2-Ethoxyethanol

(2nd Priority List)

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Strategy For Limiting Risks

Human Health

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CONTENT

0 Summary

According to the current information (INEOS 2006) only one production site of 2-ethoxyethanol is remaining in the EU. There is no known import from outside of the EU. No information is available on possible exports of 2-ethoxyethanol.

The submitted information on production in the EU indicates varying volumes for the last years production with no clear trend. Hence, the data from the years 2000- 2005 were averaged resulting in a yearly volume of approximately 1000 t/a of 2-ethoxyethanol. This volume was used for the risk assessment.

The main proportion of 2-ethoxyethanol is processed to intermediates such as the 2-ethoxyethanol tert. butyl ether in chemical industry. The smaller part is industrially used as a solvent.

2-Ethoxyethanol was chosen for risk assessment because of the previous high production volume. It was widely used in open systems, such as paints for private use, in surface treatment of metals and in repair industry. Besides the industrial use as intermediate and solvent, 2-ethoxyethanol was used for the formulation of paints, lacquers, varnishes and printing inks.

Based on the latest information (INEOS 2006), there is no remaining wide dispersive use of 2-ethoxyethanol outside the chemical industry.

The current classification of 2-Ethoxyethanol according to Annex I of the Directive 67/548/EEC (19 ATP, Index-Nr. 603-012-00-X) is

R10; Repr. Cat. 2; R60-61 - Xn; R20/21/22.

In September 2007 the proposal submitted by DE to delete R21 for 2-ethoxyethanol in Annex I was agreed by the Technical Committee on Classification and Labelling (TC C&L).

The agreed classification will be included in a future Adaption to Technical Progress (ATP).

2-Ethoxyethanol will have to be labelled with T; R60-61-10-20/22; S53-45.

According to Appendix to Directive 76/769/EEC, Point 31, the packaging of 2-Ethoxyethanol (as a substance that is toxic for reproduction-Category 2) and preparations containing 2-Ethoxyethanol must be marked legibly and indelibly as follows: ‘Restricted to professional users’.

Workers

It has been concluded from the risk assessment that there is a need for limiting the risks due to developmental toxicity in scenario 1 "production and further processing in the large scale industry" The critical exposure levels are of 0.72mg/m^3 for inhalation and 0.18 mg/kg/day for dermal contact. Inhalative and dermal exposures assessed in the Risk Assessment are higher than the critical limits (3 mg/m^3 and 0.3 mg/kg/day).

The risk reduction strategy recommends the following measures:

- to establish at community level occupational exposure limit values for 2-ethoxyethanol according to Directive 98/24/EEC
- information on the need of specific training, organisational measures and occupational hygiene in the framework of Directive 98/24EEC and specific risk assessment in the framework of Directive 92/85/EEC on improvements in the safety and health of pregnant workers

1 Background

In the framework of EU Regulation 793/93 on the evaluation and control of the risks of existing substances data are gathered, priority substances are selected, their risks are assessed and, if necessary, strategies for limiting the risks are developed. The risk assessments cover the risks to man exposed directly at the workplace or as a consumer and indirectly through the environment and the risks to the environment. 2-Ethoxyethanol is a substance on the second priority list (Regulation (EC) No. 2268/95 of the Commission of 28 September 1995).

2-Ethoxyethanol is a colourless liquid at 20 °C at room temperature and normal pressure. The Melting point is < - 80 °C, the Boiling point is 132 - 137 °C at 1013hPa, the Relative density is 0.930 at 20 °C, .the Vapour pressure is 5.3 hPa at 20 °C. 2-Ethoxyethanol is miscible with water in each ratio at 20 °C. The Partition coefficient is log Pow –0.54 to –0.10, the Flash point is 40 °C (closed cup), the Ignition temperature is 235 °C. 2-Ethoxyethanol is flammable.

Production

According to the current information (INEOS 2006) only one production site (site A) of 2-ethoxyethanol is remaining in the EU. There is no known import from outside of the EU. No information is available on possible exports of 2-ethoxyethanol.

The submitted information on production in the EU indicates varying volumes for the last years production with no clear trend. Hence, the data from the last 6 years (2000- 2005) were averaged resulting in a yearly volume of approximately 1000 t/a of 2-ethoxyethanol. This volume is used for the risk assessment. The detailed production volumes are shown in the following table:

Table 1.1: Detailed production volumes

2000	950 t/a

2001	1384 t/a
2002	1360 t/a
2003	1401 t/a
2004	485 t/a
2005	520 t/a

Processing / application (categories of use, amounts)

The main proportion of 2-ethoxyethanol is processed to intermediates such as the 2-ethoxyethanol tert. butyl ether in chemical industry. The smaller part is industrially used as a solvent.

2-ethoxyethanol was chosen for risk assessment because of the previous high production volume. It was widely used in open systems, such as paints for private use, in surface treatment of metals and in repair industry. Besides the industrial use as intermediate and solvent, 2-ethoxyethanol was used for the formulation of paints, lacquers, varnishes and printing inks.

Based on the latest information (INEOS 2006), there is no remaining wide dispersive use of 2-ethoxyethanol outside the chemical industry. The current use pattern is as follows:

Table 1.2: Current use pattern

Main category (MC)	Industrial category (IC)	Use category (UC)	Mass balance [in % of use]
Non-dispersive use (1)	Chemical industry (3)	Intermediate (33)	80
Non-dispersive use (1)	Chemical industry (3)	Solvent (48)	20

According to BUA (1995), information provided by the lead company (INEOS 1996) an additional use for 2-ethoxyethanol as anti-freeze additive for aviation fuels and for clearing runways is obsolete now and to current.

