for EGBEA:

On the three studies available for EGBEA, two were performed on rabbits and consistently showed a LD_{50} lesser than 2,000 mg/kg bw. The main toxicity symptoms were haemolysis and associated lesions. Overall, a LD_{50} of about 1,500 mg/kg bw can be taken into account for rabbits. A classification Xn; R21 is applied.

Summary dermal exposure for EGBE:

Depending on the application (occlusive or not) the LD_{50} was 500 mg/kg bw or > 2000 mg/kg bw respectively and a classification Xn; R21 is applied. The calculated LD_{50} for EGBEA on a molar basis would be 678 mg/kg bw or > 2,712 mg/kg bw, respectively.

Overall, the comparison of these dermal LD50 values on rabbits may indicate that absorption of EGBEA by dermal route tends to be lower than absorption of EGBE. However, these information cannot be used in a quantitative manner to refine the dermal absorption rate based on EGBE data.

Oral

Rat studies

In a series of studies, LD_{50} was calculated using male Carworth Wistar rats (5/group) dosed by oral route (Smyth *et al*., 1962). After a 14-day observation period, the estimated LD_{50} was 7.46 ml/kg (7,012 mg/kg bw).

Rats were given orally a 30 % emulsion (in Traganth) of EGBEA (BASF, 1963 cited in IUCLID). No more details on the protocol used are available for the moment. The LD_{50} calculated was 2,350 mg/kg bw. Animals showed blood in the urine and a decreased in haemoglobin 2-3 days after the treatment. Females were more sensitive than males.

EGBEA diluted in olive oil was administered to groups of Wistar rats to determine the per oral LD_{50} (Truhaut *et al*., 1979). The determination of the LD_{50} was made after a 14-day observation period. In the series of studies performed by Truhaut, some parameters were analysed after termination of the studies (see 4.1.2.2.1 inhalation for the details of the urinalysis, haematology and pathology performed).

LD_{50} for male rats was 3,000 ± 300 mg/kg bw and 2,400 ± 200 for females. No animals died after Day 3 of administration. Haemoglobinuria and/or haematuria were observed and decreased progressively for over one week. At necropsy, kidneys were hypertrophic and dilated with blood.

A LD_{50} value of 1,600 mg/kg bw in rats, has been reported without details, in a summary table (Nelson, 1981). This value is considered doubtful.

Mouse studies

A LD_{50} of 3,200 mg/kg bw was calculated in mice (Eastman Kodak, 1971 cited in Bibra 1987)

Mice were given orally a 20 % emulsion (in Traganth) of EGBEA (BASF, 1963 cited in IUCLID). No more details on the protocol used are available for the moment.

The LD_{50} calculated was 2,820 mg/kg bw. Animals showed blood in the urine.

Rabbit studies

EGBEA was administered orally in aqueous emulsion with Traganth at a concentration 10 % (940 mg/kg bw) and 2 % (188 mg/kg bw) to groups of three rabbits (BASF, 1964 cited in IUCLID).

The LD_{50} calculated was ca. 940 mg/kg bw. 2 of 3 animals dosed with the high concentration died within two days after the treatment. Severe haemoglobinuria and anemia were recorded. The blood values of the surviving rabbit returned to normal within three weeks after treatment. In the lower dose group, no mortality occurred.

EGBEA was administered orally to rabbits at doses of about 987 mg/kg bw and 1,983 mg/kg bw to three animals/group (BASF, 1967 cited in IUCLID).

All animals died after treatment. Clinical symptoms were atonia, convulsions, increased breathing and hyphema. In the animals of the low dose group, haemoglobinuria, low haematocrit, lymphopenia, leukocytosis and degeneration in all blood cell fraction was found. In the urine of all animals renal epithelia, erythrocytes and haemoglobin were observed. Increased blood urea was found in the high-dose animals. Pathological examinations were increased kidney weights, nephrosis, lung oedema, fatty degeneration of liver and heart and disturbed lymphopoiesis.

Cat studies

Two cats were treated with aqueous emulsion of EGBEA in Traganth at concentrations of 10% (which correspond to a dose of 940 mg/kg bw), 5 % (which correspond to a dose of 470 mg/kg bw) and 2 % (which correspond to a dose of 188 mg/kg bw) (BASF, 1964 cited in IUCLID).

No mortality occurred and no haemoglobinuria was observed.

EGBEA animal studies for acute oral route are summarised in table 4.18:

Table 4.18 - Summary of EGBEA animal studies for acute oral route

Species	LD_{50} (mg/kg)	Observations and Remarks	Reference
Wistar rats (males)	7,012 mg/kg	-	Smyth *et al.*, 1962
Rats	2,350 mg/kg	Animals showed blood in the urine and a decrease in haemoglobin 2-3 days after treatment. Females were more sensitive than males.	BASF, 1963
Rats	Males: 3,000±300 mg/kg Females: 2,400±200 mg/kg	No animals died after Day 3 of administration. Haemoglobinuria and/or haematuria were observed and decreased progressively for over one week. At necropsy, kidneys were hypertrophic and dilated with blood.	Truhaut *et al.*, 1979
Rats	1,600 mg/kg	Only LD_{50} value is reported.	Nelson 1981
Mice	3,200 mg/kg	-	Eastman Kodak, 1971
Mice	2,820 mg/kg	Animals showed blood in the urine.	BASF, 1963
Rabbits	ca 940 mg/kg	2 of 3 animals dosed with the high concentration (940 mg/kg) died within two days after the treatment. Severe haemoglobinuria and anemia were recorded. The blood values of the surviving rabbit returned to normal within three weeks after treatment. No mortality occurred at 188 mg/kg.	BASF, 1964
Rabbits	< 987 mg/kg	3 animals/group were dosed with 987 mg/kg or 1983 mg/kg. All animals died after treatment. Clinical symptoms were atonia, convulsions, increased breathing and hyphema. In the animals of the low dose group, haemoglobinuria, low haematocrit, lymphopenia, leukocytosis and degeneration in all blood cell fraction was found. In the urine of all animals renal epithelia, erythrocytes and haemoglobin were observed. Increased blood urea was found in the high-dose animals. Pathological examinations were increased kidney weights, nephrosis, lung oedema, fatty degeneration of liver and heart and disturbed lymphopoieses.	BASF, 1967
Cats	> 940 mg/kg	No mortality occurred and no haemoglobinuria was observed at 188, 470 or 940 mg/kg (2 animals/group)	BASF, 1964

Summary oral route (EGBEA data):

Some studies are available to assess acute oral toxicity using various animals. The toxicological effects were mainly haemolysis and associated lesions. All the studies are old ones, with some uncertainties about the purity and the experimental procedure, but indicate that rabbits are more sensitive with a LD_{50} around 940 mg/kg.

Summary oral route (EGBE data):

Based on EGBE results, recent studies, performed according to well defined experimental methods (Carpenter *et al*., 1956 ; Eastman Kodak, 1994) have given results between 1,000 and 2,600 mg/kg in rats. In mice, available studies exhibited LD_{50} ranging from 1,000 to 2,000 mg/kg. One study was performed in rabbits showing a LD_{50} ranging from 320 to 370 mg/kg, confirming that rabbits are more sensitive for acute toxicity via oral route. In guinea pigs, the LD_{50} calculated were 1,414 and 1,200 mg/kg. If an extrapolation is made from EGBE on a molar basis, the calculated LD_{50} for EGBEA would be 1,356-3,525 mg/kg, 1,356-2,712 mg/kg, 437-502 mg/kg and 1,627-1,917 mg/kg for rats, mice, rabbits and guinea pigs, respectively.

Overall, based on EGBEA data and EGBE, it was proposed and agreed to classify EGBEA harmful by oral route, Xn; R22.

Other routes

Mice were treated i.p. with an 8 % emulsion of EGBEA in Traganth (BASF, 1963 cited in IUCLID).

The calculated LD50 was ca. 752 mg/kg bw. Haemoglobinuria was recorded in treated animals.

4.1.2.2.2 Studies in humans

No data is available in humans for EGBEA.

Summary of human data available on EGBE data:

Data available for EGBE give the following results (see table 4.19):

Table 4.19: Summary human acute toxicity data

Estimation of absorbed dose	Patient pathology	Reference
Between 0.5 and 1 mg/kg bw	50-year woman. Suicide attempt with glass cleaner. Coma, metabolic acidosis, hypokaliemia, increase in serum creatinine level and urinary excretion of oxalate crystals	Rambourg-Schepens *et al*., 1988.
About 1 g/kg bw	23-year woman. Suicide attempt with mixture containing EGBE. Coma, breathing difficulties and metabolic acidosis. Haematuria and decreased Hb for 2 days.	Gijsenbergh *et al*., 1989.
About 750 mg/kg bw	53-year man. Suicide attempt with mixture containing EGBE. Coma, tachycardia, metabolic acidosis, hypoxemia, pulmonary oedema and ARDS. Non haemolytic anaemia with thrombopenia.	Bauer *et al*., 1992.
About 1.25 g/kg bw – 2 times separated by 9 days	18-year man. Ingestion of a glass cleaner. Metabolic acidosis and hepatic biochemical disorders. Nothing after the second ingestion.	Gualtieri *et al*., 1995, Gualtieri *et al*., 2003.
About 4.5 g/kg bw.	19-year man. Ingestion of a mixture containing EGBE. Coma, acidosis and haematuria.	Burkhart and Donovan, 1998
Between 0.4 and 1.2 g/kg bw	51-year woman. Ingestion of a mixture containing EGBE. Metabolic acidosis and mental status depression.	Mc Kinney *et al*., 2000

In conclusion, and according to this data, a LOAEL of 400 mg/kg bw can be taken into account for acute toxicity by oral route in humans. It should be noted that this is a worst case estimation derived from the Mc Kinney paper in which the possible range of exposure was between 0.4 and 1.2 g/kg bw.

4.1.2.2.3 Specific toxicity: haematotoxicity of EGBE

Mechanistic studies on the haematotoxicity of EGBE

The main toxicological property of EGBE is haematotoxicity. This is due to the metabolite BAA a metabolite of EGBE. EGBE toxicological properties (especially haematotoxicity) have been extensively studied. These studies are summarised below:

Mechanistic studies have shown that EGBE causes haematotoxicity *in vivo* in rats and that BAA causes the same effects *in vitro* at very low concentration. When metabolic pathways leading to the formation of BAA were blocked, no effects were seen on RBC. It can be concluded that BAA is responsible of hematotoxicity *in vivo*.

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 and humans (at least 30 x less sensitive than rats). In one study, dogs were very sensitive to EGBE but not to BAA.

In these studies, an increased sensitivity to haemolysis was seen in old animals and in females *in vitro* and *in vivo* with BAA, showing that the differences of metabolism between male and female could not explain totally sex difference.

In vivo or *in vitro*, haemolysis was due to a decrease of erythrocyte deformability due to erythrocyte swelling (this also explains the formation of thrombosis). 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, a study (Lomonova and Klimova, 1977) showed that repeated exposure to EGBE, 3 hours a day, 6 days a week for 4 months was more haematotoxic than the exposure to the same dose of EGBE, 6 hours a day, 3 consecutive days a week for 4 month. This study demonstrates an adaptive mechanism of "protection" when animals have a period of recovery time before a re-exposure to EGBE.

The mechanism leading to erythrocyte swelling and loss of deformability is for the moment unknown. Apparently, there is no evidence of oxidative mechanism on erythrocyte membrane. A recent study (Udden, 2002) showed that, at low doses of BAA in rats, the increase of Na^+ intra-erytrocytaire was not balanced by decrease in K^+. This mechanism leads to osmotic regulation causing an increase in the size and the cell volume of erythrocytes, a decrease of the density and of the deformability and an increase of the osmotic fragility. This mechanism could be different in humans because at high doses, no major changes in cell density and no morphological changes were seen. In humans erythrocytes, slight effects were seen with doses of 8 mM and 4 mM of BAA in vitro (Ghanayem, 1989).

Few data are available to assess the acute toxicity of EGBEA. If compared with EGBE, it can be considered that EGBEA is harmful by oral with a classification and labelling Xn; R22 and dermal with a classification and labelling Xn; R20 but not by inhalation route.

Oral route:

Based on EGBEA data and EGBE, it is proposed to classify EGBEA harmful by oral route, Xn; R22.

Respiratory route:

The extrapolation from EGBE data is contradictory with the results from the studies available on EGBEA. It may indicate that absorption of EGBEA in the respiratory tract is lower than absorption of EGBE. Although the studies are old and some have methodological deficiencies, data on EGBEA consistently indicate a low order of acute toxicity by inhalation, so the Classification and Labelling Committee has proposed to delete the existing classification Xn; R20.

Dermal route:

Based on EGBEA data, a LD_{50} of about 1500 mg/kg bw can be taken into account for rabbits and the current classification Xn; R21 is maintained.

A number of human case studies are available from attempted suicides which suggests that the human LOAEL for EGBE is in the region of 400 mg/kg bw. The extrapolation from EGBE on a molar basis shows a LOAEL of 542 mg/kg bw for EGBEA. Human data is preferred for risk characterisation, especially for EGBE and EGBEA, because its haematotoxicity is more marked in animals than in humans.

4.1.2.3 Irritation

4.1.2.3.1 Skin

Studies in animals

Primary skin irritation on rabbits has been recorded using a 10-grade scale based on the severity of the reaction observed on the belly skin of five albino rabbits exposed to EGBEA uncovered for a 24-hour period of time (Smyth *et al*., 1962). No irritation was seen in this study.

Undiluted EGBEA was administered onto rabbit skin: on the back for exposure times of 1, 5, 15 minutes and 20 hours (BASF, 1963 cited in IUCLID), and also 20 hours on the skin of the ear.

After 20 hours of exposure to the skin of the back, a questionable reddening was seen at the 24-hour post exposure observation time. No effects were seen after 1, 5 or 15 minutes of exposure. For the ear application, a slight redness and necrosis at the edge of the ear was seen at the 24-hour post exposure and a marked necrosis 7 day after. According to the criteria used, EGBEA was not irritating in this experiment.

Five or six rabbits were submitted to a skin irritation test (Jacobs *et al*., 1987). EGBEA was placed onto the shaved skin by means of a modified Finn chamber. The chamber contained a patch soaked with 0.5 ml of liquid substance or a dilution thereof (in sweet almond oil). The dilutions of the test substance used were 50, 25, 10 and 5 %. A second exposure chamber containing 0.5 ml of the control vehicle served as control. According to the authors, the scoring of erythema and oedema was performed according to the scale of Draize at 1, 24, 48 and 72 h after the removal of the patch. No individual results are presented. So, we consider that the study was insufficient for assessment. In this study, EGBEA is not irritant. This result is doubtful because method and documentation are insufficient for assessment.

EGBEA was tested for Primary Irritation on the intact and abraded skin of six rabbits using a modified Draize protocol (Truhaut *et al*., 1979). Four of the six rabbits showed very slight erythema (grade 1) at 24 hr. There was no perceptible irritation at 72 hours. The calculated PDII was 0.17.

0.5 ml of pure EGBEA was applied during 4 hours to the skin of six New Zealand white rabbits (Jacobs *et al*., 1989). Erythema was scored according to the scale of Draize at 1, 24, 48 and 72 hours after the removal of the patch but no individual results are presented. The mean values over all six rabbits for each observation time is given in the table 4.20.

Table 4.20: mean erythema scores obtained for each observation time for the 6 rabbits

Observation time	1h	24h	48h	72h
Erythema scores (standard deviation)	2.33 (0.80)	0.50 (0.55)	0.50 (0.55)	0.67 (0.57)

According to these values, EGBEA can be considered as a moderately skin irritant.

A skin irritation test was conducted in rabbits (CEC, 1990 in Lawrence *et al*., 1996) with twelve chemicals to compare in vivo data to in vitro data obtained with cytotoxicity tests on rat and human keratinocyte cultures. Six animals were exposed (occluded) to undiluted liquid EGBEA during 4 hours. Mean scores for erythema and oedema were calculated at 1, 24, 48 and 72 hours after test patch removal. The sum of the mean erythema and oedema scores was normalized to the amount of EGBEA applied at both the 1-hour and 24-hour observation point. In addition, an overall mean value for the sum of erythema and oedema scores at each individual time point was calculated and normalized to the amount of EGBEA applied.

The following results are summarised in table 4.21.

