Ethylbenzene

(1st Priority List)

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Strategy For Limiting Risks

Human Health

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CONTENT

0 Summary

Ethyl benzene is produced by a catalyzed reaction of ethylene and benzene at approx. 40 bar and temperatures around 250 °C. All manufacturers use ethyl benzene as the raw material for the production of styrene monomer. Therefore the ethyl benzene production plant and the styrene monomer plant are often situated at the same site and directly connected to each other. In some cases ethyl benzene is shipped in bulk to a styrene monomer plant. Another production method is the fractionation of mixed xylene streams which is, however, employed to a much lesser extent. These streams occur in petroleum refineries during distillation of cruide oil into petroleum products and contain ~ 80 % o-, m-, p-xylenes ("mixed xylene stream) and ~ 15-20 % ethyl benzene.

Ethyl benzene is mainly a raw material for the production of styrene (99.5 %). Styrene is further processed in the chemical industry to polystyrene which is used in large volumes in the automobile industry, in the building industry and for packaging. A small percentage of ethyl benzene (0.5 %) is used as a chemical intermediate, e.g. in the manufacture of acetophenone, cellulose acetate, diethyl benzene, propylene oxide.

The current classification of ethyl benzene according to **Annex I** of Directive 67/548/EEC (19. ATP, Index-Nr. 601-023-00-4) is **F; R11** (Highly flammable) - **Xn; R20** (Harmful by inhalation). Ethyl benzene has to be labelled with F, Xn; R11-20; S(2-)16-24/25-29.

The rapporteur (of the RAR) proposed to **add** the following classification and labelling:
R 36/37/38 Irritating to eyes, respiratory tract and to skin
R 48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation
R 65 Harmful: May cause lung damage if swallowed

This proposal has **not yet been discussed** in the EU-Working group on classification and labelling of dangerous substances under Directive 67/548/EEC.

Workers

It has been concluded from the risk assessment that there is a need for limiting the risks. The most important toxicological endpoints are repeated dose toxicity and developmental toxicity of ethylbenzene.

Conclusion (iii) applies to dermal and combined exposure in scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) for repeated dose toxicity and developmental toxicity. Dermal exposure should be controlled to levels in the range of 1.7 mg/kg/day or 120 mg/person/day (critical exposure level for systemic effects of repeated dose toxicity). If the exposure is reduced to this level, dermal risks from other endpoints, as developmental toxicity would similary and effectively be mitigated too.

Concerning inhalation exposure, the critical exposure level is 9.3 mg/m^3. The exposure values of scenario 1 (production and processing) and scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) are below this value, thus not resulting in concern.

The risk reduction strategy recommends the following measures:

- information on the need of technical and organisational measures, specific training, and occupational hygiene on company level in the framework of Directive 98/24

- to revise the occupational exposure limit value established at community level according to Directive 98/24/EEC .
- to apply the following revised classification**:**

R11	Highly flammable
R20	Harmful by inhalation
R 36/37/38	Irritating to eyes, respiratory tract and to skin
R 48/20	Harmful: Danger of serious damage to health by prolonged exposure through inhalation
R 65	Harmful: May cause lung damage if swallowed

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. Ethyl benzene is a substance on the first priority list (Regulation (EC) No. 1179/94 of the Commission of 25.05.1994).

Ethylbenzene is a highly flammable liquid at 25 °C. The Melting point is - 94.949 °C, the Boiling point is 136.186 °C at 1013hPa, the Relative density is 0.8670 at 20 °C, the Vapour pressure is 9.3 hPa at 20 °C. The Water solubility is 160 mg/l at 25 °C, the Partition coefficient is log Pow 3.13 at 25 °C, the Flash point is 23 °C, the Autoflammability is 430 °C.

Production

Ethyl benzene is produced by a catalyzed reaction of ethylene and benzene at approx. 40 bar and temperatures around 250 °C. All manufacturers use ethyl benzene as the raw material for the production of styrene monomer. Therefore the ethyl benzene production plant and the styrene monomer plant are often situated at the same site and directly connected to each other. In some cases ethyl benzene is shipped in bulk to a styrene monomer plant. All ethyl benzene plants are completely closed systems, working under controlled conditions. The process is highly automated and runs continuously. Another production method is the fractionation of mixed xylene streams which is, however, employed to a much lesser extent. These streams occur in petroleum refineries during distillation of crude oil into petroleum products and contain ~ 80 % o-, m-, p-xylenes (“mixed xylene stream) and ~ 15-20 % ethyl benzene.