According to the Danish Product Register the total annual use of 2-ethoxyethanol in 1996 exclusively in Denmark, was exceeding 2000 t/a. Currently, information about the use amounts in Norway, Sweden, Denmark and Finland are listed at SPIN (Substances in Preparations in Nordic Countries). The latest information given there is a total amount of 209.3 tonnes in 2004. Further, 2-ethoxyethanol was reported as solvent in cleaning agents/disinfectants and cosmetics for personal/domestic use. Currently, there is no personal/domestic use anymore due to a voluntary program of industry. This programme was initiated due to the toxic effects on reproduction (R 60/ R 61 labelling).

According to the German Washing and Cleansing Agents Act information on ingredients and expected production quantities is supplied to the German Federal Environmental Agency. A use of 75 t 2-ethoxyethanol / a for the application as industrial solvent is registered there (UBA 2006).

2 The Risk Assessment

2.1 Workers

2.1.1 Introductory remarks

For occupational risk assessment of 2-ethoxyethanol the MOS approach as outlined in the revised TGD (Human Health Risk Characterisation, Final Draft) is applied. This occupational risk assessment is based upon the toxicological profile of 2-ethoxyethanol and the occupational exposure assessment. The threshold levels identified in the hazard assessment are taken forward to this occupational risk assessment.

Systemic availability for different routes of exposure

Experimental data from humans and animals for 2-ethoxyethanol show high absorption percentages for the different routes of exposure: According to the RAR-chapter 4.1.2.1 on toxico-kinetics, metabolism and distribution the extent of absorption after oral exposure is assumed to be 100% (worst case). Based on human and animal data, 50 % dermal absorption is taken in the risk characterisation. 64 % absorption via the inhalation route is recommended for risk characterisation purposes in humans (experimental human data). However, for animals lower inhalation absorption percentages are assumed (30 %).

Occupational exposure and internal body burden

In table 2.1.A the exposure levels are summarised and the route-specific and total internal body burdens are identified. Risk assessment for combined exposure requires the calculation of a total internal body burden; to this end the derived route-specific percentages for absorption are used (64% for inhalation and 50% for dermal exposure).

Table 2.1.A: Occupational exposure levels and internal body burden (2-ethoxyethanol)

Exposure scenario	Inhalation shift average	Dermal contact shift average		Internal body burden of workers after repeated exposure		
				Inhalation[(1)]	Dermal[(2)]	Combined
	mg/m^3	mg/p/d	mg/kg/d	mg/kg/d		
1. Production and further processing as an intermediate	3	21[(3)]	0.3	0.27	0.15	0.42

[(1)] based on the assumption of 64% inhalative absorption; breathing volume of 10 m^3 per shift
[(2)] based on the assumption of 50% systemic availability of 2-ethoxyethanol after dermal contact
[(3)] EASE (90 % protection by suitable gloves)

MOS Approach

The MOS approach for human risk characterisation is described in detail in the TGD (Human Health Risk Characterisation, Final Draft). The following chapter contains a short introduction to the MOS approach used. The basic principle of the MOS approach is a comparison of scenario-specific MOS values (the relationship between the experimental NOAEL respectively the adjusted starting point and the exposure level) with a reference MOS (product of various assessment factors).

MOS calculation and the adequate starting point

Basically, MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. In specific situations, the MOS approach requires to convert the original NOAEL into an adequate starting point or corrected NOAEL previously to MOS calculation in order to be directly comparable to the exposure assessment. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental data should be converted to the dose unit of the exposure data. Additionally, possible differences in bioavailability between routes, as well as possible differences in bioavailability between animals and humans should be accounted for the calculation of the corrected NOAEL. If route-specific information on oral and inhalation absorption is not available, the TGD recommends to assume a 50% oral absorption and a 100% inhalation absorption. For 2-ethoxyethanol for humans 64% absorption after inhalation is assumed, whereas in animals 30% absorption percentage is taken. After dermal contact 50% absorption is used and 100% absorption after oral exposure is assumed (experimental values).

For occupational risk assessment, the corrected NOAEC for inhalation accounts for the difference of the standard respiratory volume (6.7 m^3) and the respiratory volume for light activity (10 m^3).

MOS values are calculated for different routes of exposure and for different toxicological endpoints. The routes of exposure specifically considered in occupational risk assessment are exposure by inhalation and dermal contact.

In addition, for risk assessment of combined exposure (exposure by inhalation and dermal contact) an adequate NOAEL is derived from external NOAELs and specific information on route-specific absorption. For MOS calculation, the adjusted internal starting point is divided by the internal body burden. Depending on route-specific exposure and absorption, inhalation exposure and/or dermal exposure may contribute to the internal body burden. With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Reference MOS

The MOS values calculated have to be compared with a reference MOS. The reference MOS is an overall assessment factor, which is obtained by multiplication of individual assessment factors. The Technical Guidance Document emphasises several aspects which are involved in the extrapolation of experimental data to the human situation. For these assessment factors, default values are recommended. It is important to point out that any relevant substance-specific data and information may overrule the defined default values.

Interspecies extrapolation on the one hand is based on allometric scaling (factor 4 for rats, factor 7 for mice, and factor 2.4 for rabbits). For remaining interspecies differences the TGD proposes an additional factor of 2.5.

For workers, an adjustment factor for intraspecies differences of 5 is recommended. Based on an evaluation of empirical data by Schneider et al. (2004) it is anticipated that a factor of 5 will be sufficient to protect the major part of the worker population (about 95%).

For chemical substances it is usually expected that the experimental NOAEL will decrease with increasing duration of application. Furthermore, other and more serious adverse effects may appear with prolonged exposure duration. For duration adjustment, a default factor of 6 is proposed for extrapolation from a subacute to chronic exposure. The duration adjustment factor is lower (a factor of 2) for the transition from subchronic experimental exposure to chronic exposure. For 2-ethoxyethanol the factor of 2 for an adaptation from subchronic to chronic exposure is used.