Table 4.21 – skin irritation data in the CEC study

Rabbit skin irritation data					
Concentration	PDII	Irritant class	Mean erythema score + mean oedema score Normalised to the amount of EGBEA applied		
			1 hour	24 hours	1 – 72 hours
100 %	0.08	Non-irritant	0.005	0.002	0.002

These results were compared to in vitro data. A good correlation was found between *in vivo* and *in vitro* data.

Cutaneous irritation due to EGBEA was assessed in New Zealand rabbits (Zissu, 1995) according to 2 test methods: EEC test or Draize protocol.

For the EEC method, 0.5 ml of EGBEA were applied occlusively on the shaved flank of three rabbits for 4 hours. The mean erythema and oedema scores were calculated for each animals at 24, 48 and 72 hours after application.

For the Draize method, 0.5 ml of EGBEA were applied occlusively on the two shaved flanks of six rabbits for 24 hours (intact and scarified skin). For each animal, a Primary Dermal Irritation Index (PDII) was determined.

For both methods, at 72 hour after application, histological control of the skin at the site of application was performed.

According to EC scoring, EGBEA was classified non irritant and according to the Draize method, EGBEA was considered as a slight irritant with a PDII of 1.3.

Studies in humans

Cutaneous Blood Flow Values (CBFV) were determined on humans, before and after patch application of EGBEA (Jacobs *et al.*, 1989). In a first study, each patch contained 83 µl/cm^2 of undiluted test substance on the forearm of eight volunteers and left under occlusion for 48 hours. The CBFV was measured 12 hours later.

In a second series of experiments, 10 % solution of EGBEA in water was applied on the forearm of four volunteers for an exposure period of 3 hours.

Readings were performed at 1, 24, 48 and 72 hours. CBFV were corrected according to control values post exposure.

Maximum CBFV values were observed at the 24-hour observation time: 7.5 (+/- 1.3) in comparison to 5 (+/- 0.8) for the blank. The results obtained, compared to other results obtained with animal and in vitro data, showed that EGBEA is only a slight skin irritant.

In vitro studies

Cultures of KB cells (an established cell line, derived from an oral epidermoid carcinoma) were incubated with various concentrations of EGBEA during 4 hours (Jacobs *et al.*, 1989). An uridine uptake assay was performed on these cultures. The toxicity was established by determination of the UI50 (concentration required to induce a 50 % inhibition of the uridine uptake – calculated by linear regression).

The values obtained in this assay were not in good correlation with human or animal results obtained in the same study. Therefore this test cannot be taken into account to assess the skin irritation properties of EGBEA.

Undiluted EGBEA was applied to a three-dimensional in vitro human skin analog (skin2) (De Wever and Rheins, 1994). The tissue was exposed to the test material for five minutes. 24 hours after exposure cell viability was determined by using the MTT assay.

The MTT value was 96 %. This value, close to 100 %, indicates that tissues are still viable. The in vitro data obtained with this model yielded a good correlation to the in vivo data of Draize primary dermal irritation scores (PDII). The PDII for EGBEA is 0.08 (a chemical is classified as irritant if PDII value is greater than 2).

EGBEA in DMSO solutions was tested in human keratinocyte cultures for the determination of NR50 (neutral red) and Acid Phosphatase (AP) peak values (Dickson *et al.*, 1994).

NR50 was about 4.6 mg/ml and mean AP (peak) was 8 mg/ml. These results are indicative that EGBEA is a slight irritant substance.

Skin irritation potential was assessed by exposing human and rat keratinocyte cultures to EGBEA (purity 98 %) (Lawrence *et al.*, 1996). Cultures were exposed to solutions of EGBEA in DMSO for 3 hours for determination of intracellular Acid Phosphatase (AP) activity and for 18 hours for measurement of Neutral Red (NR) uptake. The results obtained were compared with in vivo data.

The cytotoxicity determined by the intracellular assay was comparable in rat and human keratinocyte (AP_{PK} value of 16,000 µg/ml for both species). NR uptake assay data also demonstrated a similar response in rat and human keratinocyte assay (NR_{50} values of 4,600 µg/ml and 2,900 µg/ml in human and rat respectively). Overall, this test demonstrated a good correlation between *in vivo* and *in vitro* data.

A study was performed to investigate if PGE2 was indicative of the ability of various chemicals (including EGBEA – considered to be a non irritant control) to induce human skin irritation (Lawrence *et al*., 1997). EGBEA (purity 98 %) in DMSO solutions was added to human keratinocytes cultures for a 18 hour period. Neutral Red (NR) uptake assay was performed and the levels of PGE2 were determined.

The upper concentration selected (8,000 µg/ml) produced cellular injury as indicated by NR50 values. The lower concentration used elicited NR uptake at levels comparable to those of control cultures (1,000 µg/ml).

NR50 values for EGBEA was 4,600 µg/ml. No significant increases in extracellular PGE2 levels were observed, even at concentrations that produced extensive cell damages (indicated by NR50 value).

In this test PGE2 levels were in good correlation with the supposed irritant properties of the tested chemicals. EGBEA can therefore be considered as a non-irritant substance.

Summary skin irritation

Several skin irritation studies are available on EGBEA. Most of them are poorly reported and do not follow the experimental conditions recommended in the European guidelines but they all indicate that EGBEA is not irritant or slightly irritant. The studies by (Jacobs *et al*., 1987) and (Zissu, 1995) were realised in accordance with the guidelines and although individual results are not presented, the authors concluded in both studies that the substance is not a skin irritant according to the European classification criteria.

No classification is therefore proposed for skin irritation.

4.1.2.3.2 Eye

Studies in animals

Eye irritation in rabbits was recorded in a 10-grade ordinal series, based on the corneal necrosis observed after instillation of EGBEA in the eye (Smyth *et al*., 1962). A grade 2 was recorded. In the grading system, grade 1 indicated a very small area of necrosis resulting from the application of 0.5 ml of undiluted chemical and grade 5 corresponded to a severe burn from 0.005 ml of chemical. Otherwise, this is a very old study and the grading system is specific to this study. No conclusion can be drawn for eye irritation from this study.

Undiluted EGBEA was instilled in the eye of rabbits (BASF, 1963 cited in IUCLID). Observation times after treatment were 1 and 24 hours and 8 days. Slight redness and oedema were seen only 1 hour after application. No effects were recorded for the other observation times. In this study, EGBEA is considered as not irritating.

EGBEA was tested for eye irritation on six rabbits using a modified Draize protocol (Truhaut *et al*., 1979). Only two of six rabbits showed slight conjunctival redness and discharge in the first 24 hours. At 48 hours and thereafter, no irritation was apparent. According to these results, EGBEA can be considered to be non-irritant.

In vitro studies

Twenty one reference chemicals (including EGBEA 99 % pure) were examined in the Chicken Enucleated Eye Test (CEET). No effect regarding corneal swelling was observed

whereas only a slight effect regarding corneal opacity and fluorescein retention was noted. This demonstrates that EGBEA is a slight eye irritant. Twenty one chemicals, including EGBEA, were tested in a FRAME fluorescein leakage test (Clothier *et al*., 1994). A dose of 50 mg/ml was applied on a confluent layer of Madin-Darby canine kidney cells. The percentages of fluorescein leakage following and 72 h after one minute of exposure to EGBEA were 11 ± 6 % and 2 ± 0.3 % respectively. According to this result, EGBEA did not need any classification for eye irritancy. But as this method is an *in-vitro* alternative test for assessing eye irritancy not already validated in guidelines, this result should not be taken into account.

Summary eye irritation

The animal studies performed showed that EGBEA is a slight and transient eye irritant substance.

EGBEA was also tested in vitro and alternative test to the standard Draize or EC test as a slight irritant control substance. In the majority of these tests, the results were that it was not an eye irritant substance, as expected.

No classification is therefore proposed for eye irritation.

4.1.2.3.3 Respiratory tract

Cats, exposed to 460 ppm of EGBEA, showed symptoms of irritation to mucus membranes (BASF, 1965 reported in section 4.1.2.2.1). This concentration of 460 ppm is above the saturated vapour pressure of 395 ppm (at 20°C). However, the reliability of this study is questionable due to methodological deficiencies. No other animal or human studies are available.

Summary of respiratory tract data on EGBE:

Animal studies available (including repeated dose toxicity studies performed by inhalation on rats and mice) did not show any signs of significant respiratory irritation. No classification is required for this end-point for EGBE. From the human data with EGBE, it is apparent that the NOEC for respiratory irritation is > 50 ppm (expressed in EGBE) whilst the NOEL (based on effects of discomfort) is <100-200 ppm. A NOEC of 50 ppm was taken forward for risk characterisation.

Overall, considering EGBEA data and the fact 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.

4.1.2.3.4 Summary of 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.

4.1.2.4 Corrosivity

EGBEA was tested in an in vitro test to assess its corrosive properties (Corrositex method) (Gordon *et al*., 1998). No evidence of corrosion was observed. Moreover, only very slight irritation signs were observed in the in-vivo skin irritation studies.

According to EU classification criteria EGBEA cannot be considered as a corrosive substance.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In vivo studies

In a GLP sensitisation study performed according to the Buehler protocol, EGBEA (purity 99.1 %) was tested on 20 guinea pigs (Huls, 1998). Induction and challenge phases were made with undiluted substance. The test was performed according to the European technical guideline B6.

In a preliminary test, EGBEA was administered on the shaved skin of 3 guinea pigs occlusively during 6 hours, pure or diluted in corn oil at concentration of 5, 25 or 50 %. After removal of the patch, dermal reactions were assessed at 30 and 54 hours after the start of treatment. All test substance formulations did not cause any skin irritation on the 3 animals at each control time.

For the main study, pure EGBEA was applied occlusively on the skin of 20 guinea pigs during 6 hours on days 0 (induction phase I), 7 (induction phase II) and 14 (induction phase III). The skin reactions were observed 30 hours after the treatment. Grading was done according to Magnusson and Kligman grading scale. On day 28, animals were submitted to a challenge treatment (pure EGBEA, occlusively during 6 hours), animals were observed for signs of irritation 30 and 54 hours after administration.

No irritation was observed after application of pure substance. No effects were seen after challenge at the two observation times.

Respiratory tract

Considering SAR in the glycol ether family, the wide dispersive use of them and that no glycol ether has even been associated with cases of respiratory sensitisation, it can be considered that this toxicological property cannot be expected and is not relevant for risk assessment.

4.1.2.5.2 Studies in humans

No data.

4.1.2.5.3 Summary of sensitisation

In an adequate Buehler test, no signs of dermal sensitisation were seen. Considering SAR in the glycol ether family, the wide dispersive use of EGBEA and absence of any indication of EGBEA-induced dermal sensitisation in the exposed population, it is concluded that EGBEA has no sensitising properties and further testing is not considered necessary.

Considering SAR in the glycol ether family, the wide dispersive use of them and that no glycol ether has even been associated with cases of respiratory sensitisation, it can be considered that this toxicological property cannot be expected and is not relevant for risk assessment.

4.1.2.6 Repeated dose toxicity

The molecule of 2-butoxyethanol acetate is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate (see 4.1.2.1). 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 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 systemic repeated dose toxicity of EGBEA is mainly due to its metabolite EGBE. In addition to the studies performed specifically with EGBEA, the results obtained with EGBE are summarised and will be taken into account for the human health assessment.

4.1.2.6.1 Studies in animals

Inhalation

Rat studies

In a four-week inhalation study, ten rats were exposed to EGBEA six hours per day, five days per week at concentration of about 340 ppm (BASF, 1965 cited in IUCLID).

Four rats died before the last treatment. From the second exposure onwards the animals showed apathy, lateral position, hyperpnoea and some of the animals seemed to be anemic. Haemoglobinuria was observed after the first and the second exposure but not after. Haemoglobin was decreased at the beginning of the study but returned to normal from the 13th exposure onwards. Effects were more marked in females than in males.

Groups of 20 rats (10 of each sex) were exposed 4 hours/day, 5 days/week for one month to saturated air-vapor mixtures of EGBEA, corresponding to approximately 400 ppm (Truhaut *et al*., 1979). 2/3 of the rats were sacrificed at the end of the experiment, the others were allowed a one-week recovery period before sacrifice. In the series of studies performed by Truhaut, some parameters were analysed after termination of the studies (see also 4.1.2.2.1 for the details of the urinalysis, haematology and pathology examination performed).

No significant differences in body weight gains were observed between treated and control animals. From Week 2 of exposure onwards, animals started to show slight haemoglobinuria and/or haematuria.

At necropsy, kidneys were hypertrophic, swollen with blood. All other animals showed no pathology. Histologically, slight to severe lesions of tubular nephrosis, ranging from a simple cellular cloudy swelling to haemorrhagic necrosis, were seen in females when sacrificed just

after the last exposure. After one week of recovery, reversibility of the lesions was complete. In males no alterations were found. According to the authors, all the lesions observed were certainly due to the haemolysis.

Groups of 20 rats (10 males and 10 females) were exposed 4h/day, 5d/week during 10 months to a concentration of 100 ppm EGBEA (Truhaut *et al*., 1979). In the series of studies performed by Truhaut, some parameters were analysed after termination of the studies (see also 4.1.2.2.1 for the details of the urinalysis, haematology and pathology examination performed).

No effects were observed during and after the study. In the male rats, very discrete and inconstant renal lesions characterised by a few areas of tubular nephritis with tubular enlargement or atrophy in the cortical zone, together in some cases with inflammatory fibrosis and a dilatation of the Henle's loop and of the distal convoluted tubules. In a few cases a tubular enlargement with hyaline casts. In the female rats, some areas of tubular nephritis were observed in the exposed animals but also in the controls.

Mouse studies

In a four-week inhalation study, twenty mice were exposed to EGBEA six hours per day, five days per week at concentration of about 340 ppm (BASF, 1965 cited in IUCLID).

Six mice died between exposure 4 and exposure 15, however eight of twenty mice died in the control group. Clinical symptoms, particularly haemoglobinuria were not observed. Necropsy did not reveal any particular findings.

Guinea pig studies

In a four-week inhalation study, ten guinea pigs were exposed to EGBEA six hours per day, five days per week at concentration of about 340 ppm (BASF, 1965 cited in IUCLID). Eight of the ten animals used in this study were already investigated in an acute inhalation study in which they were exposed during six hours to a EGBEA concentration of 460 ppm.

No mortality occurred in this test and no findings were observed.

Rabbit studies

In a four-week inhalation study, three rabbits were exposed to EGBEA six hours per day, five days per week at concentration of about 340 ppm (BASF, 1965 cited in IUCLID). These animals were already investigated in an acute inhalation study in which they were exposed during six hours to a EGBEA concentration of 460 ppm.

All animals died after 4 or 11 exposures. A decrease in haematocrit or in haemoglobin was recorded after some exposures. All animals also exhibited haemoglobinuria at the beginning of the exposure period. At necropsy, signs of haemolytic anaemia were found in two of three rabbits.

One group of four rabbits (2 males and 2 females) were exposed 4 hours/day, 5 days/week for one month to saturated air-vapor mixtures of EGBEA, corresponding to approximately 400 ppm (Truhaut *et al*., 1979). In the series of studies performed by Truhaut, some parameters were analysed after termination of the studies (see also 4.1.2.2.1 for the details of the urinalysis, haematology and pathology examination performed).

No significant differences in body weight gains were observed between treated and control animals. From Week 2 of exposure onwards, animals started to show severe haemoglobinuria and/or haematuria. RBC counts and Hb were normal during the first three weeks of treatment and decreased slightly in two animals and severely in the other two. These latter two rabbits died during week 4. At necropsy, their kidneys were hypertrophic, swollen with blood, and their bladders were full of blood. All others animals showed no gross pathological lesions when sacrificed. Histologically, all rabbits showed necrotizing tubular nephrosis, atrophic tubular dilatation, and luminar granular deposits. At necropsy, all rabbits showed necrotizing tubular nephrosis, atrophic tubular dilatation and luminar granular deposits. According to the authors, all the lesions observed were certainly due to the haemolysis.One group of four rabbits (2 males and 2 females) were exposed 4h/day, 5d/week during 10 months to a concentration of 100 ppm EGBEA (Truhaut *et al.* , 1979). In the series of studies performed by Truhaut, some parameters were analysed after termination of the studies (see also 4.1.2.2.1 for the details of the urinalysis, haematology and pathology examination performed).