Uses

Ethyl benzene is mainly a raw material for the production of styrene (99.5 %). Styrene is further processed in the chemical industry to polystyrene which is used in large volumes in the automobile industry, in the building industry and for packaging. A small percentage of ethyl benzene (0.5 %) is used as a chemical intermediate, e.g. in the manufacture of acetophenone, cellulose acetate, diethyl benzene, propylene oxide.

2 The Risk Assessment

2.1 Workers

Introductory remarks

For occupational risk assessment of ethylbenzene the MOS approach as outlined in the TGD (Human Health Risk Characterisation, Final Draft) is applied. This occupational risk assessment is based upon the toxicological profile of ethylbenzene 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 ethylbenzene show different absorption percentages for the different routes of exposure: According to the RAR-chapter 4.1.2.1 on toxicokinetics, metabolism and distribution an adsorption percentage up to 100% is taken for the oral route. 65% is assumed for the inhalation route in humans, 45% absorption percentage after inhalation in animals. Concerning dermal absorption, percentages of 50% for humans and 70% for animals is taken for the risk characterisation.

Occupational exposure and internal body burden

Table 2.1.A: Ethylbenzene exposure levels which are relevant for occupational risk assessment and internal body burden

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/day	mg/kg/day	mg/kg/day		
1.	Production and further processing	*1.3*	*4.2*(3)	*0.06*	*0.12*	*0.03*	*0.15*
2.	Use of paints, lacquers, inks (containing 20% ethylbenzene)	*7*	*2000*(4)	*28.5*	*0.65*	*14.3*	*14.95*

(1) based on the assumption of 65% inhalation absorption; breathing volume of 10 m^3 per shift
(2) based on the assumption of 50 % systemic availability of ethylbenzene after dermal contact
(3) EASE (90 % protection by suitable gloves)
(4) Analogous data (TGD)

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 a conversion of 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 recomments to assume 50% oral absorption and 100% inhalation absorption. For ethylbenzene 65% absorption after inhalation, 50% absorption after dermal contact and 100% absorption after oral exposure are assumed (experimental values).

For occupational risk assessment, the corrected inhalation NOAEC 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 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 ethylbenzene 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.

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 an 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”.

Occupational risk assessment

Acute toxicity

Inhalation

Human data on the acute toxicity of ethylbenzene are not available. Animal data show, that high concentrations of ethylbenzene result in deaths of experimental animals. An LC_{50} of 17 600 mg/m^3 after 4 hours of ethylbenzene inhalation in rats is reported. The concentration of 8 800 mg/m^3 resulted in 2 of 6 dead rats within 14 days after inhalation period.

In another, shortly reported subacute study F344 rats, B6C3F1 mice and New Zealand rabbits were exposed for 6 hours/day on 4 consecutive days at vapour concentrations of 0, 1 700, 5 300, and 10 6000 mg/m^3 (Biodynamics, 1986). The NOAEC in rats and mice was 1 700 mg/m^3 with increased kidney and liver weights without histopathological changes. For rabbits the NOAEC was 10 600 mg/m^3.

Comparing the LC_{50}-value of ca. 17 600 mg/m^3 and the concentration of 1 700 mg/m^3 without histopathological changes with the highest exposure concentration of 7 mg/m^3 (scenario 2) a relevant risk concerning acute toxicity is not expected under normal workplace conditions.

Conclusion: ii

Dermal contact

Oral and dermal toxicity of ethylbenzene is low with LD_{50} values above 2 000 mg/kg: an oral LD_{50} of 3 500 mg/kg was determined for rats in general, and an oral LD_{50} of 5 460 mg/kg specifically for male rats; the acute dermal toxicity was tested with rabbits and revealed a dermal L_{50} of 15 500 mg/kg.

Comparing the LD_{50} of above 2 000 mg/kg with the highest dermal exposure of 28.5 mg/kg (scenario 2, use of paints, laquers and inks) a relevant risk concerning acute toxicity is not expected under normal workplace conditions.