The TGD defines two further adjustment factors (uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect). In specific cases these factors may be different from one. For 2-ethoxyethanol no further adjustment factors are used in the risk assessment.

Comparison of MOS and reference MOS

The MOS values for different toxicological endpoints and different exposure scenarios are compared with the substance- and endpoint-specific reference MOS. MOS values clearly above the reference MOS do not lead to concern, whereas MOS values that are clearly below the reference MOS are cause for concern. There may be various risk-related aspects which are not covered by default assessment factors. These additional qualitative aspects should be carefully considered when performing a risk assessment and should have adequate influence on finding of conclusions.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called “critical exposure level”. Concern will be expressed for scenarios with occupational exposure levels higher than the relevant “critical exposure level”.

2.1.2 Occupational risk assessment

Acute toxicity

Human data regarding the toxicity of 2-ethoxyethanol are sparse. Toxic effects were observed after oral uptake of mixtures of 50 – 200 ml 2-ethoxyethanol. Because no clear dose relationship after inhalation or dermal contact of 2-ethoxyethanol can be drawn from these

case reports by humans, risk assessment for acute toxicity is done on the basis of animal studies.

Inhalation exposure

LC50-values of 15.2 mg/l/4 h and 7.36 mg/l/8 h were determined in rats. Further information on effects in this study in a sub-lethal dose range is not available. Thus considerable uncertainties are connected with the estimation of an acute NAEL based on lethal doses. For risk assessment of acute inhalation toxicity (8-hour exposure) data on 2-ethoxyethanol-induced lethality are considered less relevant than the results from a rat developmental study from Doe (1984). Rats were exposed to about 0, 39, 195 and 975 mg/m^3 2-ethoxyethanol for 6 h/d on gestation day 6-15. There was no evidence for any maternal toxicity at 39 and 195 mg/m^3, whereas at 975 mg/m^3 some slight, but statistically significant haematological changes were observed. A maternal NOAEC of 195 mg/m³ and a LOAEC of 975 mg/m³ was identified.

This experimental value of 195 mg/m^3 has to be converted, because of the different absorption percentage of rat (30%) and human (64%) after inhalation. The external starting point for human lies about 2.13 fold lower than for rats and corresponds to a value of 91 mg/m^3 (195 • 0.3 / 0.64) .

For the identification of the reference MOS, (1) an adjustment factor of 2.5 for interspecies differences (the factor for allometric scaling is already implicitly applied) and (2) a factor of 5 regarding the intraspecies differences for workers are applied.. Multiplying the different adjustment factors, the reference MOS calculates to 12.5 (2.5 • 5). The critical inhalation exposure at the workplace is identified as 7.3 mg/m^3 (91 / 12.5).

There is no concern for scenario 1. Keeping in mind that only slight effects were observed at the highest dose of 975 mg/m^3 and the duration of exposure was 10 days, conclusion ii is even more justified.

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

Dermal contact and combined exposure

A dermal LD50 of 3311-4576 mg/kg was determined in rabbits. No further information is available about the dose response relationship in a sublethal dose level.

Based on the before-mentioned line of argumentation, the rat developmental study is used as key study for the assessment (see under inhalation).

The maternal NOAEC of 195 mg/m³ corresponds to an external dermal dose of 56 mg/kg/day (195 mg/m^3 multiplied with the default respiratory volume for the rat for 6 hours of 0.288 mg/kg/day). Taking a dermal absorption of 50 % into account, this external value corresponds to an internal value of 28 mg/kg/day (56 mg/kg/day • 0.5).

For the identification of the reference MOS, (1) a factor of 10 for interspecies differences (a factor for allometric scaling of 4 multiplied with a factor of 2.5 for remaining interspecies differences) and (2) a factor of 5 regarding the intraspecies differences for workers are applied. Multiplying the different adjustment factors, the reference MOS calculates to 50 (4 • 2.5 • 5). The external critical exposure level at the workplace is identified as 1.1 mg/kg/day (56 / 50). The internal critical exposure level gives a value of 0.6 mg/kg/day (28 mg/kg/day / 50).

There is no concern for scenario 1 (see table 2.1.B). Keeping in mind that only slight effects were observed at the highest dose of 975 mg/m^3 in the test and the duration of exposure was 10 days, conclusion ii is even more justified.

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

Table 2.1.B: Acute toxicity of 2-ethoxyethanol

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	91 mg/m³			56 mg/kg/day			28ay		
Reference MOS	12.5						-		
Critical exposure level	7.3 mg/m³			1.31 mg/kg/day (external dose)			0.6mg/kg/day (internal dose)		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/d)	MOS	Conclusion	Internal body burden (mg/kg/d)	MOS	Conclusion
1. Production and further processing in the large-scale industry	3	30	ii	0.3	-187	ii	0.42	-67	ii

Irritation/Corrosivity

Skin/Eye/Inhalation

In a Draize test with rabbits the substance caused mild skin irritation that reversed within 7 days. Draize eye tests with rabbits demonstrated moderate eye irritation that reversed within 10 days. The observed effects are not considered sufficient for classification. There is no concern for dermal or eye irritation at the workplace for 2-ethoxyethanol.

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

Respiratory tract

No respiratory irritation was reported in the acute inhalation studies. In a RDT study by Barbee (1984), no histopathological changes were detected. No such symptoms were reported in the other RDT studies. Thus, with respect to acute local effects on the respiratory tract, airway damage is not anticipated and no concern is expressed.

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

Sensitisation

Skin sensitisation

In a Magnusson Kligman test with guinea pigs no skin sensitisation was observed. No concern is derived.

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

Respiratory sensitisation

No information on the sensitising potential of the substance at the respiratory tract is available. For the time being a valid study to investigate respiratory sensitisation in experimental animals cannot be recommended. However, 2-ethoxyethanol is not suspected to be a potent respiratory sensitizer in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern with respect to respiratory sensitisation at the workplace.