No effects were observed during and after the study. Histologically, slight renal lesions were seen in treated rabbits compared to controls. Renal lesions characterised by a few areas of tubular nephritis with tubular enlargement or atrophy in the cortical zone, together in some cases with inflammatory fibrosis and a dilatation of the Henle's loop and of the distal convoluted tubules are only observed. Those effects were observed as well in the control animals but to a lesser extent.

According to (Truhaut *et al*., 1979), all the renal damage observed may have resulted either from haemolysis or from direct action of the glycol metabolites on the kidney, inducing haematuria. The first hypothesis was considered by the author as the most probable as the marked anemia observed is more likely to have resulted from haemolysis than from true haematuria; the histological examinations have shown no oxalate crystals in the tubules.

Cat studies

In a four-week inhalation study, three cats were exposed to EGBEA six hours per day, five days per week at concentration of about 340 ppm (BASF, 1965 cited in IUCLID). These animals were already investigated in an acute inhalation study in which they were exposed during six hours to a EGBEA concentration of 460 ppm.

Salivation and nausea were noted during the first exposure and hyperpnoea during the second exposure. A decrease in haemoglobin (about 45 % after the fourth exposition) was observed and returned to normal values after 9 exposures. No haemoglobinuria nor liver impairment was seen in this study.

Summary of inhalation route

In studies performed with EGBEA, signs of haematotoxicity and associated lesions were seen on all species except guinea pigs. N(L)OAEC were tentatively determined and are summarised in the table 4.22. However due to the limitations of these studies, only one concentration tested, a limited number of tested animals, the lack of quantitative information and the fact that some of the effects were also observed in the control group and that these studies were quite old, it was considered that more robust studies available on EGBE should be preferably used.

It was therefore considered that these studies are not reliable for risk assessment. The results obtained with EGBE studies can be taken into account (see summary of inhalation route (EGBE data)).

Table 4.22 – Summary EGBEA Repeated Dose Toxicity studies by inhalation route

Study	NOAEC (ppm)	Effects	Reference
Rats			
4 weeks, 6hr/d, 5d/w, 340 ppm	-	Mortality, apathy, hyperpnoea, anemia.	BASF, 1965
4 weeks, 4hr/d, 5d/w, 400 ppm	LOAEC : 400 ppm (in females)	Haemoglobinuria and haematuria. Renal lesions.	Truhaut *et al*., 1979
10 months, 4h/d, 5d/w, 100 ppm.	NOAEC ≤ 100 ppm	Very slight renal lesions but also seen in controls.	Truhaut *et al*., 1979
Mice			
4 weeks, 6h/d, 5d/w, 340 ppm	-	Mortality (6/20 but 8/20 in controls)	BASF, 1965
Rabbits			
4 weeks, 6h/d, 5d/w, 340 ppm	-	Mortality (3/3). Signs of haemolytic anaemia in all animals.	BASF, 1965
4 weeks, 4hr/d, 5d/w, saturated air-vapour mixture	LOAEC : 400 ppm	Mortality (2/4) Haemoglobinuria and haematuria	Truhaut *et al*., 1979
10 months, 4h/d, 5d/w, 100 ppm.	LOAEC : 100 ppm	Very slight renal lesions seen also in controls but to a lesser extent.	Truhaut *et al*., 1979
Guinea pigs			
4 weeks, 6h/d, 5d/w, 340 ppm	NOAEC = 340 ppm	No findings	BASF, 1965
Cats			
4 weeks, 6h/d, 5d/w, 340 ppm	-	Sign of haematotoxicity (decrease in haemoglobin)	BASF, 1965

Summary of inhalation route (EGBE data)

Many studies assessing EGBE are available on rats, and mice. A few short studies using dogs, guinea-pigs and non human primates have also been conducted.

In rats and mice, common toxicity signs together with effects similar to those observed in acute administration. The main effect was haemolysis, which was consistently observed and sometimes associated with secondary hepatic effects (Kupffer cells pigmentation and absolute and relative liver weight increases). Other effects were decreases of body weight gain, hyaline degeneration of the olfactive epithelium, effects on the forestomach and effects on the WBC sub-populations (T lymphocyte). In these studies, a NOAEC of 25 ppm in rats (Bushy Run Research Center, 1981) and a LOAEC of 31 ppm in mice and rats can be established based on haemolysis, as the only significant primary effect (NTP, 2000). The LOAEC of 31 ppm (coming from a six month satellite group in the NTP, 2000 104-week study) is taken into account for the risk characterisation.

Dermal

No data are available for EGBEA repeated dose toxicity by dermal route.

Summary of dermal route (EGBE data)

Two studies are available on rabbits to assess the toxicity of repeated doses of EGBE administered dermally. In one study, signs of toxicity were recorded and were limited to transient signs of haemolysis on rabbits. This study led to a NOAEL of 450 mg/kg bw/d due to haematological effects seen at 900 mg/kg bw/d. (Bushy Run Research Center, 1980). Given that this study was performed only during 9 days, the NOAEL of the second study on rabbits, which was performed during 13 weeks, could be more reliable for the risk characterisation. This NOAEL was 150 mg EGBE/kg bw/d (Wil Research Lab., 1983).

A mouse study, designed for the assessment of EGBE effects on the immune system, gives a NOAEL of 1,000 mg/kg bw/day.

The NOAEL of 150 mg/kg bw/day was considered in the Risk Assessment Report of EGBE for repeated dose toxicity, following dermal exposure. The cross-reading with EGBE data is performed and a NOAEL of 150 mg EGBE/kg bw i.e. 203 mg EGBEA/kg bw was taken into account for the repeated toxicity by dermal route (cf extrapolation factor, 4.1.3).

Oral

Rat and mice studies

No data are available for EGBEA repeated dose toxicity by oral route on rat.

Summary of oral route (EGBE data)

Six studies on rats and two on mice are available on EGBE. Effects seen by oral route were body weight reduction, haemolysis, hepatic effects and local irritation effects. Irritation to the forestomach was seen after gavage dosing and, to a far lesser extent, after subcutaneous and intraperitoneal injection. This difference is most likely due to the higher local concentration after gavage dosing. Overall, a LOAEL of 69 and 82 mg/kg bw/d of EGBE (in males and females respectively) can be fixed in a three-month study detailed below.

EGBE (lot no. BT00504LP, Aldrich Chemical Co., USA, purity ≈ 99 %) was administered in drinking water at concentrations of 0, 750, 1500, 3000, 4500 or 6000 ppm to groups of 10 male and 10 female F344/N rats for 13 weeks. These concentrations provided target dose levels of 0, 100, 150, 250, 400 or 650 mg/kg bw per day. Estimates of compound

consumption based on water consumption by rats were 69, 129, 281, 367 and 452 mg/kg/day for males and 82, 151, 304, 363 and 470 mg/kg/day for females. Supplemental groups of 10 rats/sex/group/time point were included for haematology and clinical chemistry observations at weeks 1 and 3 (NTP, 1993).

No NOAEL was identified in this study, based on cytoplasmic alterations in hepatocytes of both male and female rats at 750 ppm, equal to 69 mg EGBE/kg bw per day (i.e 94 mg EGBEA/kg bw/d) and 82 mg EGBE/kg bw per day (i.e. 111 mg EGBEA/kg bw/d) in males and females respectively.

Rabbit studies

In a five-week gavage study, three rabbits were treated with about 188 mg/kg EGBEA per day, five days per week (BASF, 1964 cited in IUCLID). These animals were already investigated in an acute peroral toxicity study in which they were administered 188 mg/kg EGBEA only one time. Clinical symptoms were recorded and haematological investigations, examination of liver function, urine analysis and pathological examinations at necropsy were performed.

With the exception of a slightly decreased haematocrit in two of three rabbits at the end of the study, no other substance related findings were observed.

Cat studies

In a five-week gavage study, two cats were treated with about 188 mg/kg EGBEA per day, five days per week (BASF, 1964 cited in IUCLID). These animals were already investigated in an acute peroral toxicity study in which they were administered 188 mg/kg EGBEA only one time. Clinical symptoms were recorded and haematological investigations, examination of liver function, urine analysis and pathological examinations at necropsy were performed.

Slight imbalances were seen in one animal. At the end of the study a decrease in the number of erythrocytes and of haemoglobin of about 30-50 % were found. These findings were reversible in 2-3 weeks. No haemoglobinuria was observed.

Summary oral route

Limited data is available for assessing the toxicity of EGBEA by oral route. Signs of haematotoxicity were observed in the two available studies and in the two species tested. EGBE testing has given the following results : effects seen by oral route were body weight reduction, haemolysis, hepatic effects and local irritation effects. Overall, a LOAEL of 69 and 82 mg EGBE/kg bw/d (in males and females respectively) can be fixed based of the NTP study (1993).

On a molar basis, an extrapolation of this EGBE LOAEL to an EGBEA LOAEL would be about 94 and 111 mg EGBEA/kg, for males and females respectively.

Summary of repeated dose toxicity studies on 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 sub-populations (T lymphocyte). In these 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 NOAEL will be taken into account in deriving appropriate assessment factors.

Slight effects on the immune system were seen in rats, mice and humans on NK cells or T lymphocyte sub-population. In the human study, co-exposure to a number of chemicals does not allow reliable conclusions to be drawn for EGBE alone. In the rodent studies, however a NOAEL of 1000 mg/kg bw in mice by dermal route can be established. The effects seen were small. A role of EGBE in the induction of immunotoxicity has not been developed to a point where it can be used in risk characterisation.

For the dermal route, an 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 found in a 13 -week drinking water study (haemolytical effects).

As humans are far less sensitive than other species (except Guinea Pig) to the haemolytical properties of EGBE, we have tried to assess separately haemolytical effects and related effects and other specific toxic effects which could be induced by EGBE. For all the studies, no specific relevant toxic effects, other that haemotoxicity, can be identified.

For the risk characterisation, haemotoxicity will be the end point chosen keeping in mind the interspecies differences (human/rodents) to calculate margin of safety. No other lesion has been identified which can be specifically attributed to treatment with EGBE.

4.1.2.6.2 Studies in humans

No data

4.1.2.6.3 Summary of 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. 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 (see 4.1.2.6.1).

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.

For oral route, a LOAEL of 94 and 111 mg/kg/day for male and female rats expressed in EGBEA (haemolytical effects) was derived from a 13 week oral study in rats with EGBE where a LOAEL of 69 and 82 mg/kg/day for male and female rats respectively was derived for EGBE.

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.

The identified N(L)OAEL(C) for EGBE or EGBEA are summarised in the table 4.22bis:

Table 4.22 bis: LOAEL(C) / NOAEL(C) for EGBE and EGBEA

	Oral	Inhalation	Dermal
End point	LOAEL	LOAEC	NOAEL
EGBE Value	69 mg/kg bw/day (male rat)	31 ppm (152 mg/m³)	150 mg/kg bw/day
EGBEA value	94 mg/kg bw/day (male rat)	31 ppm (206 mg/m³)	203 mg/kg bw/d

As humans are far less sensitive than other species (except Guinea Pig) to the haemolytical properties of EGBEA, we have tried to assess separately haemolytical effects and related effects and other specific toxic effects which could be induced by EGBEA. For all the studies, no specific relevant toxic effects, other that haemotoxicity, can be identified. For the risk characterisation, haemotoxicity will be the end point chosen keeping in mind the interspecies differences (human/rodents) to calculate margin of safety. No other lesion has been identified which can be specifically attributed to treatment with EGBEA.

4.1.2.7 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.

Studies *in vitro*

No data on EGBEA.

4.1.2.7.1 Studies *in vivo*

No data on EGBEA.

Summary of mutagenicity data on EGBE:

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 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. The same publication reported a significant result at 20 mM with BAL, whereas another study found no effect at concentrations up to 7.6 mM. There have been no mammalian cell mutation studies with BAA.

There have been reports of significant activity of EGBE in tests for SCE induction and cell transformation, but, again, the results have been inconsistent. Furthermore, the significant SCE results could be artefacts due to cell cycle delay. There is also some indication of inhibition of gap-junctional intercellular communication in a single study with EGBE and its two major metabolites. A single assay for UDS induction used a technique that is now considered to be invalid, if a significant response is obtained.

No evidence for chromosomal aberration induction has been found in a number of mammalian cell culture studies with EGBE, or in one with BAL 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 possibility of non-disjunction occurring and not being detected in these assays appears to be remote, because BAA produced no evidence of aneugenicity *in vitro*. BAA is rapidly formed *in vivo* and is by far the most prevalent blood metabolite of EGBE, so exposure of possible target cells to either EGBE or BAL at high concentrations is brief. The balance of the evidence suggests that EGBE do not pose a significant mutagenic potential *in vivo*.

In vivo genotoxicity test in mammals for EGBE and its metabolites are summarised in table 4.23:

Table 4.23: *In vivo* tests in mammals for the genotoxicity of EGBE and its metabolites

Test system	Source & purity of chemical	Result[a]	Dose[b] (LED/HID)	Reference
EGBE				
DNA adducts, Sprague-Dawley rat brain, kidney, liver, spleen & testis, *in vivo* (^{32}P-post-labelling)	Merck, Germany 99 %	- (at 24 h)	120 mg/kg bw orally x 1	Keith *et al*., 1996
Methylation level of DNA, Sprague-Dawley rat brain, kidney, liver, spleen & testis *in vivo*	Merck, Germany 99 %	-		Keith *et al*., 1996
Methylation level of DNA, FVB/N transgenic mouse brain, kidney, liver, spleen & testis *in vivo*	Merck, Germany 99 %	-		Keith *et al*., 1996
Micronucleus test, CD-1 mouse bone-marrow cells *in vivo*	Merck, Germany 99 %	-	800 mg/kg bw i.p. x 1	Elias *et al*., 1996
Micronucleus test, B6C3F$_1$ mouse bone-marrow cells *in vivo*	Dow Chemical, USA >99 %	-	550 mg/kg bw i.p. x 3	NTP, 2000
Micronucleus test, male F344/N rat bone-marrow cells *in vivo*	Dow Chemical, USA >99 %	-	450 mg/kg bw i.p. x 3	NTP, 2000
BAL				
No data available				
BAA				
Micronucleus test, CD-1 mouse bone-marrow cells *in vivo*	Janssen Chimica, Belgium >99 %	-	200 mg/kg bw i.p. x 1	Elias *et al*., 1996

[a] +, positive; –, negative; NT, not tested;
[b] LED, lowest effective dose; HID, highest ineffective dose

4.1.2.7.2 Summary of mutagenicity

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.

4.1.2.8 Carcinogenicity

The molecule of 2-butoxyethanol acetate is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate (see 4.1.2.1). 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 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 carcinogenicity properties of EGBEA could be assessed via a read-across from EGBE data.

4.1.2.8.1 Studies in animals

No data.

4.1.2.8.2 Studies in humans

No data.

4.1.2.8.3 Summary of carcinogenicity

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

Summary of carcinogenicity data on EGBE data:

"**Mechanism of haemangiosarcomas formation in male mice and its significance for human health.**

Haemangiosarcomas, which arise from the endothelial cell component of the liver (Frith and Ward, 1979), have been observed to increase in incidence in male mice treated with EGBE, but not in female mice or rats of either sex at high exposure concentrations of EGBE. The apparent species and sex specificity of this response may impact upon the human risk assessment process so possible mechanisms for the induction of these tumours are addressed in this section. The compound-specific experimental data are described in preceding sections of this document.

While some *in vitro* studies for genotoxicity have reported significant responses to exposure to EGBE or its metabolites, others have not and there is no evidence from *in vivo* studies for clastogenic activity or for covalent interactions with DNA. It is considered, therefore, that there is a lack of evidence for a role for genotoxicity induced by EGBE or its metabolites in the neoplastic process.

A possible alternative mechanism of haemangiosarcomas induction can be based on the haematotoxicity of the major urinary metabolite, BAA. It has been established that BAA is the metabolite that induces haemolytic anaemia in mice of both sexes. However, it also induces anaemia in rats, this species being slightly more sensitive than mice. For the haemolysis hypothesis to be sustained, there should be, therefore, other species and sex differences amongst the rodents that are important components of this mechanism.