Conclusion: ii

Irritation/Corrosivity

Acute Inhalation

In humans, high concentrations of ethylbenzene vapours are irritating to mucous membranes of the eyes, nose and respiratory tract.

Chemical burns of the eyes, mouth, face, and trunk after a leakage of a pipeline with ethylbenzene are reported.

Acute exposure to vapours of ethylbenzene in air concentrations of 0.5% and 1% (equivalent to 5000 and 10 000 ppm) produced immediate intense irritation to the conjunctiva and nasal mucous membranes in guinea pigs. A concentration of 0.2% (2 000 ppm) produced moderate eye and nasal irritation within one minute and a concentration of 0.1% (1 000 ppm) caused slight nasal irritation.

Comparing the value of 1 000 ppm (corresponding to 4 340 mg/m^3) with the exposure value of 7 mg/m^3 a relevant risk concerning to irritation is not expected under normal workplace conditions.

Conclusion: ii

Sensory irritation

Sensory irritation by airborne ethylbenzene was reported from animal data. A test, made with male Swiss-Webster mice showed a RD50-value of 4 060 ppm. Alarie introduced the air concentration of 0.03 x RD50 as prediction of an exposure level with a minimal or low degree of sensory irritation in humans. The according air concentration for ethylbenzol calculates to 122 ppm or 530 mg/m^3 (4 060 ppm x 0.03). Analysis of experimental and human data on sensory irritation mainly is based on the relationship between RD50 values in animals and human thresholds for sensory irritation (and not on the corresponding relationship for minimal experimental effects). For that reason it is preferred to start risk assessment with the general approach (0.03 x RD50) instead of using lower experimental effect levels for which there is no specific experience as to adequate adjustment factors.

In workers the stinging and burning sensation caused by stimulation of the trigeminus nerve which is closely connected to respiratory depression is generally perceived within few minutes after exposure. Thus stimulation of the trigeminus nerve, unlike other effects, does

not depend significantly on exposure duration. The main trigger for effects seems to be the air concentration of the substance. Risk assessment therefore does not correct for exposure duration and short term values are also included in MOS calculation.

The exposure level of about 530 mg/m^3 is chosen as starting point concerning respiratory depression. In this range of exposure a relevant effect is not anticipated to occur in humans. For evaluation of the resulting MOS values no further aspects have to be taken into account. The corresponding reference MOS is considered to be 1.

The highest identified inhalative exposure values are described for scenario 2 with an exposure value of 7 mg/m^3. Based on the combined interpretation of the RD50 data and human experience conclusion ii is applied for these occupational exposure scenarios with respect to sensory irritation of ethylbenzene.

Conclusion: ii

Table 2.1.B: MOS values for sensory irritation of ethylbenzene

	Inhalation		
Starting point for MOS calculation	530 mg/m^3		
Reference MOS	1		
Critical exposure level	530 mg/m^3		
	Exposure (mg/m^3)	MOS	Conclusions
1 Production and further processing	1.3	407	ii
2 Use of paints, lacquers, inks (containing 20% ethylbenzene)	7	76	ii

Dermal/Eyes

Data on skin irritation tests according to international test guidelines are not available. On the basis of two available tests with rabbits a moderate skin irritation potential after single application of the substance and a high defatting potential leading to severe effects after repeated skin contact can be concluded.

Ethylbenzene caused grade 2-3 injury of the eyes of rabbits out of a scale of 10, based on the degree of corneal necrosis after instillation of various amounts and concentration of the chemical.

A classification and labelling as Xi, Irritant, R 36/38 irritating to the eys and skin is warranted.

On the grounds that control measures exist which can minimise dermal exposure and corresponding risk of irritation, conclusion ii is proposed. However, these controls must be implemented and complied with to reduce the risk of damage to skin and the eyes.

Conclusion: ii

Sensitization

Dermal contact

Animal data on skin sensitisation tests are not available.

Kligman conducted a maximisation test with 10% ethylbenzene (no data on purity) in petrolatum on 25 volunteers. Ethylbenzene produced no sensitisation reactions. No concern is expressed.