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

Repeated dose toxicity

Local effects

Inhalation exposure and dermal contact

Local effects were not described in the dermal studies and repeated inhalation studies. The only note from a study from Barbee et al. (1984) of “increased incidence of lacrimation and

mucoid nasal discharge at all concentrations from week 2 through week 10 " is not robust enough for the risk assessment. In addition, no such findings were reported in any other inhalation toxicity study available for 2-ethoxyethanol.

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

Systemic effects

No information on the effects in humans after repeated exposure to 2-ethoxyethanol is available.

Repeated administration of 2-ethoxyethanol by oral and inhalation routes produced adverse effects in several experimental animals (rats, mice, rabbits and dogs). Target organs are the blood and hematopoietic system and the male reproductive system. The occurred effects seen at the animals are thought to be relevant for man.

Inhalation exposure

There are several inhalation studies with different experimental animals available. The study which is judged to serve as key study for the assessment of inhalation exposure is a 13-week rabbit study. The rabbits were exposed to 0, 25, 100 or 400 ppm 2-ethoxyethanol vapours (equal to 0, 92.5, 390, or 1480 mg/m^3) for 6 h/day, 5 days/week. At 1480 mg/m^3 a weight reduction of testis and slight focal seminiferous tubule degeneration was observed. In addition hematocrit value, hemoglobin concentration and erythrocyte count were decreased. Based on these effects the value of 390 mg/m^3 is taken as NOAEC.

The experimental NOAEC of 390 mg/m^3 is (1) adapted by a factor of 0.46 (0.3 / 0.64) to account for absorption differences after inhalation between experimental animals (30%) and humans (64%). %), (2) is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers and (3) withan for humans. This results in an adjusted inhalation starting point of 90 mg/m^3 (390 • 0.46 • 6.7/10 • 6/8).

The following adjustment factors are applied for the identification of the reference MOS. For (1) interspecies differences the default factor is 2.5 (the factor for allometric scaling is already implicitly applied), for (2) intraspecies differences (workers) the default factor is 5, and for (3) duration adjustment a factor of 2 is used. Thus the reference MOS calculates to 25 (2.5 • 5 • 2). The critical inhalation exposure level at the workplace is identified as 4.83.6 mg/m^3 (90 / 25).

The shift average value for inhalation is reported as 3 mg/m^3 for production and further processing of 2-ethoxyethanol. The exposure level in this occupational scenario is lower than the critical inhalation exposure. There is no concern for this scenario. For corresponding MOS values see table 2.1.C.

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

Dermal contact

Dermal studies with repeated application are not available. Thus studies with other routes of application are taken into account. After viewing of all described studies, the above-mentioned well performed inhalation study is preferred to other described oral gavage or drinking water studies.

For MOS calculation the NOAEC of 390 mg/m^3 from the above mentioned inhalation study in rabbits has to be transferred into an external dermal dose.

The experimental NOAEC of 390 mg/m^3 is multiplied with the breathing volume of 0.230 m^3/kg/day (0.48 l/min/kg respiratory rate for rabbits • 60 min • 8 h). This gives a value of 45.290 mg/kg/day of inhaled 2-ethoxyethanol (390 mg/m^3 • 0.230 m^3/kg/day). Considering the 30% absorption after inhalation the external value of 90 mg/kg/day corresponds to an uptake of 627 mg/kg/day (internal value). Considering the dermal exposure situation, this internal value has to be multiplied with 2, because the dermal absorption is 50%. This gives an external starting point of 254 (627 • 2). Thus the value of 254 mg/kg/day is taken as starting point for MOS calculation (table 2.1.C).

The following assessment factors are taken for the calculation of the reference MOS: (1) a factor of 2.4 • 2.5 (rabbit) for interspecies, (2) a factor of 5 for intraspecies differences, and (3) a duration factor of 2 is used. Altogether the reference MOS calculates to 30 (2.4 • 2.5 • 5 • 2) the corresponding critical exposure level calculates to 0.9 mg/kg /day (2 3054 / 60).

The calculated exposure value for dermal contact of 0.3 mg/kg/day is lower than the critical dermal exposure level of 0.9 mg/kg /day. There is no concern expressed for this scenario. For corresponding MOS values see table 2.1.C.

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

Combined exposure

The principle of calculation and evaluation of MOS is the same as above for dermal systemic effects. The internal starting point of 627 mg/kg/day is divided by a reference MOS of 30 (see above, dermal exposure) which results in a critical exposure level of 0.45 mg/kg/day. Compared with the exposure value of combined exposure of 0.42 mg/kg/day the critical exposure level reaches borderline. However, no concern is derived for scenario 1. The combined exposure values and the respective MOS values are listed in table 2.1.C.

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

Table 2.1.C: Repeated dose toxicity of 2-ethoxyethanol (systemic effects)

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	90 mg/m³			254 mg/kg/day (external dose)			627mg/kg/day (internal dose)		
Reference MOS	25			60			60		
Critical exposure level	.3.6 mg/m³			0.9 mg/kg/day			0.45 mg/kg/day		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/d)	MOS	Conclusion	Internal body burden (mg/kg/d)	MOS	Conclusion
1. Production and further processing in the large-scale industry	3	30	ii	0.3	180	ii	0.42	64	ii

Mutagenicity

2-Ethoxyethanol was negative in bacterial gene mutation tests and in a gene mutation test with mammalian cells. Positive results from in vitro chromosomal aberration tests and in vitro SCE tests are not taken into consideration because the concentrations were extremely high. The negative in vivo micronucleus test indicates that the substance does not cause clastogenicity in vivo. No concern is derived.

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

Carcinogenicity

Two long-term studies in rats and mice with 2-ethoxyethanol did not give a hind, that the substance is a potent carcinogen. Concern is not derived.