Following the haemolysis produced by exposure to EGBE, haemosiderin is deposited in several cell types in liver, including Kupffer cells and hepatocytes of mice and rats. In addition, it has been recognised that murine endothelial cells have a significant phagocytic activity (Steffan *et al*., 1986), which may, therefore, serve as a mechanism by which insoluble iron complexes or senescent erythrocytes can enter these cells. Ferrous iron in haemosiderin can undergo redox cycling, the oxidative portion of which produces ferric iron and the highly reactive and damaging hydroxyl radical according to the Fenton reaction:

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + {}^{\bullet}OH + OH^-$$

The possible development of oxidative stress as a result of these iron deposits was studied in hepatocytes of male rats and mice (see Mechanistic studies of liver pathology, above), with the conclusion that rat hepatocytes in culture are markedly less susceptible to oxidative stress than are mouse hepatocytes. The antioxidant capacity of the endothelial cells of the liver of rats is much less than that found in either the hepatocytes or the Kupffer cells (DeLeve, 1998 ; Sporalics, 1999). Therefore, if there should be similar haemosiderin deposition in endothelial cells, Kupffer cells and hepatocytes, the endothelial cells would be the least well protected and thereby suffer the greatest oxidative damage. An *in vivo* study (Siesky *et al*., 2002) has demonstrated that treatment of male mice with EGBE at dose levels (orally administered by gavage) equivalent to those that were associated with increased incidences of haemangiosarcomas in a 2-year inhalation experiment leads to oxidative damage to hepatic DNA and lipid and increased DNA synthesis, particularly in endothelial cells, but also in hepatocytes. None of these effects occurred in rats. The *in vivo* and *in vitro* demonstrations of species differences in susceptibility to oxidative stress are, therefore, consistent with each other and the hypothesis that oxidative stress is an essential component of the process leading to haemangiosarcomas development in male mice treated with EGBE.

In addition, an *in vivo* study of possible differences between male and female mice does suggest that there is a marginally greater susceptibility of male mouse liver to oxidative damage than of female mouse liver. This sex difference does not seem to be large in terms of measurements of either acute oxidative DNA damage or lipid peroxidation, but there did remain a larger reserve of antioxidant potential in the females than in the males. Accordingly, it would not be possible to predict with any assurance that haemangiosarcomas would develop in males, but not in females. Indeed, the neoplastic response was not large even in the male mice, so it could be that a particular critical level of oxidative damage had been surpassed in the males, but had not been attained in the females. (Deguchi *et al*., 1995) showed that the presence of female sex hormones imparts higher antioxidant properties than do male sex hormones. This same group (Okada, 1996) also found much lower levels of lipid peroxidation in female mouse kidney than in male mouse kidney. This result demonstrates that there is a higher level of protection in female than in male mouse kidney. It also demonstrates that sex-related differences in susceptibility to oxidative damage are not restricted to the liver and, therefore, the consequences of such damage may show a sex-related incidence pattern in other organs of the body.

In response to BAA, human erythrocytes in culture are clearly much less sensitive than the rodent cells by at least an order of magnitude. Furthermore, haemotoxicity was not observed in the two available occupationally exposed people or in volunteers under controlled conditions to EGBE (see 4.1.1.1 in the EGBE's report). Exceptionally high exposure to EGBE, as encountered in a single case of attempted suicide in an adult (estimated dose 4500 mg/kg bw), did show that it is possible for human erythrocytes to be damaged as a result

of exposure to EGBE, but the effects require doses that are close to lethal (they were not seen in other attempted suicide cases where the estimated doses were at least 1000 mg/kg bw) and are not encountered in occupational circumstances or in normal consumer use (see 4.1.1.2 in the EGBE's report). Consequently, they should not be considered in an assessment of risk. In cases of accidental poisonings of children, no evidence of haemolytic effects has been found. Therefore, if haemolysis is an essential requirement for the induction of haemangiosarcomas by EGBE then man is not a susceptible species.

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. The weakness in this argument is that haemosiderin deposition was reported to occur in Kupffer cells, whereas its occurrence or otherwise in sinusoidal endothelial cells has not been reported. However, it has been demonstrated that active oxygen species can migrate from Kupffer cells to the adjacent endothelial cells (Klaunig, 2004), and an endothelial cell response, in the form of proliferation, has been demonstrated in male mice, but not male rats (Seisky *et al*., 2002), at dose levels that are associated with an increased incidence of haemangiosarcomas in male mouse liver.

Relevant information from studies not involving EGBE

The process by which haemangiosarcomas incidence is increased in male $B6C3F_1$ mice treated with EGBE has been presented as a compound-specific mechanism. Elements of this mechanism may be applicable to other chemicals that induce haemangiosarcomas, but it is extremely unlikely that generalisations can be made that include all of the steps described. This is because of:

- differences in metabolism and kinetics between species, sexes and routes of administration for specific compounds;
- the interplay of other toxicological processes (e.g., genetic toxicity) that may modify fundamentally, or to a lesser degree, the pathway leading to haemangiosarcomas development;
- chance differences in incidence between sexes (particularly when the incidence is low);
- missing information, such as the lack of haematological data (particularly in older studies).

Results have been summarised (Table 4.85 in the EGBE's report) on chemicals tested for carcinogenicity in $B6C3F_1$ mice and/or F344/N rats for which evidence of haemosiderin deposition is available in relatively complete reports that are in the public domain (specifically, NCI and NTP reports). In compiling this list, it was evident that some chemicals

did not cause haemosiderin deposition in the liver, but did so in other organs. These have not been included. Also, in the columns listing the haemangiosarcoma induction response, it is stressed that the incidences refer only to the liver. Thus, the emphasis is on the relationships between haematotoxicity, haemosiderin deposition and haemangiosarcoma in the liver. In this organ, it was expected on the basis of the current hypothesis that, while the reasons for haematotoxicity might be different after exposure to different chemicals, the hepatic response to hepatic deposition of haemosiderin should be the same for any chemical, including EGBE. In other organs, modifying factors may prevail. The spatial relationships between the phagocytic cells and the cell populations in which the neoplastic response arises might be different from those found between Kupffer cells and hepatic sinusoidal endothelial cells; there may also be differences in protective capacity, e.g., splenic phagocytes have a higher antioxidant capacity than do sinusoidal endothelial cells (DeLeve, 1998).

The data show that mice are more susceptible to haemangiosarcoma development than are rats, and male mice are more sensitive than female mice. None of the chemicals that are listed in section C (male mice) of table 4.85 (in the EGBE's report) induced haemangiosarcomas in section D (female mice) and only those chemicals in section C that demonstrably induced a life-long exposure of the liver to Kupffer cell pigmentation also induced increases in hepatic haemangiosarcoma incidence. At first glance, the main conclusion to be reached is that most of the data remain consistent with the suggested mechanism, in that significant haemosiderin deposition does not occur in cases where there is an absence of an increased incidence of haemangiosarcomas. However, some results require further investigation. It is not suggested that haemosiderin deposition is the only mode of action that can result in haemangiosarcomas. The highest incidence of haemangiosarcomas occurred in male mice gavaged with pentachloroanisole. In this series of experiments, the Kupffer cell pigmentation observed at 13 weeks did not contain iron, bile or PAS-positive material. It appears that special staining techniques were not applied to the pigment found in the 2-year study, therefore it is not known if it was haemosiderin or the non-iron pigment found in the 13 week study. It is also noted that material was more prevalent in hepatocytes than in Kupffer cells. If it were not haemosiderin then pentachloroanisole would cease to be of use in looking for support for the mechanism.

Another case requiring discussion is C.I.Pigment Red 3, which did not induce haemangiosarcomas in either mice or rats, but haemosiderin deposition was observed in spleen and a "green-brown pigment" occurred in Kupffer cells. The latter was not identified as haemosiderin in the report and, if it were not haemosiderin, then C.I.Pigment Red 3 would cease to be of use in looking for support for the proposed mechanism. Furthermore, if haemolytic anaemia was produced by C.I.Pigment Red 3 in mice, it was transient – unlike in rats – as suggested by the haematological changes observed at the end of the preliminary 2-week study, but not at the end of the 13-week study (p.62 of NTP TR 407). This contrasts with the haematotoxic activity of EGBE, which persisted for at least 12 months (the longest period examined). This does lend some support to the hypothesis that life-long exposure of the liver to Kupffer cell pigmentation is required as a pre-requisite for an increase in liver haemangiosarcoma rates in male mice.

In the case of methyleugenol, haemosiderin deposits were found in the livers of female mice, but not of male mice or in rats of either sex. Haemangiosarcomas were not induced, whereas there were increases in hepatocellular neoplasms. Although the mice in this study were infected with *Helicobacter hepaticus*, it was argued that this did not compromise the outcome. Even in the EGBE study, the increase in haemangiosarcomas incidence in male mice was modest and did not occur in female mice; therefore, the absence of these neoplasms in female

mice of the methyleugenol study does not conflict with their proposed mechanism of induction by EGBE.

The conclusion that can be reached is that, in addition to EGBE, only two compounds support the pattern of chronic haemosiderin deposition and increased incidence of haemangiosarcomas in male mice but not female mice, these being *p*-chloroaniline and *p*-nitroaniline. Another group has recently studied the possible association liver hepatic haemangiosarcomas and chemically induced haemosiderosis in mice in the US NTP database (Nyska *et al*., 2004) and reached essentially the same conclusion. In addition to the qualitative association described here, however, (Nyska *et al*., 2004) also showed that there was a very high statistically significant association between hepatic haemangiosarcomas and Kupffer cell pigmentation.($p < 0.001$). In all cases, the cause of the haemosiderosis was haemolysis due to the chemical.

There are very few rodent studies with other compounds that are capable of providing support for the hypothesis proposed to explain the low level increased incidence of haemangiosarcomas in male mice exposed to EGBE. The available evidence is, however, consistent with the hypothesis. Currently, the most likely mechanism is that proposed, based on metabolism to BAA, followed by rodent erythrocyte-sensitive haemolysis, deposition of iron-protein complexes in the liver and the sustained generation of toxic (cytotoxic or DNA damaging) radicals from this source.

Human studies have demonstrated an enormously increased risk for hepatocellular cancer in hereditary haemochromatosis (e.g. (Niederau *et al*., 1985) found an increased risk of 219, based on 16 cases) that has been attributed to the toxic effects of iron, but there also seems to be slightly increased risks for extra-hepatic cancers. Some studies have found genetic associations between several cancers and the most common mutation, C282Y, of the HFE gene that causes hereditary haemochromatosis. Such associations only occur, however, in the presence of a particular allele of the transferrin receptor gene. This suggests that the increased cancer risk is due to the effects of iron (Dorak *et al*., 2002). Additionally and independently of the genetic factors, dietary iron appears to be a risk factor for some cancers, e.g., colorectal cancer (Nelson, 2001), and dietary iron overload has been associated with about a 10-foldgreater risk of hepatocellular carcinoma among black Africans (Mandishona *et al*., 1998). Focussing specifically upon liver angiosarcoma, however, the frequently quoted risk factors for this rare human cancer (0.5 – 2.5 cases per 10^7 people), which include hereditary haemochromatosis, contribute to explain no more than about 20 % of the published cases. Indeed, apart from occupational exposure to vinyl chloride, the aetiology of this cancer remains largely unknown (Zocchetti, 2001). Therefore, it is not possible to conclude whether iron plays any role in human angiosarcoma.

Relationship between chemicals inducing haematoxicity and haemangiosarcomas in B6C3F1 mice and F344 rats are summarised in the table 4.24:

Table 4.24: Summary of relationship between chemicals inducing haematoxicity and haemangiosarcomas in B6C3F1 mice and F344 rats (incidences are given for control, low, middle and high dose groups, respectively).

A. Male Rats

Chemical	Haematology indicating toxicity to erythrocytes	Incidence of Kupffer cell pigmentation (KCP) or hepatic haemosiderin (HS) at 2 years	Kupffer cell pigmentation (KCP) or hepatic haemosiderin (HS) observed at 3 months	Incidence of hepatic haemangiosarcoma	Reference **
EGBE	Yes, at 14 wks	KCP: 23/50, 30/50, 34/50, 42/50	KCP	0/50, 0/50, 1/50, 0/50	TR484
o-Nitroanisole	Yes, at 2 & 13 wks	KCP: 0/20, 1/20, 18/20	KCP	None	TR416
p-Chloroaniline	Yes, at 13 wks	HS: 1/49, 0/50, 0/50, 26/50	KCP	None	TR351
Pentachloroanisole	Normal at 13 wks.	KCP: 0/50, 1/50, 4/50	None (hypertrophy of Kupffer cells)	None	TR414
Pyridine	Yes, at 13 wks	KCP: 4/50, 11/50, 20/50, 25/50	HS, but cell-type not identified	None	TR470
Titanocene dichloride	Yes, at 2 wks	KCP: 1/60, 39/60, 41/60	None	None	TR399 (rats only)
D&C Yellow No. 11	No haematology	KCP: 7/50, 15/51, 23/51, 26/54	KCP	None	TR463 (rats only)
Butyl benzyl phthalate		KCP, 0/59, 1/58, 6/59, 6/58		None	TR458
Cupferron (N-hydroxy-N-nitroso-benzenamine)	No haematology.	HS: 0/49, 15/48, 28/43	No data	None	TR100
No significant haemosiderin/pigmentation deposition was observed with: Methyleugenol, 2,4-diaminophenol.2HCl, CI Pigment Red 3.					

B. Female Rats

Chemical	**Haematology indicating toxicity to erythrocytes**	**Incidence of Kupffer cell pigmentation (KCP) or hepatic haemosiderin (HS) at 2 years**	**Kupffer cell pigmentation (KCP) or hepatic haemosiderin (HS) observed at 3 months**	**Incidence of hepatic haemangiosarcoma**	**Reference**
EGBE	Yes, at 14 wks	KCP: 15/50, 19/50, 36/50, 47/50	KCP	None	TR484
o-Nitroanisole	Yes, at 2 & 13 wks	KCP: 8/20, 2/20, 20/20	KCP	None	TR416
Pentachloroanisole	Normal at 13 wks.	Pigmentation in hepatocytes	None (hypertrophy of Kupffer cells)	None	TR414
Pyridine	Yes, at 13 wks	KCP: 6/50, 2/50, 6/50, 17/50	HS, but cell-type not identified	None	TR470
Titanocene dichloride	Yes, at 2 wks	KCP : 3/60, 45/61, 50/60	None	None	TR399 (rats only)
CI Pigment Red 3	Yes, at 2 & 13 wks.	KCP : 0/50, 3/50, 14/50, 41/50*	Pigment (type & cell-type not identified)	None	TR407
D&C Yellow No.11	No haematology	KCP: 9/50, 11/51, 16/50, 32/51	KCP	None	TR463 (rats only)
Butyl benzyl phthalate		KCP: 4/60, 1/60, 6/60, 10/60		None	TR458
Cupferron (N-hydroxy-N-nitroso-benzenamine)	No haematology	HS: 0/48, 9/44, 33/44	No data	None	TR100
No significant haemosiderin/pigmentation deposition was observed with: Methyleugenol (anaemia at 14 wks), 2,4-diaminophenol.2HCl, butylbenzyl phthalate, *p*-chloroaniline					

C. Male Mice

Chemical	**Haematology indicating toxicity to erythrocytes**	**Incidence of Kupffer cell pigmentation (KPC) or hepatic haemosiderin (HS) at 2 years**	**Kupffer cell pigmentation (KPC) or hepatic haemosiderin (HS) observed at 3 months**	**Incidence of hepatic haemangiosarcoma**	**Reference**
EGBE	Yes, at 14 wks	KCP: 0/50, 0/50, 8/50, 30/50	KCP	0/50, 1/50, 2/50, 4/50	TR484
p-Chloroaniline	Yes, at 14 wks.	KCP/HS: 0/50, 0/49, 0/50, 50/50	KCP	2/50, 2/49, 1/50, 6/50	TR351
Pentachloroanisole	No haematology	KCP: 1/50, 50/50, 50/50	KCP (but not containing iron)	2/50, 8/50, 10/50	TR414
p-Nitroaniline	Yes, at 2 & 13 wks	KCP: 1/50, 1/50, 8/50, 50/50	KCP	0/50, 1/50, 2/50, 4/50	TR418
o-Nitroanisole	Yes, at 13 wks	KCP: 0/50, 0/50, 3/50, 16/50	No	2/50, 2/50, 1/50, 0/50	TR416
CI Pigment Red 3	Normal at 13 wks	KCP : 0/50, 5/50, 30/50, 41/50*	No	0/50, 1/50, 1/50, 0/50	TR407
2,4-Diaminophenol.2HCl	No haematology at 13 wks. Yes, at 15 months	KCP: 0/50, 44/50, 47/50	No	1/50, 0/50, 1/50	TR401
No significant haemosiderin/pigmentation deposition was observed with: Methyleugenol, Pyridine, Cupferron					

D. Female Mice

Chemical	**Haematology indicating toxicity to erythrocytes**	**Incidence of Kupffer cell pigmentation (KPC) or hepatic haemosiderin (HS) at 2 years**	**Kupffer cell pigmentation (KPC) or hepatic haemosiderin (HS) observed at 3 months**	**Incidence of hepatic haemangiosarcoma**	**Reference**
EGBE	Yes, at 14 wks	KCP: 0/50, 5/50, 25/50, 44/50	KCP	0/50, 0/50, 1/50, 0/50	TR484
p-Chloroaniline	Yes, at 14 wks	KCP: 0/50, 0/50, 1/50, 46/50		1/50, 0/50, 0/50, 1/50	TR351
Pentachloroanisole	No haematology	KCP: 0/50, 37/50, 48/50		0/50 0/50, 1/50	TR414
p-Nitroaniline	Yes, at 2 & 13 wks	KPC: 1/50, 1/50, 4/50, 39/50		1/50, 1/50, 0/50, 0/50	TR418
Methyleugenol	No haematology	HS: 0/50, 11/50, 24/50, 19/50*		0/50, 1/50, 0/50, 0/50	TR491
CI Pigment Red 3	Normal at 13 wks	KCP: 2/50, 1/50, 1/50, 29/50*		0/50, 0/50, 1/50, 0/50	TR407
2,4-Diaminophenol.2HCl	No haematology at 13 wks. Yes, at 15 months	KCP, 0/50, 31/50, 50/50		None	TR401
No significant haemosiderin/pigmentation deposition was observed with: Pyridine, Cupferron, *o*-Nitroanisole					

*See discussion in the text.