Conclusion: ii

Inhalation

No information on respiratory sensitisation is available. However, in view of the fact that during all the years of use specific case reports have not been reported, ethylbenzene seems at least not to be a strong respiratory sensitizer in humans. For the time being no animal model is available which would be able to verify the question of respiratory sensitisation. In summary concern is not expressed.

Conclusion: ii

Repeated dose toxicity

Local effects

Inhalation and dermal contact

See under chapter of Irritation. No further realizable information concerning local effects are available.

Conclusion: ii

Systemic effects

Repeated exposure of ethylbenzene (oral and inhalation route) affects the nervous system and leads to effects at the liver and kidney in experimental animals.

Inhalation exposure

An increase in liver and kidney weight of rats and mice without histopathological alterations has been found in several studies. According to the RAR-chapter 4.1.2.5 these changes are most probably related to enzyme induction. The NOAEL in a guideline oral 90 day study with rats was 75 mg/kg bw/d (LOAEL 250 mg/kg bw/d) based on indications for a mild regenerative anemia and liver changes indicative of microsomal enzyme induction.

Repeated inhalation exposure to ethylbenzene vapor was irreversibly ototoxic in rats (Gagnaire et al., 2007). Auditory dysfunction was localised in the mid frequencies and corresponded to the loss of cochlear outer hair cells, the sensory cells in the inner ear. Hearing loss and cell damage increased with concentrations exposed. In a 90 day rat inhalation study (6 hours/day, 6 day/week) the NOAEC for ototoxicity was extrapolated to be 114 ppm (500 mg/m^3). According to several case reports, where hearing deficits in humans occupational exposed to organic solvents or from people after solvent abuse is described (for review cf Risk Assessment Reports on toluene and styrene) this rat data are taken to be relevant for humans.

Thus, this extrapolated NOAEC of 114 ppm (500 mg/m^3) is taken for the risk assessment of repeated dose toxicity.

The extrapolated NOAEC of 114 ppm (500 mg/m^3) from the rat is (1) multiplied with a factor of 0.45 (for rat absorption percentage of 45%), divided by a divisor of 0.65 (for human absorption percentage after inhalation of 65%) and (2) multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. Further differences regarding the the experimental inhalation duration (6 hours/day, 6 days/week) and the working conditions (8 hours/day, 5 days/week) are not considered, because they roughly balance each other. The calculation results in an adjusted inhalation starting point of 232 mg/m^3 (500 • 0.45 / 0.65 • 6.7/10).

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 9.3 mg/m^3 (232 / 25).

The highest shift average value for inhalation is reported in scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) with a value of 7 mg/m^3. With a critical exposure level of 9.3 mg/m^3 there results no concern for this endpoint. For corresponding MOS values see table 2.1.C.

Conclusion: ii

Dermal contact and combined exposure

No information is available for systemic toxicity after repeated dermal exposure. Therefore the extrapolated NOAEC of 114 ppm (500 mg/m^3) from the 90 day inhalation rat study is taken for dermal risk assessment.

Expressed as (external) dose the value of 500 mg/m^3 corresponds to 190 mg/kg/day (500 mg/m^3 • default respiratory volume for the rat for 8 hours of 0.38 m^3/kg). With a rat adsorption percentage of 45% after inhalation the internal starting point corresponds to 86 mg/kg/day (190 mg/kg/day • 0.45). To get the (external) value for dermal contact the dermal absoption percentage of 50% for humans has to be included. Thus the internal value has to be multiplied with a factor of 2. This results in an adjusted external starting point of 172 mg/kg/day (86 mg/kg/day • 2).

The following adjustment factors are applied for the identification of the reference MOS. For (1) interspecies differences the adjustment factor is 4 • 2.5 (factor 4 for allometric scaling and

factor 2.5 for remaining interspecies differences), 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 100 (4 • 2.5 • 5 • 2). The critical external dermal exposure level at the workplace is identified as 1.7 mg/kg/day (172 / 100). The internal critical exposure level is 0.86 mg/kg/day (86 / 100).

The exposure scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) for dermal contact is reported as 28.5 mg/kg/day. The exposure level in this occupational scenario is nearly 15 fold higher than the critical dermal exposure value of 1.7 mg/kg/day. Concern is expressed for dermal exposure of this scenario 2. Because of the concern for dermal exposure also for combined exposure of scenario 2 concern is expressed as well. Scenario 1 does not reach concern. For corresponding MOS values see table 2.1.C.