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

Fertility impairment

Human data are available that describe a correlation between the exposure to glycol ethers and subfertility and sperm effects. However workers were exposed to mixtures of substances and quantitative data of a dose response relationship are not described. Thus risk characterisation concerning fertility impairment is based on experimental results.

Inhalation exposure

2-Ethoxyethanol was applied to mice in a multigeneration study via drinking water (800, 1500 und 2600 mg/kg/day). The NOAEL for fertility impairment in this study was 800 mg/kg/day for both sexes. At 1500 mg/kg/day the number of live pubs/litter and proportion of pubs born alive in comparison to controls were decreased. Histopathological investigations did not show any effects in female gonades, while sperms were already affected at 1500 mg/kg/day. However, the lowest dose of 800 mg/kg/day was not checked for sperm effects, therefore, this study is not taken for the risk assessment.

Instead of the above described multigeneration study, the 13 weeks rabbit study, which was also used for the assessment of repeated dose toxicity, is taken for the assessment of fertility impairment. In the rabbit study over 13 weeks (6 hours/day, 5 days/week), a NOAEC of 390 mg/m^3 (100 ppm) was determined. Histopathological effects in gonades were found at the LOAEC of 1480 mg/m^3 (testis weight reduction and slight focal seminiferous tubule degeneration). The NOAEC of 390 mg/m^3 is used for the MOS calculation.

Most of the calculation steps for this endpoint are identical with the calculation of repeated dose toxicity. Therefore at this place the steps are described only shortly to avoid repetition (for detailed calculation steps see under chapter repeated dose toxicity). The experimental NOAEC of 390 mg/m^3 corresponds in an adjusted inhalation starting point of 90 mg/m^3.

Adjustment factors for the identification of the reference MOS are: (1) the default factor of 2.5 for interspecies differences and (2) the default factor of 5 for intraspecies differences (workers). This gives a reference MOS of 12.5 (2.5 • 5). The critical inhalation exposure level at the workplace is identified as 67.2 mg/m^3 (90 / 12.5).

The exposure level for scenario 1 with 3 mg/m^3 is lower than the critical inhalation exposure of 7.2 mg/m³. There is no concern for this scenario. For corresponding MOS values see table 2.1.D.

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

Dermal contact

Dermal fertility studies are not available. Therefore the above mentioned inhalation study is used for the risk assessment.

For MOS calculation the NOAEC of 390 mg/m^3 is transferred to an external starting point of 54 mg/kg/day (detailed calculation steps are described above under repeated dose toxicity dermal contact).

Assessment factors for the calculation of the reference MOS are: (1) a factor of 2.4 • 2.5 (rabbit) for interspecies differences and (2) a factor of 5 for intraspecies differences. Altogether the reference MOS calculates to 30 (2.4 • 2.5 • 5) the corresponding critical exposure level calculates to 1.8 mg/kg /day (54 / 30).

The calculated exposure value for dermal contact of 0.3 mg/kg/day is lower than the critical dermal exposure level of 1.8 mg/kg /day. There is no concern expressed for this scenario. For corresponding MOS values see table 2.1.D.

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

Combined exposure

The principle of calculation and evaluation of MOS is the same as above for dermal systemic effects. The internal starting point of 27 mg/kg/day is divided by a reference MOS of 30 (see above, dermal exposure) which results in a critical exposure level of 0.9 mg/kg/day. No concern is derived for this scenario 1.

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

Table 2.1.D: Fertility impairment of 2-ethoxyethanol

	Inhalation	Dermal	Combined						
Starting point for MOS calculation	90 mg/m³	54 mg/kg/day (external value)	27 mg/kg/day (internal value)						
Reference MOS	12.5	30	30						
Critical exposure level	7.2 mg/m³	1.8 mg/kg/day	0.9 mg/kg/day						
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/	MOS	Conclusion	Internal body burden	MOS	Conclusion

Developmental toxicity

Human data are available that describe a correlation between spontaneous abortion and exposure to glycol ethers. However women were exposed to mixtures of substances and quantitative data of a dose response relationship are not described. Thus quantitative risk assessment is based on animal data.

Animal data show embryotoxic and teratogenic effects in several species via different route of application. Developmental effects were induced already at dose levels without obvious maternally toxic effects, respectively borderline effects.

Inhalation exposure

The study which is judged to serve as key study for the risk assessment of developmental effects is the rat inhalation study (whole chamber administration) with 2-ethoxyethanol from (Doe 1984b). In this study 24 female rats/group were exposed to 2-ethoxyethanol at concentrations of 0, 10, 50, or 250 ppm (appr. 38, 190, or 950 mg/m^3), 6 hours/day on g.d. 6-15. There was no evidence for any maternal toxicity at 10 and 50 ppm, whereas at 250 ppm slight haematological changes were observed. Developmental effects were seen at 50 ppm (i.e. unossified cervical centra, partial ossification of the second sternebrae, extra ribs) and 250 ppm (increase in the incidence of late uterine deaths and in the proportion of dams affected). From this study a $NOAEC_{developmental\ effects}$ of 10 ppm (39 mg/m^3) is derived.

The experimental NOAEC of 39 mg/m^3 is (1) adapted by a factor of 0.46 (0.3 / 0.64) to account for absorption differences after inhalation between experimental animals (30%) and humans (64%), (2) is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers and (3) with a factor of 6/8 to account for differences between the experimental inhalation duration of 6 h per day and an average working day for humans of 8 h per day. This results in an adjusted inhalation starting point of 9 mg/m^3 (39 • 0.46 • 6.7/10 • 6/8).

The reference MOS consists of (1) the default factor of 2.5 for interspecies differences and (2) the default factor of 5 for intraspecies differences (workers). This gives a reference MOS of 12.5 (2.5 • 5). The critical inhalation exposure level at the workplace is identified as 0.72 mg/m^3 (9 / 12.5).