**NTP Technical Report Numbers

Mechanism of forestomach tumour formation in mice and its significance for human health.

Squamous cell papilloma and carcinoma of the forestomach have been induced in female mice, with some evidence (that does not reach a level of significance) for an increase in male mice. In contrast, there is no evidence for the induction of forestomach tumours or even preneoplastic effects, such as hyperplasia, in rats of either sex in the 2 year study, although hyperplasia was observed in female rats in a 14 week study in which higher exposure concentrations were used.

EGBE is a liquid with low vapour pressure that can therefore deposit on the fur of animals in whole body exposure experiments. The inhaled vapour may also condense in the nasopharynx. By both this mechanism and as a result of grooming contaminated fur, EGBE can achieve a significant exposure by the oral route, even in inhalation experiments. Although this is a plausible explanation for the toxic and tumourigenic effects of EGBE on the forestomach, only small amounts of EGBE (< 10 mg/kg) were found on the fur of mice at the end of 6 hr, whole body exposures to 250 ppm (the highest concentration used in the NTP carcinogenicity experiment). In addition, dosage of mice by either intraperitoneal or subcutaneous injection also resulted in forestomach lesions. It is clear, therefore, that EGBE accumulates in the forestomach as a result of a combination of processes. In addition to grooming of EGBE present on the fur of the mice and, possibly, mice licking the walls of the exposure chamber, it is likely that salivary excretion as well as mucocilliary transport of material deposited in the bronchi, followed by ingestion, are other means by which exposure of the stomach could have occurred during the study.

The stomach of rats and mice consists of a forestomach (not found in man) and a glandular portion. The forestomach acts as a storage organ, where ingested material can remain for several hours, before it is transferred to the glandular portion in which there is a rapid transit and the first stages of digestion occur. Again, this is not the only mechanism that results in prolonged exposure of this organ. EGBE and, to a lesser extent, BAA is also eliminated more slowly from forestomach tissue than from either blood or other tissues following either oral gavage or intraperitoneal injection. Consequently, there is greater potential for damage to be induced by toxic substances in the forestomach than in the glandular stomach.

Study of the stomachs of mice orally administered either EGBE or BAA shows that, at the doses used, there was no damage to the glandular stomach by either compound and that damage in the form of hyperkeratosis occurred in the forestomach at lower doses of BAA than of EGBE. There is significant alcohol and aldehyde dehydrogenase activity in both parts of the stomach in rats and mice. While there was little difference in the activity of aldehyde dehydrogenase in rats and mice, there were major species differences in alcohol dehydrogenase activity, the mouse enzyme having very much higher affinity constants and maximal rates than the rat enzyme, when using EGBE as the substrate. Therefore, there is greater potential for EGBE to be metabolised to BAA in the forestomach of mice than in the forestomach of rats.

Hyperplasia and hyperkeratosis are histological responses to exposure to a wide range of chemicals that also produce papilloma and squamous cell carcinoma of the forestomach. Many of these chemicals are devoid of genotoxicity, the neoplasms apparently developing as a result of persistent cellular damage and sustained hyperplasia (Kroes and Webster, 1986). While there is nothing unique to rodents about this process, the fundamental differences in physiology and function between the 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 proposal is substantiated by the lack of any neoplastic response in the glandular stomach of mice exposed to EGBE under conditions that produce forestomach tumours.

PROPOSED MECHANISMS OF ACTION ASSESSED WITHIN THE IPCS FRAMEWORK

Introduction

The experiments that form the bases for these evaluations of mechanism of carcinogenic action are summarised in the preceding sections of this document.

EGBE, when delivered as a vapour, induces tumours of the forestomach in female mice and haemangiosarcomas of the liver in male mice. There was also some evidence (which did not reach statistical significance) for an increase in forestomach tumours in male mice. Neither of these tumours do not occur in the other sex in mice and no significant elevation of tumour incidence is found in rats. These findings have not been verified in independent experiments.

Postulated Mode of Action for the Induction of Tumours of the Forestomach in Female Mice.

The proposed mechanism of action for production of tumours in the forestomach is the local generation, as well as accumulation of cytoxic metabolite(s) that induce a sustained, compensatory cell proliferation, neoplasia arising out of this proliferating cell population. The neoplasia was mainly papillomas, a single squamous cell carcinoma arising in the highest dose group of female mice.

Key Events

The following important steps are involved in the generation of forestomach tumours:

Enhanced exposure of the forestomach to EGBE and its metabolites from multiple external and internal sources. EGBE delivered to female mice by inhalation was distributed throughout the internal organs and was present in the stomach contents within 5 min after exposure. It was present in the mucosa of the forestomach, the buccal cavity and the oesophagus 24 and 48 h after exposure, but the high levels observed in the forestomach was in contrast to the much lower levels found in the glandular stomach and the duodenum. EGBE was also found on fur and in the buccal cavity, oesophagus and stomach contents. EGBE delivered to female mice by intravenous injection was selectively concentrated in several tissues, including liver, bone, Harderian glands and buccal cavity. The mucosa of the forestomach and glandular stomach were also labelled, but to similar extents. After EGBE administration by this route or subcutaneous injection, both EGBE and butoxyacetic acid were excreted in saliva and found in the stomach periods for prolonged periods.

Metabolism to cytotoxic metabolite(s), most probably butoxyacetic acid, if not already presented to the forestomach in this form. EGBE is metabolised by preparations from the forestomach and glandular stomach of rats as well as mice. The enzymes principally responsible for EGBE metabolism are alcohol and aldehyde dehydrogenase (a minor oxidative pathway is mediated by cytochromeP450 enzymes).These enzymes are found in both the glandular stomach and forestomach of rats and mice, but whereas they are concentrated in the stratified squamous epithelium of the forestomach, their distribution is diffuse in the glandular stomach of both species. There are no major species differences in the tissue average activity of aldehyde dehydrogenase, but the maximum rate of alcohol dehydrogenase activity is up to an order of magnitude higher in mice than in rats.The forestomach is a target tissue because EGBE entering the stomach is held there and because

the metabolising enzymes are concentrated in the superficial layers of the forestomach. BAA has shown to be a more potent in producing adverse effects on the forestomach than EGBE. It may be that there is a species difference in part because the rate of metabolism of EGBE to 2-butoxyacetaldehyde is slower in rats than in mice, hence it is probable that either the generation of the more cytotoxic butoxyacetic acid is slower, or its maximum concentration is lower in rats than in mice.

Cytotoxicity and *cell proliferation*, as indicated by epithelial hyperplasia, was often accompanied by ulceration in a two-year inhalation experiment in mice, especially in females, but these responses were not reported in rats. Administration of undiluted EGBE to male and female mice by gavage induced dose-related irritation of the forestomach; the compensatory cell proliferation was confirmed by immunochemical staining. Similar forestomach lesions could be induced by EGBE administered by intraperitoneal or subcutaneous injection and by butoxyacetic acid given orally. This metabolite was more potent than EGBE itself.

Squamous cell papillomas or carcinomas were significantly increased only at the highest concentration in female mice. It also appears that mice may be more susceptible to the induction of forestomach tumours than rats, the background incidence being higher in mice.

- **Dose-Response Relationship**. In female mice, the incidence and severity of epithelial hyperplasia of the forestomach increased with rising dose in female mice, as did the incidence of ulceration of the forestomach. Ulceration occurred in male mice also, but the incidences were lower and not clearly concentration related.

- **Temporal Relationship.** In a 14 week inhalation study in mice, epithelial hyperplasia of the forestomach was observed at 125 ppm and above and had progressed at 250 ppm or 500 ppm (the highest concentration) to inflammation, necrosis and ulceration. Thus, preneoplastic events preceded neoplasia, which was only observed in the two-year study.

- **Strength, Consistency and Specificity of Association of the Tumour Response with Key Events.** There has not been any investigation of the association of key events with a neoplastic outcome at the level of individual female mice. In broad terms, however, it is clear from the dose-response and the temporal relationships that there is consistency in these events. The induction of forestomach tumours has been observed only in a single experiment. The entire chain of events has not, therefore, been verified by independent study. Such verification should be more readily achieved by oral administration of EGBE directly into the forestomach, by gavage; however, such an experiment would have little applicability to occupational or consumer exposures.

- **Biological Plausibility and Coherence.** As generalisations, chemicals that do not induce carcinogenesis through mutagenesis do so by modes of action that include an increase in cell proliferation, either by mitogenesis or by stimulating reparative cell proliferation provoked by cytotoxicity. Based on the evidence available, the latter mode of action is biologically plausible for the induction of forestomach tumours in female mice by EGBE.

- **Other Modes of Action.** While no other mode of action has been proposed, genetic toxicity has been considered and rejected. Other possibilities could include aberrant control of gene expression because of alkylation of regulatory proteins (e.g., in

chromatin), with ensuing loss of genetic stability. No studies have been conducted to investigate such a mechanism.

- **Assessment of the Postulated Mode of Action.** The data available are fully consistent with the proposed mechanism for the induction of forestomach tumours in female mice. The apparent female sex specificity is likely to be due to chance.

- **Uncertainties, Inconsistencies and Data Gaps.** The experimental observations are consistent with the general hypothesis proposed; however, there are two areas that require more specific reasoning. These are: the species difference in response and the progression from hyperplasia to neoplasia. The proposed reason for the difference in response between rats and mice is the differences in kinetic properties of the rat and mouse alcohol dehydrogenase. Whether this actually leads to a difference in concentration or quantity of butoxyacetic acid in the forestomach is unknown. As an alternative hypothesis, mice may be more susceptible than rats to the induction of forestomach tumours. This suggestion is based on the observed higher incidence of forestomach tumours in untreated mice. It is not known how proliferation of apparently normal cells becomes transformed into neoplasia. This criticism can be levelled at any non-genotoxic mechanism of carcinogenesis (but see 1.3.5 in the EGBE's report). There is consistency within the database as currently known. It would be expected, however, that exposure of male mice by inhalation to somewhat higher concentrations of EGBE should also lead to forestomach neoplasia. Similarly, exposure of female and male rats to higher concentrations could also lead to neoplasia if such concentrations could be tolerated. Since the lower concentrations used in the two-year inhalation experiment with rats were selected on the basis of carefully executed shorter term studies to identify the maximum tolerated dose, this hypothetical experiment would be unlikely to be successful.

Postulated Mode of Action for the Induction of Hamangiosarcomas of the Liver in Male Mice.

The proposed mechanism of action for production of haemangiosarcomas of the liver is the deposition of haemosiderin in relevant cell-types, possibly including endothelial cells from which haemangiosarcomas arise, and the generation of cytotoxic reactive oxygen species that either induce genetic changes by this secondary mechanism or sustained cell proliferation within the endothelial target tissue, neoplasia arising out of this proliferating cell population.

Key Events

The following important steps are involved in the generation of haemangiosarcomas:

Metabolism to haemolytic metabolite(s), most probably butoxyacetic acid. EGBE is principally metabolised by alcohol dehydrogenase and aldehyde dehydrogenase to 2-butoxyacetaldehyde and butoxyacetic, respectively. Butoxyacetic acid is a more potent haemolytic agent than either of its precursors; furthermore, these precursors appear not to be haemolytic unless they are metabolised. Inhibition of aldehyde dehydrogenase reduced the haemolytic activity of 2-butoxyacetaldehyde. At least *in vitro*, butoxyacetic acid causes haemolysis at much lower concentrations in rat erythrocytes than in human erythrocytes.

Haemolysis caused by butoxyacetic acid and followed by persistent, dose related anaemia results in haemosiderin deposition in the liver. This material has been observed in Kupffer

cells and hepatocytes of both mice and rats, but there is currently no evidence for haemosiderin deposition in endothelial cells. Since haemolysis occurs in mice and rats of both sexes, it is necessary to provide a rationale for the specificity of the neoplastic response to male mice; however, this could be difficult in view of the low (although statistically significant) tumourigenic response in male mice.

Cell toxicity resulting from the iron-mediated generation of reactive oxygen species from haemosiderin. Compared to rats and female mice, male mice have a reduced antioxidant capacity in the liver, causing them to be more susceptible to oxidative damage; however, it is not clear that this difference is important, given the greater inherent susceptibility of male mice to the neoplasm of interest. Oral administration of EGBE to mice at doses up to 600 mg/kg bw/day for up to 90 days produced increased DNA synthesis in endothelial cells during the first 14 days of exposure and in hepatocytes after 90 days. Increased oxidative damage was also observed mice in this experiment, while no change was observed in rats.

Haemangiosarcomas arise from the endothelial target cells and are significantly increased in male mice to 8% in the 250 ppm group. It also appears that male $B6C3F_1$ mice may be more susceptible to haemangiosarcomas than are female mice (control incidence rates in NTP experiments being about 2.5% in males and 0.9% in females) and mice are more susceptible than F344 rats (none having been reported in control groups in NTP experiments). Thus, the apparent sex and species specificity could merely be a reflection of inherent sensitivity.

- **Dose-Response Relationship.** Haemolysis and persistent anaemia have been shown to occur in a dose related manner in a number of experiments. In two-year inhalation experiments, Kupffer cell pigmentation was significantly increased over that seen in control animals for male and female rats exposed at 62.5 or 125 ppm, male mice at 125 or 250 ppm and female mice at 62.5, 125 or 250 ppm. The increases observed in the male and female mice were dose related, but the incidence of Kupffer cell pigmentation was greater in female mice than in male mice. A significant increase in the incidence of haemangiosarcomas occurred only in male mice and only at the highest exposure concentration of EGBE.

- **Temporal Relationship.** The experiments show that haemolysis is an acute response and anaemia is a sustained response to repeated exposure to EGBE. Haemosiderin deposition is observed in short-term experiments and therefore it is present for a considerable period before the emergence of the haemangiosarcomas, which occurred at increased incidence only in a two-year inhalation exposure experiment.

- **Strength, Consistency and Specificity of Association of the Tumour Response with Key Events.** Data from experiments with other chemicals show that mice are more susceptible to haemangiosarcoma development than are rats, and male mice are more sensitive than female mice, but the database in support of the hypothesis that life-long exposure of the liver to Kupffer cell pigmentation is a pre-requisite for an increase in liver haemangiosarcoma rates in male mice is small, after exclusion of doubtful examples.