Conclusion: iii

Table 2.1.C: MOS values for repeated dose toxicity of ethylbenzene, systemic effects

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	233 mg/m^3			172 mg/kg/day			86 mg/kg/day		
Reference MOS	25			100			100		
Critical exposure level	9.3 mg/m^3			1.7 mg/kg/day			0.86 mg/kg/day		
	Exposure (mg/m^3)	MOS	Conclusions	Exposure (mg/kg/d)	MOS	Conclusions	Internal body burden (mg/kg/d)	MOS	Conclusions
1. Production and further processing	1.3	180	ii	0.06	2 870	ii	0.15	573	ii
2. Use of paints, lacquers, inks (containing 20% ethylbenzene)	7	33	ii	28.5	6	iii	14.95	5.7	iii

Mutagenicity

Ethylbenzene produced consistently negative results in bacterial gene mutation tests and in the yeast assay on mitotic recombination. In mouse lymphoma mammalian mutation assays a weak positive response was reported but only at doses with strong cytotoxicity. No clear conclusion can be drawn regarding *in vitro* chromosomal aberration. Without S-9 mix there were equivocal increases in chromosomal aberration frequencies and micronuclei in CHO and SHE cells, respectively, or a negative result in a rat liver cell line. With S-9 mix ethylbenzene did not cause chromosomal aberrations in CHO cells. An *in vitro* SCE test was clearly negative with and without S-9 mix. *In vivo*, ethylenzene was clearly negative in two micronucleus assays and in a mouse liver UDS assay. In conclusion, on the basis of various mutagenicity tests *in vitro* and *in vivo*, there is currently no relevant indication that ethylbenzene is a germ cell mutagen.

Conclusion: ii

Carcinogenicity

Long-term inhalation exposure on rats and mice (0, 75, 250 and 750 ppm ethylbenzene for 104 weeks, 6 hours/day, 5 days/week) was carcinogenic in F344 rats and B6C3F1 mice. A significant increase of tumor incidences has been observed in the kidneys (renal tubule adenoma and carcinoma), testis (interstitial cell adenoma), liver (adenoma and carcinoma) and lung (alveolar/bronchiolar adenoma and carcinoma).

There was no concordance in carcinogenic response between rats and mice. Elevated rates of kidney tumors were seen in male and female rats. Each of other tumors occurred in one sex and in one species only. Genotoxicity data did not indicate a direct DNA damaging effect.

With reference to the RAR-chapter 4.1.2.7 there is sufficient evidence that kidney tumors in male and female rats are associated with the high strain-specific incidence of chronic progressive nephropathy (CPN) that is unknown for humans. For tumors in the testis, liver and lung high or very high spontaneous rates occur in the mouse and rat strains used. Ethylbenzene may exert its carcinogenic action by enhancement of tumor development in genetically disposed animals or by reduction in latency periods in tumor development.

Although the detailed mechanisms underlying the increases in tumor rates are presently not clarified, it appears likely that the mode of carcinogenic action of ethylbenzene possesses species and strain specificity. Therefore the toxicological significance and relevance to human health of these findings is uncertain. It appears unlikely from the data available that ethylbenzene poses a carcinogenic risk for humans exposed.

Conclusion: ii

Reproductive toxicity

Fertility impairment

No human data are available. In a guideline 2-generation study in rats by inhalation, no effects on reproduction were noted at exposure levels up to and including 500 ppm with minimal parental toxicity at this exposure level (decreased body weight, increased liver weight). In the preceding 1-generation study no effects on reproduction were found up to and including 1 000 ppm. The findings from the functional tests on fertility with the 1- and 2-generation studies are supported with the results from repeated dose toxicity studies without adverse findings by weight and histopathology of reproductive organs, sperm parameters and estrous cyclicity. Thereby no such adverse effects were found in guideline studies after 13 weeks of inhalation at 1 000 ppm, after 2 years of inhalation at 750 ppm (apart from possibly neoplastic related testicular effects) and after 13 weeks of oral gavage application at 750 mg/kg.

Based on the available data, there seems to be no specific risk for fertility effects.