There is concern for 2-ethoxyethanol related developmental toxicity in scenario 1. The exposure value 3 mg/m^3 for inhalation is nearly fourfold higher than the corresponding critical exposure level of 0.72 mg/m^3. For corresponding MOS values see table 2.1.E.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

Dermal contact

Dermal studies concerning developmental effects are not available. Therefore, the above-mentioned developmental rat inhalation study with the NOAEC of 39 mg/m^3 is taken for MOS calculation.

The experimental NOAEC of 39 mg/m^3 is multiplied with with the breathing volume of 0.384 m^3/kg/day (0.8 l/min/kg respiratory rate for rats • 60 min • 8 h). This gives a value of 15 mg/kg/day of inhaled 2-ethoxyethanol (39 mg/m^3 • 0.384 m^3/kg/day). Considering the 30% absorption after inhalation the external value of 15 mg/kg/day corresponds to an uptake of 4.5 mg/kg/day (internal value). Considering the dermal exposure situation, this internal value has to be multiplied with 2, because the dermal absorption is 50%. This gives an external starting point of 9 (4.5 • 2). Thus the value of 9 mg/kg/day is taken as starting point for MOS calculation (table 2.1.C).

The following assessment factors are taken for the calculation of the reference MOS: (1) a factor of 4 • 2.5 (rat) for interspecies and (2) a factor of 5 for intraspecies differences. Altogether the reference MOS calculates to 50 (4 • 2.5 • 5) the corresponding critical exposure level calculates to 0.18 mg/kg /day (9 / 50).

The critical exposure level of 0.18 mg/kg/day is lower than the dermal exposure value of 0.3 mg/kg /d. There is concern for this scenario. For corresponding MOS values see table 2.1.E.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

Combined exposure

The principle of calculation and evaluation of MOS is the same as above for dermal systemic effects. The internal starting point of 4.5 mg/kg/day is divided by a reference MOS of 50 (see above, dermal exposure) which results in a critical exposure level of 0.09 mg/kg/day.

There is concern for combined exposure.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

Table 2.1.E: Developmental toxicity of 2-ethoxyethanol

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	9 mg/m³			9 mg/kg/day			4.5 mg/kg/day		
Reference MOS	12.5			50			50		
Critical exposure level	0.72 mg/m³			0.18 mg/kg/day			0.09 mg/kg/day		
	Exposure (mg/m³)	MOS	Conclusion	Exposure (mg/kg/d)	MOS	Conclusion	Internal body burden (mg/kg/d)	MOS	Conclusion
1. Production and further processing in the large-scale industry	3	3	iii	0.3	30	iii	0.42	10.7	iii[(1)]

[(1)]conclusion iii already results from inhalation and dermal exposure, therefore no specific concern for combined exposure is indicated

2.1.3 Summary of occupational risk assessment

As a result of occupational risk assessment for 2-ethoxyethanol, concern is risen for developmental toxicity and risk reduction measures have to be initiated. Table 2.1.F gives an overview about the conclusions of the toxicological endpoints of 2-ethoxyethanol. For the endpoints acute toxicity, irritation, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity and fertility no concern is expressed.

Table 2.1.F: Endpoint-specific overall conclusions for the occupational risk assessment of 2-ethoxyethanol

Toxicological endpoints		concern
Acute toxicity	inhalation	ii
	dermal	ii
	combined	ii
Irritation/ Corrosivity	dermal	ii
	eye	ii
	acute respiratory tract	ii
Sensitisation	skin	ii
	respiratory	ii
Repeated dose toxicity	local, inhalation	ii
	local, dermal	ii
	systemic, inhalation	ii
	systemic, dermal	ii

Toxicological endpoints		concern
	systemic, combined	ii
Mutagenicity		ii
Carcinogenicity	inhalation	ii
	dermal	ii
	combined	ii
Fertility impairment	inhalation	ii
	dermal	ii
	combined	ii
Developmental toxicity	inhalation	iii
	dermal	iii
	combined	iii[(1)]

[(1)]conclusion iii already results from dermal exposure and/or inhalation, therefore no specific concern for the combined exposure scenario is indicated

Risk estimation is mainly based on animal inhalation studies. Based on human and animal data, 50 % dermal absorption is taken in the risk characterisation. 64 % absorption via the inhalation route is recommended for risk characterisation purposes in humans (experimental human data). However, for animals lower inhalation absorption percentages are assumed (30 %).

The most important toxicological endpoint is the developmental toxicity of 2-ethoxyethanol.

Tables 2.1.G (inhalation) and 2.1.H (dermal contact) try to visualize the risk profile of 2-ethoxyethanol. According to the tables you will find the relatively high risks on the left, the relatively low risks on the right side of the tables.

Table 2.1.G: Ranking of health risks for workers (inhalation)

Exposure scenario	Exposure level in mg/m³	Developmental toxicity	Repeated dose toxicity, systemic	Acute toxicity	Fertility
		Critical exposure level in mg/m^3			
		0.72	3.6	7.2	7.2
1. Production and further processing in the large scale industry	3	iii	ii	ii	ii

Table 2.1.H: Ranking of health risks for workers (dermal contact)

Exposure scenario	Exposure level in mg/kg/day	Developmental toxicity	Repeated dose toxicity, systemic	Acute toxicity	Fertility
		Critical exposure level in mg/kg/day			
		0.18	0.9	1.1	1.8
1. Production and further processing in the large scale industry	0.3	iii	ii	ii	ii

2.2 Consumers

3 Current Risk Reduction Measures

Classification and labelling

The current classification of 2-Ethoxyethanol according to Annex I of the Directive 67/548/EEC (19. ATP, Index-Nr. 603-012-00-X) is

R10; Repr. Cat. 2; R60-61 - Xn; R20/21/22.