- **Biological Plausibility and Coherence.** It has long been proposed (e.g., for peroxisome proliferators) that increased, persistent generation of reactive oxygen species can result in neoplasia by an indirect genotoxic mechanism. It has been shown that EGBE does increase oxidative damage in cells, as demonstrated by the generation of malondialdehyde, a deposition product of lipids, and 8-

hydroxydeoxyguanosine, an oxygen adduct of DNA, and that differences in reduced antioxidant concentrations within cells may be responsible for sex and species differences in response. Nevertheless, no substance has been shown unequivocally to induce tumours through this mechanism.

- **Other Modes of Action.** While no other mode of action has been proposed, genetic toxicity has been considered and rejected. Other possibilities could include aberrant control of gene expression because of alkylation of regulatory proteins, as suggested for forestomach tumours, but there is no evidence to support this suggestion either for the forestomach mucosa or endothelial cells of the hepatic sinusoids. Kinetic studies with liver slices suggest that concentrations of 2-butoxyacetaldehyde that might induce genetic damage are unlikely to be reached under the conditions of the long-term inhalation experiments.

- **Assessment of the Postulated Mode of Action.** Haemangiosarcomas are uncommon and their incidence in this experiment was low (4/49) although out with the historical control range, at the highest dose. Because this is a low increase in incidence, and because it has not been confirmed, it is difficult to assign any mechanism. With the rejection of genotoxicity as a possible mechanism and the strong evidence for a potential source of reactive oxygen species within the liver, it is reasonable to presume that these may play a definitive role in neoplasia.

Uncertainties, Inconsistencies and Data Gaps. By their nature, reactive oxygen species are difficult to localise in the target tissue. In addition, the generator of these cytotoxic species, haemosiderin, has not been demonstrated in endothelial cells, from which haemangiosarcomas arise. Haemosiderin was demonstrated in Kupffer cells, so reactive oxygen species could arise in these cells, and the recent demonstration in one study of the migration of reactive oxygen species from Kupffer cells to endothelial cells does suggest a manner in which the latter might be damage. The involvement of cytokines secreted by Kupffer cells has been suggested in the case of peroxisome proliferators, but the target in those cases is the hepatocytes. A similar interplay of cytokines between Kupffer cells and endothelial cells may be involved in the case of haemosiderin deposition, but this remains to be demonstrated and may not be necessary in view of the alternative suggestion. A fundamental major uncertainty is that it is unknown if the observation in a single experiment of a low, barely significant incidence of haemangiosarcomas in male mice is reproducible or whether it might also be observable in female mice, should the experiment be repeated. However, there is reason to expect that female mice would be less susceptible to this lesion. Summary of carcinogenicity

EGBE is carcinogenic in male mice, where it causes a low incidence of haemangiosarcomas, and female mice, where is causes an increased incidence of forstomach tumours. It is not carcinogenic in rats. Genotoxicity is not an important toxicological property of this chemical and it is unlikely that the low, variable and uncertainly defined genotoxic activity can be the cause of the carcinogenic responses. Hypotheses have been proposed and supported by experiment data in an attempt to explain the carcinogenic responses. These have been described above. In the case of forestomach tumours, the argument that they arise in a tissue subject to sustained abuse and consequent repair is clear. It is likely that this finding is in reality not sex specific but merely due to chance that the low level incidence in females rose above the level of statistical significance but it did not do so in males. In the case of the haemangiosarcomas, data from experiments with other chemicals show that mice are more susceptible to haemangiosarcoma development than are rats, and male mice are more

sensitive than female mice, but the database in support of the hypothesis that life-long exposure of the liver to Kupffer cell pigmentation is a pre-requisite for an increase in liver haemangiosarcoma rates in male mice is small, after exclusion of doubtful examples. With the rejection of genotoxicity as a possible mechanism, strong evidence for a potential source of reactive oxygen species within the liver, and a mode of action where each step has at least some supporting data, it is reasonable to presume that these may play a role in the neoplasia.

With regard to human relevance, the mechanism proposed for the induction of haemangiosarcomas strongly suggests that EGBE is not likely to be a carcinogenic hazard under conditions of normal handling and use, because human erythrocytes are demonstrably more resistant to haemolysis than are rodent erythrocytes. The mechanism proposed for the induction of forestomach tumours would also point to a lack of human relevance under conditions of normal handling and use. As stated recently (IARC, 2003), while people do not possess forestomachs, they do have comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus. Thus, in principle, carcinogens targeting the forestomach squamous epithelium in rodents are relevant for man. However, the relevance for man is probably low for agents that have no demonstrable genotoxicity and that are solely carcinogenic for the forestomach squamous epithelium in rodents after oral administration. Consequently, for these agents, the mode of carcinogenic action could be specific to the experimental animals (IARC, 2003). EGBE satisfies only some of these conditions. On the other hand, there are proposed mechanisms that are supported by experimental evidence to show how this chemical, even when inhaled, can accumulate in the forestomach contents, where it can remain for many hours to cause damage directly or after its metabolism to BAA.

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. Therefore, an appropriate classification for *"No classification"* is proposed for *carcinogenicity*. This classification proposal was agreed by the C&L working group. Moreover, the last IARC evaluation (2004) published in 2006 has classified EGBE in the list 3 of carcinogens : *not classifiable as to their carcinogenicity to humans (Group 3)* on the basis of *limited evidence* in experimental animals and *inadequate evidence* in humans.

Since the only carcinogenic effects can be considered secondary to haemolysis, and haemolysis is the key end point for repeat dose toxicity, no separate risk characterisation is necessary for the cancer end point. If there are no concerns for repeat dose toxicity, it can be considered that there will be no concerns for cancer either."

The same conclusion applies for EGBEA.

4.1.2.9 Toxicity for reproduction

2-butoxyethanol acetate is rapidly cleaved, presumably by esterases, into 2-butoxyethanol and acetate (see 4.1.2.1). 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 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 reproductive toxicity of EGBEA could be assessed via a read-across from EGBE data. The results obtained with EGBE will be taken into account.

4.1.2.9.1 Effects on fertility

No data

4.1.2.9.2 Developmental toxicity

No data

Summary of reproductive toxicity data on EGBE:

"Unlike EGME and EGEE, 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 (it should be noted that 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).

Haemotoxicity described in § 4.1.2.2.3 generally occurred at low doses of EGBE whatever the route of administration used. In theses studies, data on haemolysis were often observed with acute dosing. Developmental toxicity studies would require daily dosing with test material, which may produce more marked effects on haematopoietic parameters. In addition, female mice and rats were more affected by EGBE haemolysis than males. Thus, these data demonstrate that the concentrations of EGBE used in these developmental toxicity studies were adequate to produce severe maternal anemia of the magnitude sufficient to cause effects on embryo/foetal survival. These data give plausible support to the hypothesis that the effects seen in developmental toxicity studies with EGBE were due to haemolysis and subsequent maternal anemia.

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."

Based on this data, there is no concern for EGBEA for developmental toxicity but a NOAEL of 720 mg/kg on fertility derived from the continuous breeding study with EGBE can be used for EGBEA. On a molar basis, the NOAEL for EGBEA for fertility is 976 mg/kg bw/d and will be used in the risk characterisation.

4.1.2.9.3 Summary of toxicity for reproduction

For EGBEA, assessment of the toxicity for reproduction is based on EGBE data. Based on this data, there is no concern for EGBEA for developmental toxicity but a NOAEL of 720 mg/kg on fertility derived from the continuous breeding study with EGBE can be used for EGBEA. On a molar basis, the NOAEL for EGBEA for fertility is 976 mg/kg bw/d and will be used in the risk characterisation.

4.1.3 Risk characterisation [6]

4.1.3.1 General aspects

The human population may be exposed to EGBEA at the workplace, both from use of consumer products and indirectly via the environment (see 4.1.1.1, 4.1.1.2, 4.1.1.3 and 4.1.1.4)

EGBEA is rapidly hydrolysed in blood to EGBE and acetate. All systemic effects observed with EGBEA are typically also observed with EGBE.

From the oral absorption studies it is concluded that oral absorption is complete. For risk characterisation 100 % oral absorption should be assumed.

From human volunteers inhalation studies, an absorption of 55 % to 60 % has been measured. These values varies from the theoretical absorption value of 80 %, calculated from various studies, due to a wash in / wash out mechanism on the surface of the respiratory tract. For risk characterisation, 60 % inhalation exposure should be assumed (highest measured value).

As it is indicated in EGBE RAR: “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 general, dermal absorption of liquid EGBE varies between 20 to 30 % of applied dose in rats. Variations are seen in the reported values for individual humans for the rate of absorption (ranging from 0.064 mg/cm^2/hr to 1.66 mg/cm^2/hr *in vitro* and from 0.826 to 11.3 µg/cm^2/hr *in vivo*). 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). According to the PbPk model, for a worst case exposure (100 % of the body exposure with no cloths), internal dose of EGBE due to the percutaneous uptake when a subject is exposed to EGBE as vapour would be 15 to 27 % (this range being not negligible compared to the dose due to inhalation). For

[6] 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.

risk characterisation, dermal absorption of liquid EGBE can be assumed to be 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 but keeping in mind that this value has been demonstrated only during extreme exposure conditions (high temperature, high humidity and overalls clothing) which can be considered to be the worst case of exposure.

Absorption coefficients taken into account for the calculations of internal doses are reported in the table 4.25:

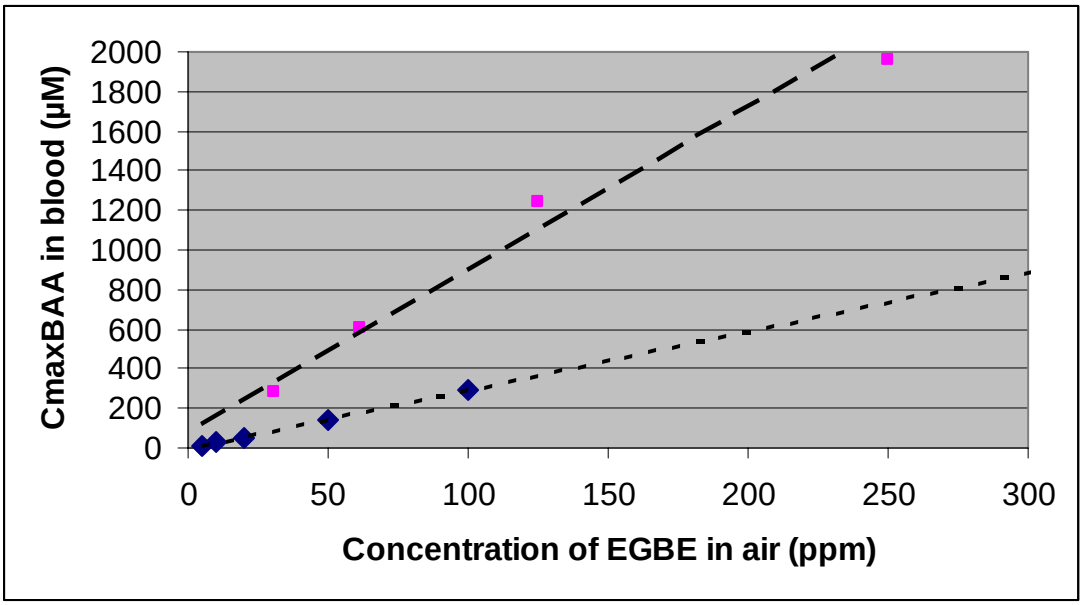
Table 4.25: absorption coefficients taken into account for the calculations of internal doses

	Oral	Inhalation	Dermal route	
% of absorption	100 %	60 %	EGBE liquid	EGBE vapour
			30 % [1]	39 % of the internal dose [1]

[1] Maximum worst case percentage, can be reassessed for each scenario in a case by case basis if needed.

For interspecies extrapolation, PBPK models exist for the rat, mouse and human. These enable the internal dose of EGBE to be estimated with some precision. Of the models available, that from (Corley *et al*., 1994 and 1997) is considered the most complete and appropriate for potential use in the derivation of an interspecies extrapolation factor for oral exposure because it has been experimentally validated, covers relevant routes of exposure, and addresses both the distribution and excretion of the metabolite BAA which is invariably the key substance of interest. For the inhalation route, the model of Lee *et al*. (1998) was used to estimate BAA blood concentrations in female rats following inhalation exposure to EGBE because it is a recent extension of the (Corley *et al*., 1994 and 1997) model for inhalation exposures and includes added parameters for female rats.

The PBPK model allows the concentration of the proximate toxicant (BAA) to be predicted following either inhalation or oral exposure to EGBE. The following four steps are carried out to obtain a human equivalent concentration (HEC), following a similar approach to that adopted by the US EPA (US EPA, 1999): (1) calculate the internal dose metric (C_{max} BAA in blood) corresponding to the female rat LOAEL, using the actual experimental exposure pattern (6hrs/day, 5 days/week) in the model simulation; (2) verify that steady state was achieved (e.g., no change in BAA C_{max} as a result of extending the exposure; (3) simulate the internal dose metric (C_{max} BAA in blood) for humans inhaling EGBE and 4) calculate the HEC (mg/m^3) that results in this internal dose C_{max} BAA. The relationship between EGBE exposure and resultant BAA for humans and female rats as used in step 3 is shown below:



Note: Data for rats is the upper line, data for humans the lower line

In humans cases of massive ingestions the main toxic effect was a metabolic acidosis with sometimes haematotoxicity. For haematotoxicity, humans are much less sensitive than rodents and according to human studies, it appears that there is not a great intraspecies sensitivity (no influence of age or haematological status). Moreover, this end point was not the most sensitive end point for acute toxicity in human because in case of massive ingestions haemotoxicity was not observed in all cases. But metabolic acidosis was observed in all case. The lowest dose leading to metabolic acidosis in human was 400 mg/kg (LOAEL) for EGBE.

As human data is preferred if exists, this LOAEL will be taken into account for the risk characterisation. As no data exists in human by dermal or inhalation route, an extrapolation of this LOAEL obtained with EGBE will be done for risk characterisation for these routes using appropriate route to route extrapolation factors. ”Only very slight irritation sign were observed in animals or in vitro tests. But, according to EC classification criteria, EGBEA does not warrant classification for skin, eye and respiratory tract irritation. Cats, exposed to 460 ppm of EGBEA, showed symptoms of irritation to mucus membranes (BASF, 1965) but in a study of limited reliability. From the human data with EGBE, it is apparent that the NOEC for respiratory irritation is > 50 ppm (expressed in EGBE) whilst the NOEC (based on effects of discomfort) is <100-200 ppm (expressed in EGBE). However 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. No sensitisation properties linked directly to EGBEA or EGBE were seen from the available data on human and animal.

For repeated dose toxicity, it has been shown that rodents are much more sensitive than human to the haemolytical effects of EGBE and EGBEA, therefore if a NOAEL based on these effects is used for risk characterisation, the MOS used should reflect the sensitivity of rodents. Kupffer cell pigmentation is secondary to the haemolytic effects. Effects on spleen (including spleen fibrosis) can also be related also to haemolysis. This effect usually occurs following administration of substances which is able to cause iron accumulation in the splenic red pulp (Goodman *et al*., 1984 - Weinberger *et al*., 1985). 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.

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 with EGBE. For the oral route, a LOAEL of 69 and 82 mg/kg/day for male and female rats respectively was derived from a 13 week oral study in rats with EGBE which corresponds to a LOAEL of 94 and 111 mg/kg/day for male and female rats expressed in EGBEA (haemolytical effects).

For dermal exposure, a cross-reading with EGBE data is performed and a NOAEL of 150 mg EGBE/kg bw (the highest dose tested) i.e. 203 mg EGBEA/kg bw is taken into account for the repeated toxicity by dermal route. Since all key effects are induced by haemolysis in rodents, a NOAEL based on haemotoxicity will be used in the risk characterisation. The selection of an appropriate interspecies chemical safety assessment factor (CSAF) must take into account the lower sensitivity of humans to BAA than rats (or mice). IPCS have proposed splitting the CSAF two components representing the toxicokinetic and toxicodynamic adjustment factors (AK_{AF} and AD_{AF} respectively). The toxicokinetic factor is taken account of by use of the PBPK model described above. The AD_{AF} factor needs to be set to an appropriate value to reflect the lower sensitivity of humans to haemolysis. 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 would be to propose a value of 0.1.

For mutagenicity, it can be estimated that EGBEA is not of concern of genotoxicity based on the EGBE data.