Conclusion: ii

Developmental toxicity

Data from a 2-generation study and prenatal toxicity studies and a developmental neurotoxicity study are available. From the results of these studies there is no indication for substance induced teratogenicity (up to and including 2000 ppm) or developmental toxicity

(up to and including 500 ppm). In the presence of maternal toxicity there is indication for slight fetotoxicity (reduced fetal body weight and occasional increases in skeletal variations) with a NOAEC for fetotoxicity and maternal toxicity of 500 ppm.

However, a reduction of postnatal viability and pup survival, respectively weanling body weight gain was found in a 1-generation reproduction toxicity study with Sprague Dawley rats which inhaled 100, 500 and 1 000 ppm (Strump, 2003; Faber et al., 2007, see also RAR-chapter 4.1.2.9). Based on increased postnatal mortality and body weight gain depression in the offspring a NOAEC of 100 ppm (441 mg/m^3) was derived for developmental toxicity. This value is used for the quantitative risk assessment of developmental effects after inhalation and also after dermal contact.

Inhalation exposure

The NOAEC of 100 ppm (441 mg/m^3) from the rat is (1) multiplied with a factor of 0.45 (for rat absorption percentage of 45%) and divided by a divisor of 0.65 (for human absorption percentage after inhalation of 65%) and (2) multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. Further differences regarding the the experimental inhalation duration and the working conditions are not considered, because there is no detailed information about exposure conditions. The calculation gives an inhalation starting point of 205 mg/m^3 (441 • 0.45 / 0.65 • 6.7/10).

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. Thus the reference MOS calculates to 12.5 (2.5 • 5). The critical inhalation exposure level at the workplace is identified as 16.4 mg/m^3 (205 / 12.5).

The shift average value for inhalation is reported as 7 mg/m^3 for scenario 2 of ethylbenzene. The exposure level in this occupational scenario is higher than the critical inhalation exposure of 16.4 mg/m³. No concern is derived. For corresponding MOS values see table 2.1.D.

Conclusion: ii

Dermal contact and combined exposure

The NOAEC of 100 ppm (441 mg/m^3) from the 1-generation rat study is taken for dermal risk assessment (see above).

The NOAEC of 441 mg/m^3 corresponds to an external dose of 127 mg/kg/day (441 mg/m^3 • default respiratory volume for the rat for 6 hours of 0.288 m^3/kg). With a rat adsorption percentage of 45% after inhalation the internal critical exposure level corresponds to 57 mg/kg/day (127 mg/kg/day • 0.45). To get the (external) value for dermal contact the dermal absoption percentage of 50% for humans has to be included. Thus the internal value has to be multiplied with a factor of 2. This gives an external starting point of 114 mg/kg/day (57 mg/kg/day • 2).

The following adjustment factors are applied for the identification of the reference MOS. For (1) interspecies differences the adjustment factor is 4 • 2.5 (factor 4 for allometric scaling and factor 2.5 for remaining interspacies differences), for (2) intraspecies differences (workers) the default factor is 5. Thus the reference MOS calculates to 50 (4 • 2.5 • 5). The critical

dermal exposure level at the workplace is identified as 2.3 mg/kg/day (114 / 50). The internal critical exposure level is 1.1 mg/kg/day (57 / 50).

The shift average value for dermal contact is reported as 28.5 mg/kg/day for scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene). The exposure level in this occupational scenario is about 12 fold higher than the critical dermal exposure of 2.3 mg/kg/day. Concern is expressed regarding dermal and combined exposure for this scenario 2. For corresponding MOS values see table 2.1.D.

Conclusion: iii

Table 2.1.D: MOS values regarding developmental effects of ethylbenzene

	Inhalation			Dermal			Combined		
Starting point for MOS calculation	205 mg/m^3			114 mg/kg/day			57 mg/kg/day		
Reference MOS	12.5			50			50		
Critical exposure level	16.4 mg/m^3			2.3 mg/kg/day			1.1 mg/kg/day		
	Exposure (mg/m^3)	MOS	Conclusions	Exposure (mg/kg/d)	MOS	Conclusions	Internal body burden (mg/kg/d)	MOS	Conclusions
1 Production and further processing	1.3	158	ii	0.06	1900	ii	0.15	380	ii
2 Use of paints, lacquers, inks (containing 20% ethylbenzene)	7	29	ii	28.5	4	iii	14.95	3.8	iii

Summary of conclusions for the occupational risk assessment

As result of occupational risk assessment for ethylbenzene, concern is expressed and risk reduction measurs have to be initiated. The most important toxicological endpoints are repeated dose toxicity and developmental toxicity. For all other endpoints no concern is expressed. Table 2.1.E indicates the toxicological endpoints of concern for ethylbenzene.