In September 2007 the proposal submitted by DE to delete R21 for 2-ethoxyethanol in Annex I was agreed by the Technical Committee on Classification and Labelling (TC C&L).

The agreed classification will be included in a future Adaption to Technical Progress (ATP).

2-Ethoxyethanol will have to be labelled with

T; R60-61-10-20/22; S53-45

According to Appendix to Directive 76/769/EEC, Point 31, the packaging of 2-Ethoxyethanol (as a substance that is toxic for reproduction-Category 2) and preparations containing 2-Ethoxyethanol must be marked legibly and indelibly as follows: 'Restricted to professional users'.

Abbreviations:

Reprotox. Cat. 2	Toxic for reproduction-Category 2
R 60	may impair fertility
R 61	may cause harm to unborn child
T	toxic
Xn	harmful
R 10	Flammable
R 20/21/22	harmful by inhalation, in contact with skin and if swallowed
R 20/22	harmful by inhalation and if swallowed
S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). [Safety phrases S1, S2 and S45 are obligatory for all very toxic, toxic and corrosive substances and preparations sold to the general public. See Foreword to Annex I of Directive 67/548/EEC, 1994 O.J. (L 381) 5].
S53	Avoid exposure - obtain special instructions before use.

3.1 Workers

As a result of its classification as a hazardous substance 2-Ethoxyethanol is subject to general regulations concerning its supply and handling.

Safety data sheets

In accordance with Regulation (EC) No 1907/2006 of the European Parliament and of the council of 18 December 2006, corrected in May 07 and amended in November 07 (Regulation (EG) Nr. 1354/2007) anyone placing 2-Ethoxyethanol on the market has to provide a safety data sheet to the professional user.

The information system for hazardous substances and preparations in the form of labelling and the safety data sheets is considered sufficient in principle to provide the user with appropriate information for the selection of suitable occupational safety measures.

Occupational safety and health regulations

Regarding the production and use of 2-Ethoxyethanol the following directives are primarily applicable as general regulations for occupational safety and health at the European level:

- 98/24/EC on the protection of workers from the risks related to exposure to chemical agents at work
- 89/656/EEC on the use of personal protective equipment
- 92/85/EEC improvements in the safety and health of pregnant workers, workers who have recently given birth and women who are breastfeeding

Only limited knowledge is available about the extent to which the EU Member States have in each case transposed these basic requirements into national law.

Occupational exposure Limits

The following occupational exposure limits (OEL) and short term exposure levels (STEL) apply for 2-Ethoxyethanol in the EU (Ariel WebInsight 5.1, 2008; GESTIS International limit values 2008, www.dguv.de/bgia/de/gestis/limit_values/index.jsp):

Country	OEL (mg/m^3)	STEL (mg/m^3)
Greece (2001)	74	-
United Kingdom (2007)	37	-
Poland	20	
France (2008),	19	-
Germany (2006), Switzerland (2007)	19 (Remark "Z")	152
Austria (2007), Hungary (2000),	19	76
Sweden (2007)	19	40

The Netherlands (2007)	19	38
Denmark (2008), Iceland (2001)	18.5	-
Belgium (2007), Norway (2007), Ireland (2007), Spain (2008), Italy (2008), Portugal (2004), USA (ACGIH) (2008)	18	-
Finland (2007)	7.5	-

(Remark "Z": This OEL does not exclude the risk of developmental toxicity)

There are no occupational exposure limit values for 2-Ethoxyethanol according to Directive 98/24/EEC at community level.

Personal Protection Equipment (PPE) against dermal and eye exposure

According to community legislation workers have to be provided with suitable PPE if their health is at risk due to exposure against chemicals. PPE that protects against the risks of 2-Ethoxyethanol is available. The type of filter and the material of gloves, material thickness and breakthrough time have to be specified in the Safety Data Sheet.

Are existing controls sufficient to limit occupational risks?

It has been concluded from the risk assessment that there is a need for limiting the risks due to developmental toxicity. The critical exposure levels are of 0.72mg/m^3 for inhalation and . 0.18 mg/kg/day for dermal contact. Inhalative and dermal exposures assessed in the Risk Assessment are higher than the critical limits in scenario 1 "production and further processing in the large scale industry" (3 mg/m^3 and 0.3 mg/kg/day).

With regard to the CEL of 0.72mg/m^3 derived for the endpoint "developmental toxicity" current OELs are not sufficient to protect female workers against risks for the fetus in case of pregnancy.

Dermal exposure was assessed with the EASE model.The input parameterwere: non dispersive use, direct handling, intermittent, gloves worn, efficacy of gloves 90%. Though the assessment supposes, that gloves are worn, the exposure assessed is still higher than the critical exposure level. So, the mere the use of gloves is not a reliable means to control risks of developmental toxicity from dermal exposure

3.2 Consumers

2-Ethoxyethanol is currently regulated under Council Directive **76/769/EEC**, as last amended by Dir 2007/51/EC (31st amendment and 16th ATP) (Restrictions on the marketing and use of

dangerous substances):
Appendix to Directive 76/769/EEC, Point 31 -- Toxic for reproduction: category 2: Without prejudice to the other points of Annex I to Directive 76/769/EEC: May not be used in substances and preparations placed on the market for sale to the general public in individual concentration equal to or greater than: -- either the concentration specified in Annex I to Directive 67/548/EEC, or -- the concentration specified in point 6, Table VI, of Annex I to Directive 88/379/EEC where no concentration limit appears in Annex I to Directive 67/548/EEC. Without prejudice to the implementation of other Community provisions relating to the classification, packaging and labelling of dangerous substances and preparations, the packaging of such substances and preparations must be marked legibly and indelibly as follows: "Restricted to professional users". By way of derogation, this provision shall not apply to: (a) medicinal or veterinary products as defined by Directive 65/65/EEC; (b) cosmetic products as defined by Directive 76/768/EEC; (c)-- motor fuels which are covered by Directive 85/210/EEC, -- mineral oil products intended for use as fuel in mobile or fixed combustion plants, -- fuels sold in closed systems (e.g. liquid gas bottles); (d) artists' paints covered by Directive 88/379/EEC. Last amended by OJ (L 33) 28, 4 February 2006.