Assessment of the toxicity for reproduction of EGBEA is based on EGBE data. This compound seems to have no specific effects on fertility. A NOAEL of 720 mg/kg was derived from the continuous breeding study for fertility effects with EGBE. Based on EGBE data, the NOAEL for reproduction toxicity for EGBEA is estimated at 976,3 mg/kg bw.

For developmental studies, embryonic and foetal effects seen in animals were related to maternal toxicity (haemolysis) with EGBE. Overall, it was not possible to obtain a suitable NOAEL for developmental toxicity relevant for humans and based on animals studies with EGBE. 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. EGBEA is therefore assumed also as having no concern for this end-point and no need for risk characterisation is assumed.

For carcinogenicity, some effects were seen in mice in the 2-year studies with EGBE. 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 assess for carcinogenicity. The other tumours (mouse forestomach) are considered not relevant to humans; no risk characterisation is needed for them. The same conclusion applies for EGBEA.

The selected NOAEL(C) or LOAEL(C) used for the risk characterisation are reported in the table 4.26:

Table 4.26 - Summary of effects

Substance name	Inhalation (N(L)OAEC)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	NA	NA	542 mg/kg expressed in EGBEA based on a human LOAEL of 400 mg/kg with EGBE
Irritation / corrositivity	NA	NA	NA
Sensitization	NA	NA	NA
Repeated dose toxicity (local)	NA	NA	NA
Repeated dose toxicity (systemic)	31 ppm (rat LOAEC on EGBE haemolytic effects)	203 mg EGBEA/kg (rabbit NOAEL on EGBE haemolytic effects)	94 mg EGBEA /kg (rat LOAEL on EGBE hepatic effects)
Mutagenicity	NA	NA	NA
Carcinogenicity	NA	NA	NA
Fertility impairment	NA	NA	976 mg EGBEA /kg (mouse NOAEL on EGBE effects)
Developmental toxicity	NA	NA	NA

4.1.3.2 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.

4.1.3.2.1 Acute toxicity

According to acute toxicity data of EGBE in human (suicide attempts cases) a LOAEL of 542 mg/kg by oral route can be taken into account (extrapolation of the 400 mg/kg taken for EGBE). As limited data exist in humans by dermal or inhalation route an extrapolation route to route of this LOAEL is done. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.27 - Assessment factors applied for the calculation of minimal MOS for acute toxicity (for inhalation and dermal route).

Interspecies differences	1 (human data)
Intraspecies differences	3 (workers: homogen population)
Type of effect	1
Extrapolation LOAEL to NOAEL	5
Confidence of the database	1

Minimal MOS	15 for inhalation and dermal routes

This minimal MOS is quite conservative due to the less severity of the effects observed with EGBEA by the dermal and inhalation routes, in comparison with effects observed with EGBE.

Inhalation route:

First, the oral LOAEL of 400 mg EGBE/kg has to be extrapolated to an oral LOAEL for EGBEA:

LOAEL (EGBEA) = 400 x 1.356 = 542 mg/kg expressed in EGBEA.

Then, the oral LOAEL for EGBEA needs to be extrapolated to a inhalation LOAEC to compare with inhalation exposure.

The dose of 542 mg/kg by oral route correspond to 542 mg/kg of internal dose (100 % absorption by oral route). To obtain this internal dose by inhalation, it is necessary to add internal dose due to inhalation of vapours and internal dose due to percutaneous penetration of vapours. The ratio between these two doses has been calculated 61% / 39 % respectively. Leading to:

542 x 0.61 = 330 mg/kg of internal dose due only to inhalation and

542 x 0.39 = 211 mg/kg of internal dose due only to percutaneous absorption of vapours.

- To obtain 330 mg/kg of internal dose in one day, a worker of 70 kg with a respiratory volume of 10 m^3/worday, with an absorption factor of 60 % for inhalation uptake should be exposed to

330 mg/kg * 70 kg / 10 m^3 / 0.60 = 3850 mg/m^3.

This value is the extrapolated LOAEC and should be compared with exposure levels.

The MOSs between the LOAEC and the inhalation exposure levels are mentioned in table 4.28. The MOSs are evaluated by comparison with the minimal MOS (table 4.27). The conclusions are given in the table 4.28. Based on the risk assessment for inhalation exposure, it is concluded that toxicity due to acute exposure are not expected. **Conclusion ii** is reached for all occupational scenarios.

Table 4.28 - Occupational risk assessment of EGBEA for acute toxicity.

Scenario		Risk assessment for inhalation exposure			Risk assessment for dermal exposure of liquid EGBE		
		8-hour TWA inhalation (mg/m^3)	MOS[1]	Conclusion	Estimated Skin exposure mg/day (mg/kg bw/d)	MOS[2]	Conclusion
1 - Manufacture		0.48	8021	ii	42 (0.6)	3011	ii
2 - Formulation		23	167	ii ii	2000 (28.6)	63	ii
3 - Use of end products	3.1 Coating/Painting						
	3.11 Industrial:						
	- spraying	13.3	289	ii	2000 (28.6)	63	ii
	- other work	13.3	289	ii	430 (6.1)	296	ii
	3.12 decorative	13.3	289	ii	117 (1.7)	1063	ii
	3.2 Printing						
	3.21 Silk screening	11	350	ii	23 (0.3)	6023	ii
	3.22 General printing	30	128	ii	168 (2.4)	753	ii

1- calculation based on a respiratory volume of 10 m^3/worday, a worker bw of 70 kg, an absorption factor of 60 %, an internal dose due to inhalation uptake (61 %) and dermal uptake of vapour (39 %) and an oral LOAEL of 542 mg/kg bw.

2- calculation based on a worker bw of 70 kg, an absorption factor of 30 % and an oral LOAEL of 542 mg/kg bw. Worst case.

Dermal route:

First, the oral LOAEL of 400 mg EGBE/kg has to be extrapolated to an oral LOAEL for EGBEA:

LOAEL (EGBEA) = 400 x 1.356 = 542 mg/kg expressed in EGBEA.

Then, the oral LOAEL for EGBEA needs to be extrapolated to a dermal LOAEL to compare with dermal exposure.

Oral dose of 542 mg/kg would give an internal dose of 542 mg/kg (100 % absorption by oral route). To reach this dose with a dermal exposure to liquid EGBEA, the external dose should be :

542 / 0.3 = 1807 mg/kg bw

because 30% is assumed to be the worst case percentage of absorption of liquid EGBEA by dermal route.

This LOAEL of 1807 mg/kg bw should be compared with estimated skin exposures. The MOSs between the LOAEL and the dermal exposure levels are mentioned in table 4.28. The MOSs are evaluated by comparison with the minimal MOS (table 4.27). The conclusions are given in the table 4.28. Based on the risk assessment for dermal exposure, it is concluded that toxicity due to acute exposure are not expected. **Conclusion ii** is reached for all occupational scenarios.

Combined exposure:

Given the conclusions for the scenarios 1, 2 and 3 drawn for the dermal and inhalation routes separately and the large range of MOS calculated, it is assumed that internal exposure of the worker as result from uptake via both routes in these scenarios will not give rise to acute toxic effects (**conclusion ii).**

4.1.3.2.2 Irritation and corrosivity

Skin

EGBEA is not a skin irritant substance. No concern. **(Conclusion ii)**

Eye

EGBEA is not an eye irritant substance. No concern. **(Conclusion ii)**

Respiratory tract

Since EGBEA is not predicted as having respiratory tract irritant properties, it is concluded that EGBEA is of no concern with regard to respiratory tract irritant for workers **(conclusion ii)**.

4.1.3.2.3 Sensitisation

Given the results from the dermal sensitisation study it is concluded that EGBEA is of no concern for workers with regard to skin sensitisation **(conclusion ii)**.

There are neither data from human experience nor other indications for respiratory sensitisation but this toxicological end-point is not expected for EGBEA **(conclusion ii).**

4.1.3.2.4 Repeated dose toxicity

Based on the EGBE studies, some data can be used to derive MOS for interspecies differences. It is clearly demonstrated that rodent blood cells are much more sensitive than human ones (at least 100 times), for this effect, a conservative factor of 0.1 will be used.

As it is indicated in EGBE RAR:

"it is clear from the available data that haemolysis is the primary and critical response elicited in the main animal test models (rats and mice) following inhalation, oral or dermal exposure to EGBE. Blood from humans, pigs, dogs, cats, and guinea pigs is less sensitive to haemolysis by BAA. In sensitive species, EGBE produces a characteristic toxicity that is revealed clinically by the appearance of haemoglobinuria and pathologically by changes in a variety of blood parameters. A 100-fold greater concentration of BAA (10mM) is required for human erythrocytes to develop pre-haemolytic changes consistent with those seen in the rat (0.1mM). Such *in vivo* blood concentrations are unlikely to occur under normal conditions of human exposure to BE. Haemolysis did not occur with any blood from any individual, even sensitive sub-populations, when exposed *in vitro* to BAA(10 mM). Studies have also shown that potentially sensitive human sub-populations, including the children, the elderly and those with sickle cell anemia are also equally resistant to the effect.

PBPK models exist for the rat, mouse and human.

These can be applied to derived the appropriate toxicokinetic element of the interspecies assessment factor. The use of the model is described in the General Aspects section and is applied here as follows:

Step 1: Calculate C_{max} for BAA in blood corresponding to female rat LOAEL

Female rat (critical species and sex) LOAEC = 31 ppm.
Resultant C_{max} BAA from such an exposure= 285 µM.

Step 2: Verify steady state.

There were no changes in the C_{max} of BAA in blood during any 24-hour simulation period using a 6 hours/day, 5 days/week exposure regime at the female rat LOAEL, indicating that steady state was achieved.

Steps 3 and 4: Calculate the C_{max} for BAA in blood for humans continuously exposed to EGBE vapour and calculate the $LOAEL_{HEC}$ for EGBE for human exposures producing the same C_{max} of BAA in blood as that that produces effects in rats.

For a BAA concentration of 285 µM, the HEC = 98 ppm (474mg/m^3).

Equivalent human doses for LOAEL(C) / NOAEL(C) for EGBE are reported in table 4.29:

Table 4.29: Equivalent human doses for LOAEL(C) / NOAEL(C) for EGBE

	Oral	Inhalation	Dermal
End point	LOAEL	LOAEC	NOAEL
Value	69 mg/kg/day (male rat)	31 ppm (152mg/m³)	150 mg/kg/day
Equivalent BAA C_{max} concentration	129 µM	285 µM	
Equivalent human dose	9.5 mg/kg/day	97 ppm (474mg/m³)	

The values used for risk characterisation of repeat dose for EGBEA then become as follows:
- oral: 12.9 mg/kg/d for EGBEA
- inhalation: 97 ppm for EGBEA (645 mg/m³).

Assessment factors applied for the calculation of minimal MOS for repeated dose toxicity (for inhalation and dermal route) are reported below:

Table 4.30 - Assessment factors applied for the calculation of minimal MOS for Repeated dose toxicity (for inhalation and dermal route).

Interspecies differences	0.1 (toxicodynamic factor) inhalation: toxicokinetic element taken into account by PBPK model dermal: Additional factor of 4 to account for allometric scaling of rats to humans
Intraspecies differences	5 (default for workers population)
Duration of study	No factor required. The critical study is 6 months in duration and the effects for this end-point (haemolysis) would not be expected to be more severe compared to lifetime exposure. (haemolysis due to EGBE is considered to be an acute or sub-acute effect on rodents, moreover in some studies animals tended to "recover" (red blood cells being less sensitive) with long times of exposure.
Type of effect	1
Extrapolation LOAEL to NOAEL	3 for oral and inhalation. The effects were mild at this dose and there is evidence to show that the LOAEL is near the threshold level for effects of concern (eg NOAECs from other studies) 1 for dermal exposure
Confidence of the database	1
Minimal MOS	1.5 (oral and inhalation) 2 (dermal)

Note that the critical LOAEC used for the inhalation risk characterisation is derived from a whole body inhalation exposure study (as are all similar studies). These animals will have been subjected to exposure by both the dermal and inhalation routes. The dermal absorption rates in rats and mice are also higher than in humans. Therefore it is not necessary to make a correction for additional uptake from dermal absorption of vapours.

Oral exposure

No oral exposure has been identified for workers, therefore there are no concerns for this route of exposure.

Inhalation

An inhalation LOAEC of 645 mg/m³ (expressed in EGBEA) has been calculated using the PBPK model. The MOSs between the LOAEC and the inhalation exposure levels are mentioned in table 4.31. The MOSs are evaluated by comparison with the inhalation minimal MOS (table 4.30) and conclusions are given in the table 4.31:

Table 4.31 - Occupational risk assessment of EGBEA for Repeated dose toxicity.

Scenario		Risk assessment for inhalation exposure			Risk assessment for dermal exposure of liquid EGBEA		
		8-hour TWA inhalation (mg/m^3)	MOS[1]	Conclusion	Estimated Skin exposure mg/day (mg/kg bw/d)	MOS[2]	Conclusion
1 - Manufacture		0.48	1344	ii	42 (0.6)	338	ii
2 - Formulation		23	28	ii	2000 (28.6)	7	ii
3 - Use of end products	Coating/Painting - Industrial						
	- spraying	13.3	48	ii	2000 (28.6)	7	ii
	- other work	13.3	48	ii	430 (6.1)	33	ii
	- decorative	13.3	48	ii	117 (1.7)	119	ii
	Silk screening	11	59	ii	23 (0.3)	4676	ii
	General printing	30	21	ii	168 (2.4)	84	ii

Based on the risk assessment for inhalation exposure, it is concluded that toxicity due to repeated dose exposures are not expected. **Conclusion ii** is reached for all occupational scenarios.

Dermal exposure

Exposure values are compared with the NOAEL of 150 mg/kg/d of EGBE corresponding to 203 mg/kg/d of EGBEA.

It is not possible to use the PBPK approach for the dermal assessment and a more conventional approach is therefore used.

See previous table and table showing derivation of MOSs. The MOSs between the NOAEL and the dermal exposure levels are mentioned in table 4.31. The MOSs are evaluated by comparison with the dermal minimal MOS (table 4.30) and conclusions are given in the table 4.31.

Based on the risk assessment for dermal exposure, it is concluded that toxicity due to repeated dose exposures are not expected.

Conclusion ii is reached for all occupational scenarios.

Combined exposure

For the combined exposures the estimated internal doses are calculated from the biological exposure data. The inhalation LOAEC is chosen for comparison, as this is lower than the equivalent for the dermal route.

So the LOAEC of 645 mg/m³ would lead to an internal dose of 645 mg/m^3 x 10m³/day x 0.6/70kg = 55.3 mg/kg/day.

This internal dose should be compared with internal doses calculated from exposures in each scenario (inhalation + dermal) and calculated as follow:

Inhalation exposure will give internal dose of:

X (value of the 8-hour TWA inhalation (mg/m^3)) x 10 m^3 (inhaled air during a workday) x 0.6 (percentage of absorption by inhalation) / 70 (mean bw of a worker) = Y (inhalation internal dose).

This value does not take into account the possible dermal absorption of vapour during the 8hr TWA. It has been demonstrated that dermal absorption of vapour could count for 39 % of the internal dose. To take into account this value (which is not negligible) the value of internal dose due to dermal exposure to vapours (Z) should be added to the former value (Y). Z represents 39 % of the total internal dose and can be calculated as follow:

Z = 0.39/0.61 x Y = 0.64 Y

The total internal dose due to inhalation exposure (inhalation output + dermal vapour penetration output) is Y + Z = 1.64 Y

In this case, an internal dose of about 35.4 mg/kg (0.64Y) can be calculated, to obtain a total internal dose of 90.7 mg/kg due to inhalation and dermal absorption of EGBEA.

The values are summarised in the following table:

Table 4.32 - Occupational risk assessment of EGBEA for Repeated dose toxicity.

Scenario	Internal dose after exposure to 8-hour TWA (mg/kg bw) Y+Z	Internal dose after Dermal exposure to liquid EGBEA (mg/kg bw) worst case (based on maximal dose)	Total internal dose (inhalation + dermal exposure)	MOS	Ccl
1 - Manufacture	0.07	0.18	0.25	363	ii
2 - Formulation	3.23	8.6	11.8	7.7	ii
3 - Use of end products					
3.1 Coating/Painting - Industrial					
- spraying	1.87	8.6	10.5	8.6	ii
- other work	1.87	1.8	3.7	24.5	ii
- decorative	1.87	0.5	2.4	37.8	ii
3.2 Silk screening	1.5	0.1	1.6	56.7	ii
3.3 General printing	4.21	0.7	4.9	18.5	ii

The worst case minimal MOS required for the combined inhalation/dermal route is 2.