2-Ethoxyethanol is also regulated as follows:

Regulation **1907/2006/EC** (REACH), Annex XVII, Marketing and Use Restrictions, Point no(s):30 and Annex XVII, Appendix 6, Category 2 Reproductive Toxins derived from Directive 67/548/EEC.

Cosmetics Directive **76/768/EEC**, as corrected by OJ (L 136) 52, 24 May, Annex II - Prohibited Substances (Reference Number: 666), 2008 and Annex III, Part 1 - Restricted Substances: The use in cosmetic products of substances classified as carcinogenic, mutagenic or toxic for reproduction, of categories 1 or 2, under Annex I to Directive 67/548/EEC is prohibited.

European Norm EN 71-9, Tables 2(A-I) (Toy Safety: Limits of Organic Chemical Compounds) (February 2005): Limit value of 0,5 mg/l applies to total amount of 2-Methoxyethyl acetate, 2-Ethoxyethanol, 2-Ethoxyethyl acetate, Bis(2-methoxyethyl) ether, and 2-Methoxypropyl acetate.

Directive 96/82/EC on the control of major accident hazards involving dangerous substances, Annex I, OJ (L 10) 13, 14 Jan 1997, as amended by Directive 2003/105/EC, OJ (L 345) 97, 31 Dec 2003:
This substance is in the category of "Flammable" substances in Part 2 of Directive 82/501/EEC. The qualifying quantities are 5000 tonnes (Articles 6 and 7) and 50000 tonnes (Article 9).

Regulation 1980/2000 on products which contain dangerous substances and may not be eligible for a positive Eco-Label based on criteria, OJ (L 237) 1, 21 Sep 2000.

(Source: Ariel WebInsight 5.1, 2008)

4 Possible Further Risk Reduction Measures

4.1 Workers

The following further Risk Reduction Measure are considered to be probably effective :

- Occupational Exposure Limit
- Training, organisational measures and occupational hygiene

The options are assessed in section 5.

5 Assessment of Possible Further Risk Reduction Measures

The TGD requires that possible further risk reduction options be examined against the following criteria

- effectiveness
- practicality
- economic impact
- monitorability.

5.1 Workers

Exposure reduction by technical and organisational measures and personal protection accepted means in workplace legislation.

In order to put these instruments into action on company level and to make them enforcable in the framework of worker protection legislation it is recommended to establish an occupational exposure limit for 2-Ethoxyethanol .

The OEL should take into account the risk assessment (critical exposure level of 0.72mg/m^3 for the most critical effect developmental toxicity). The OEL will also trigger that personal protective equipment is provided if workplace concentrations exceed the OEL.

Within the framework of workplace legislation an occupational exposure limit is an enforceable and effective means to make exposure control obligatory. If this OEL takes into account the risk assessment, it can also be considered to be an effective means for health protection in the workplace. It can be monitored by existing techniques of workplace measurement.

The economic impact of an OEL can not be assessed. However, taking in account the measured data provided by the only manufacturer, an OEL in the range of the CEL could be complied with under the current technology without further effort. The median of measurement is < 0.01 mg/m³. The 95^{th} percentile of 3.0 mg/m³ (TWA) that was taken forward for risk assessment seems to be associated with special situations where the OEL might be exceeded and PPE is an accepted measure in the framework of workplace legislation .

Training, organisational measures and occupational hygiene and specific Risk Assessment in the framework of Directive 92/85/EEC on improvements in the safety and health of pregnant workers,

The risk assessment has resulted in concern because of dermal exposure. For the most critical endpoint (developmental toxicity) the critical exposure level is 0.18 mg/kg/day and lower than the dermal exposure that has been assessed (0.3mg/kg/day), even though gloves were supposed to b worn. The risks from dermal exposure cannot be reduced by estabishing an OEL.

Exposure can in principle be reduced by organisational measures that reduce the frequency, duration and area of exposure by means of gloves, training to work cleanly, appropriate use of

PPE and personal hygiene. Training, information and hygienic measures are foreseen in the framework of workplace legislation. 2-ethoxyethanol is a substance, that is labelled with R61 "may cause harm to unborn child". Therefore employers have to perform a specific risk assessment to protect pregnant workers and women and to give special consideration to measures that protect this workforce. Inintended and accidental dermal exposure in cases of spills or accidents should also be taken in to account. As only a limited number of skilled workers is occupied, risk assessment, training, special information about developmental risks, organisational measures and occupational hygiene in the framework of workplace legislation are regarded to be sufficient for limiting the risks of dermal exposure.

Especially it is supposed that the efficacy of gloves can be improved by training to modify the factors that limit their performance to the 90% assumed in risk assessment:
- unintended contamination during the handling of used gloves,
- limited protection of suitable gloves at real working conditions (e.g. mechanical stress),
- time of use exceeding the permeation time of the gloves with regard to the substance.

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5.2 Consumers

6 Further Risk Reduction Measures Recommended

6.1 Workers

The risk reduction strategy recommends the following measures:

- to establish at community level occupational exposure limit values for 2-ethoxyethanol according to Directive 98/24/EEC

- information on the need of specific training, organisational measures and occupational hygiene in the framework of Directive 98/24 and specific risk assessment in the framework of Directive 92/85/EEC on improvements in the safety and health of pregnant workers

6.2 Consumers

7 Marketing And Use Restrictions

Not applicable

8 Possible Monitoring Arrangements

9 Organisations consulted