According to the results obtained, there are no concerns for repeat dose exposure for all the scenarios.**(conclusion ii)**.

4.1.3.2.5 Mutagenicity

Given the results from the mutagenicity studies performed with EGBE it is concluded that EGBEA is of no concern for workers with regard to mutagenicity **(conclusion ii)**.

4.1.3.2.6 Carcinogenicity

Based on EGBE data: “as the mechanism of haemangiosarcomas in male mice is related to haematotoxicity, the risk characterisation made for repeated dose toxicity (RDT) is also relevant for carcinogenicity. The other tumours seen in the animal studies being not relevant to humans no risk characterisation is needed for them.”

See RDT risk characterisation section.

There are no concerns for carcinogenicity for all scenarios. **(conclusion ii)**.

4.1.3.2.7 Toxicity for reproduction

It is possible to derive a no effect level of 720 mg/kg/day for fertility effects of EGBE based on a continuous breeding study in mice, corresponding to 976 mg EGBEA/kg/day. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.33: Assessment factors applied for the calculation of minimal MOS fertility effects.

Interspecies differences	10
Intraspecies differences	5 (workers: homogen population)
Type of effect	1
Confidence of the database	1
Minimal MOS	50

Internal dose extrapolated from the NOAEL would be 976 mg/kg bw (100 % oral absorption). This value should be compared with estimated internal doses due to exposure.

It is necessary in this case to correct the inhalation value for the dermal absorption of vapour during the 8hr TWA as it is being compared to a NOAEL derived from an oral study. It has been demonstrated that dermal absorption of vapour EGBE could count for 39 % of the internal dose of EGBE. To take into account this value (which is not negligible) the value of internal dose due to dermal exposure to vapours (Z) should be added to the former value (Y). Z represents 39 % of the total internal dose and can be calculated as follow:

$Z = 0.39/0.61 \times Y = 0.64\ Y$

The total internal dose due to inhalation exposure (inhalation output + dermal vapour penetration output) is $Y + Z = 1.64\ Y$. The values for Y are shown in the table used for the repeat dose combined route assessment.

Table 4.34 summarises risk characterisation for inhalation exposure, dermal exposure and combined exposure:

Table 4.34: Risk characterisation for reprotoxicity

Scenario	Internal dose after exposure to 8-hour TWA (mg/kg bw) Y+Z [1]	MOS Inhalation only	Internal dose after Dermal exposure to liquid EGBE (mg/kg bw) worst case (based on maximal dose)	MOS dermal only	Total internal dose (inhalation + dermal exposure)	MOS Combined	Ccl inhalation, dermal and combined
1 - Manufacture	0.07	13942	0.18	5422	0.25	3904	ii
2 - Formulation	3.23	302	8.6	113	11.8	82	ii
3 – Use of end products							
3.1 Coating/Painting							
- Industrial							
- spraying	1.87	522	8.6	113	10.5	93	ii
- other work	1.87	522	1.8	542	3.7	264	ii
- decorative	1.87	522	0.5	1952	2.4	406	ii
3.2 Silk screening	1.54	633	0.1	9760	1.6	610	ii
3.3 General printing	4.21	232	0.7	1394	4.9	199	ii

a: non dispersive use, b: wide dispersive use

1) internal dose for exposure to EGBE vapour is due to inhalation uptake (10 m3 a workday, a worker of 70 kg bw and 60 % of absorption) and to percutaneous absorption of vapour EGBE (39 % of the total internal dose)

The calculated MOS should be compared with worst-case minimal MOS: 50.

Conclusion ii is reached for all scenarios.

The developmental toxicity studies for EGBE clearly indicate that the developmental effects observed are a consequence of and secondary to maternal toxicity. Any formal risk characterisation for humans using this data would not be meaningful. The available data does not suggest that EGBE shares the developmental toxicity properties of certain other glycol ethers. There is no other data, which indicates potential developmental toxicity concerns. Therefore the conclusion is that there is no concern for this end point for EGBEA, conclusion (ii). **(conclusion ii)**.

4.1.3.2.8 Summary of risk characterisation for workers

Conclusion (ii) applies for all scenarios concerning each end-point.

4.1.3.3 Consumers

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.

For risk characterisation, a value of 30 % for dermal absorption and a value of 60 % for inhalation exposure can be taken into account (see table below).

Table 4.35 - Internal dose exposures

Scenario	Inhalation (mg/kg/d)	Skin (mg/kg/d)	Sum of exposures (mg/kg/d)
Paints	0.67	3.15	4.24

4.1.3.3.1 Acute toxicity

According to acute toxicity data of EGBE in human (suicide attempts cases) a LOAEL of 542 mg/kg by oral route can be taken into account (extrapolation of the 400 mg/kg taken for EGBE). As limited data exist in humans by dermal or inhalation route an extrapolation route to route of this LOAEL is done. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.36 - Assessment factors applied for the calculation of minimal MOS for acute toxicity (for inhalation and dermal route).

Interspecies differences	1 (human data)
Intraspecies differences	10
Type of effect	1
Extrapolation LOAEL to NOAEL	5
Confidence of the database	1
Minimal MOS	50

The MOSs between the LOAEC and the inhalation exposure levels are mentioned in table 4.37. The MOSs are evaluated by comparison with the minimal MOS (table 4.36). The conclusions are given in the table 4.37.

Table 4.37 - MOSs and conclusions for acute toxicity

Scenario	Inhalation		Dermal		Sum of exposures	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
3 – Paints	815	ii	172	ii	127	ii

Based on the modelisation for the paint scenario, it is concluded that the toxicity due to acute exposure is not expected. So **conclusion ii** is reached.

4.1.3.3.2 Irritation and corrosivity

Skin

EGBEA is not a skin irritant substance. No concern. **(Conclusion ii)**

Eye

EGBEA is not an eye irritant substance. No concern. **(Conclusion ii)**

Respiratory tract

Since EGBEA is not predicted as having respiratory tract irritant properties, it is concluded that EGBEA is of no concern with regard to respiratory tract irritant for consumers **(conclusion ii)**.

4.1.3.3.3 Sensitisation

No concern

4.1.3.3.4 Repeated dose toxicity

Assessment factors applied for the calculation of minimal MOS for repeated dose toxicity (for inhalation and dermal route) are reported in table 4.37:

Table 4.37 - Assessment factors applied for the calculation of minimal MOS for Repeated dose toxicity (for inhalation and dermal route).

Interspecies differences	0.1 (toxicodynamic factor) inhalation: toxicocinetic element taken into account by PBPK model dermal: Additional factor of 4 to account for allometric scaling of rats to humans
Intraspecies differences	10
Duration of study	No factor required. The critical study is 6 months in duration and the effects for this end-point (haemolysis) would not be expected to be more severe compared to lifetime exposure. (haemolysis due to EGBE is considered to be an acute or sub-acute effect on rodents, moreover in some studies animals tended to "recover" (red blood cells being less sensitive) with long times of exposure.
Type of effect	1
Extrapolation LOAEL to NOAEL	3 for oral and inhalation The effects were mild at this dose and there is evidence to show that the LOAEL is near the threshold level for effects of concern (eg NOAECs from other studies) 1 for dermal exposure
Confidence of the database	1
Minimal MOS	3 (oral and inhalation) 4 (dermal)

Risk characterisation

For repeated dose toxicity, daily exposure level has to be averaged over a year. So the internal exposure dose used for risk characterisation will be :

$$\frac{\text{internal dose x number of events over a year}}{365}$$

As very worst-case approach risk characterisation for a daily use of paint has also been conducted.

Internal dose exposure depending on scenarios average over a year were calculated and are summarised in table 4.38:

Table 4.38: Internal dose exposure depending on scenarios average over a year

Scenario	Number of events	Inhalation (mg/kg/d)	Skin (mg/kg/d)	Sum of exposures (mg/kg/d)
3 – Painting daily use	365 events/year	0.67	3.15	4.24
3 – Painting average over the year	10 events/year	0.018	0.086	0.104

Inhalation

An inhalation LOAEC of 645 mg/m³ (expressed in EGBEA) has been calculated using the PBPK model. The MOSs between the LOAEC and the inhalation exposure levels are mentioned in table 4.39.

The MOSs are evaluated by comparison with the inhalation minimal MOS (table 4.37) and conclusions are given in the table 4.39.

Dermal exposure

Exposure values are compared with the NOAEL of 150 mg/kg/d of EGBE corresponding to 203 mg/kg/d of EGBEA.

It is not possible to use the PBPK approach for the dermal assessment and a more conventional approach is therefore used

Internal NOAELs have to be calculated and to be compared with the internal daily exposures by skin and by inhalation and to the sum of internal exposures.

For combined exposure, the NOAEL concerning the dermal exposure will be chosen as it is more protective for consumers.

The respiratory volume for an adult is 20 m^3 and the mean bodyweight is 60 kg. The absorption of EGBE by inhalation is 60 %. So the internal NOAEL by inhalation will be :

$$\frac{645 \text{ x } 20 \text{ x } 0.6}{60} = 129 \text{ mg/kg/d}$$

The dermal absorption factor is 30%. So the internal NOAEL by dermal route will be :

$$203 \text{ x } 0.3 = 60.9 \text{ mg/kg/d}$$

Consumer risk assessment of EGBEA for repeated dose toxicity is reported in table 4.39:

Table 4.39 - Consumer risk assessment of EGBEA for Repeated dose toxicity.

Scenario	Inhalation		Dermal		Sum of exposures	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
3 – Paints daily use	192	ii	19	ii	14.4	ii
3 – Paints average over the year	7166	ii	705	ii	585	ii

According to the results obtained, there are no concerns for repeated dose exposure for the scenarios.**(conclusion ii)**.

4.1.3.3.5 Mutagenicity

Given the results from the mutagenicity studies performed with EGBE it is concluded that EGBEA is of no concern for consumers with regard to mutagenicity **(conclusion ii)**.

4.1.3.3.6 Carcinogenicity

Based on EGBE data: "as the mechanism of haemangiosarcomas in male mice is related to haematotoxicity, the risk characterisation made for repeated dose toxicity (RDT) is also relevant for carcinogenicity. The other tumours seen in the animal studies being not relevant to humans no risk characterisation is needed for them."

See RDT risk characterisation section.

There are no concerns for carcinogenicity for all scenarios. **(conclusion ii)**.

4.1.3.3.7 Toxicity for reproduction

It is possible to derive a no effect level of 720 mg/kg/day for fertility effects of EGBE based on a continuous breeding study in mice, corresponding to 976 mg EGBEA/kg/day. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.40: Assessment factors applied for the calculation of minimal MOS fertility effects.

Interspecies differences	10
Intraspecies differences	10
Type of effect	1
Confidence of the database	1
Minimal MOS	100

Risk characterisation for inhalation exposure, dermal exposure and combined exposure is summarised in table 4.41:

Table 4.41 - Consumer risk assessment of EGBEA for toxicity reproduction.

Scenario	Inhalation		Dermal		Sum of exposures	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
3 – Paints	1467.67	ii	309.84	ii	230	ii

The developmental toxicity studies for EGBE clearly indicate that the developmental effects observed are a consequence of and secondary to maternal toxicity. Any formal risk characterisation for humans using this data would not be meaningful. The available data does not suggest that EGBE shares the developmental toxicity properties of certain other glycol ethers. There is no other data, which indicates potential developmental toxicity concerns. Therefore the conclusion is that there is no concern for this end point for EGBEA, conclusion (ii). (conclusion ii).

4.1.3.3.8 Summary of risk characterisation for consumers

Conclusion (ii) applies for all scenarios concerning each end-point.

4.1.3.4 Humans exposed via the environment

The key health effects 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 RDT via inhalation route corrected with PbPk modelling to obtain human internal dose of 90.7 mg/kg/d for EGBEA see also calculation of internal NOAEL by inhalation in the worker part in chapter 4.1.3.2.4.) 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.

4.1.3.4.1 Summary of risk characterisation for exposure via the environment

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

This conclusion applies for all endpoints in relation to local and regional exposure.

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 physico-chemical properties (**conclusion ii**).

5 RESULTS [7]

5.1 INTRODUCTION

5.2 ENVIRONMENT

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

5.3.1.1 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.

Conclusion (ii) applies for all end points and for all scenarios

5.3.1.2 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.

5.3.1.3 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.

[7] 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.

5.3.2 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.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
AP	Acid phosphatase
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
ATSDR	Agency for toxic substances and disease registry (USA)
AUC	Area Under The Curve
B	Bioaccumulation
BAA	Butoxy Acetic Acid
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BEL	Biological exposure level
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CBFV	Cutaneous Blood Flow Value
CEC	Commission of the European Communities
CEET	Chicken Enucleated Eye Test
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European council of the paint, printing ink and artists' colours industry
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)

DMSO	Dimetylsulfoxyde
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EAA	Ethoxy Acetic Acid
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EGEEA	Ethylene Glycol Etyl Ether Acetate
EGBE	Ethylene Glycol Butyl Ether
EGBEA	Ethylene Glycol Butyl Ether Acetate
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GAG	Glycosaminoglycans
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission

HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
INRS	Institut national de recherche et de sécurité (France)
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEL	No Observed Adverse Effect Level

NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
NR50	Neutral Red uptake inhibition 50 %
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PDII	Primary Dermal Irritation Index
PEC	Predicted Environmental Concentration
PGE2	Prostaglndin E2
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDH	Succinate DeHydrogenase

SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STEL	Short-term exposure limit
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TLV	Threshold limit value
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
TWA	Time-weighted average
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A

Methods of calculation of exposures

Scenario : paints

Inhalation

ConsExpo 4.1 report

file name: C:\Documents and Settings\DE-Saint-Jores\Mes documents\BERPC\substances\EGBA\EGBA.Ce4
Report date: 28/02/2008

Product

EGBA

Compound

Compound name :	EGBA	
CAS number :	112-07-2	
molecular weight	160	g/mol
vapour pressure	40	Pascal
KOW	1,51	10Log

General Exposure Data

exposure frequency	10	1/year
body weight	60	kilogram

Inhalation model: Exposure to vapour : evaporation

weight fraction compound	20	%
exposure duration	360	minute
room volume	25	m3
ventilation rate	0,5	1/hr
applied amount	5	kilogram
release area	28	m2
application duration	360	minute
mol weight matrix	400	g/mol
mass transfer rate	2,95E3	m/min

Uptake model: Fraction

uptake fraction	0,6	fraction
inhalation rate	20	m3/day

Output

Inhalation (point estimates)

inhalation mean event concentration :	972	mg/m3
inhalation mean concentration on day of exposure:	243	mg/m3
inhalation air concentration year average :	6,65	mg/m3/day
inhalation acute (internal) dose :	48,6	mg/kg
inhalation chronic (internal) dose :	1,33	mg/kg/day

Integrated (point estimates)

total external dose:	81	mg/kg
total acute dose (internal):	48,6	mg/kg
total chronic dose (internal):	1,33	mg/kg/day

So the total external exposure by inhalation in one day is :

$$C_{tot\ (mg/kg/d)} = \frac{V_r \times h_p \times C_{paint}}{24 \times W_b}$$

C_{tot} = external exposure by inhalation
V_r = respiratory volume in one day
W_b = mean bodyweight for a consumer (60 kg)

$$E_{ii} = E_{ei} \times abs_i$$

E_{ii} = internal exposure by inhalation
abs_i = percentage of absorption by inhalation

Dermal

$$E_{ed} = \frac{Cp \times t_e \times S_h \times Q_h}{W_b}$$

E_{ed} = external dermal exposure
Q_p = Quantity of product used
S_h = surface of hands
Q_h = Quantity of paint transferred to the hands
t_e = duration of exposure
W_b = mean bodyweight for a consumer (60 kg)

$$E_{id} = E_{ei} \times abs_i$$

E_{id} = internal dermal exposure
abs_i = percentage of absorption by skin

European Commission

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The report provides the comprehensive risk assessment of the substance 2-butoxyethanol acetate 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 man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

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.

The human health risk assessment concludes that there is no concern for workers, consumers, for humans exposed via the environment and for human health (physico-chemical properties).