Table 2.1.E indicates the toxicological endpoints of concern for ethylbenzene

Table 2.1.E: Endpoint-specific overall conclusions

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

1) conclusion iii already results from dermal exposure, therefore no specific concern for the combined exposure scenario is indicated

Risk estimation is mainly based on animal inhalation studies. Based on experimental data an adsorption percentage of 45% is taken for the rat inhalation route, whereas for humans an absorption percentage of 65 % is assumed. For the dermal pathway an absorption percentage of 50% is assumed for humans.

The most important toxicological endpoints are repeated dose toxicity and developmental toxicity of ethylbenzene. On the background of the exposure assessment and the proposed critical exposure levels, the according health risks especially after dermal contact have to be reduced.

Conclusion (iii) applies to dermal and combined exposure of scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) after repeated dose toxicity and regarding developmental toxicity. The exposure value of this scenario with a value of 28.6 mg/kg/day is about 17 fold higher than the critical exposure level of 1.7 mg/kg/day (systemic effects after

repeated exposure) and about 12 fold higher than the critical exposure level, resulting from developmental toxicity.

For inhalation the critical exposure level of 9.3 mg/m^3 results from systemic effects after repeated exposure. The inhalation exposure values of scenario 1 (production and processing) with 1.3 mg/m^3 and scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) with 7 mg/m^3 are below this value, thus reaching no concern.

2.2 Consumers

3 Current Risk Reduction Measures

Classification and labelling

The current classification of ethyl benzene according to **Annex I** of Directive 67/548/EEC (19. ATP, Index-Nr. 601-023-00-4) is **F; R11** (Highly flammable) - **Xn; R20** (Harmful by inhalation). Ethyl benzene has to be labelled with F, Xn; R11-20; S(2-)16-24/25-29.

The rapporteur (of the RAR) proposed to **add** the following classification and labelling:
R 36/37/38 Irritating to eyes, respiratory tract and to skin
R 48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation
R 65 Harmful: May cause lung damage if swallowed

This proposal has not yet been discussed in the EU-Working group on classification and labelling of dangerous substances under Directive 67/548/EEC.

Abbreviations:

F	Highly flammable
R11	Highly flammable
Xn	Harmful
R20	Harmful by inhalation
R 36/37/38	Irritating to eyes, respiratory tract and to skin
R 48/20	Harmful: Danger of serious damage to health by prolonged exposure through inhalation
R 65	Harmful: May cause lung damage if swallowed
S(2-)	Keep out of the reach of children
S 16-	Keep away from sources of ignition - No smoking
S 24/25-	Avoid contact with skin and eyes
S 29	Do not empty into drains

3.1 Workers

As a result of its classification as a hazardous substance ethyl benzene 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 ethyl benzene 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 ethyl benzene 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

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

Industrial activities using ethyl benzene present opportunities for occupational exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use.

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

Country	OEL		STEL	
Norway (2007)	20 mg/m^3	5 ml/m^3	-	-
France (2008)	88.4mg/m^3	20 ml/m^3	442 mg/m^3	100 ml/m^3

Country	OEL		STEL	
Poland	100 mg/m^3		350 mg/m^3	
Sweden (2007)	200 mg/m^3	50 ml/m^3	450 mg/m^3	100 ml/m^3
Iceland (2001)	200 mg/m^3	50 ml/m^3	884 mg/m^3	200 ml/m^3
The Netherlands (2007)	215 mg/m^3	50 ml/m^3	430 mg/m^3	100 ml/m^3
Denmark (2008)	217 mg/m^3	50 ml/m^3	-	-
Finland (2007)	220 mg/m^3	50 ml/m^3	442 mg/m^3	100 ml/m^3
Swiss (2007)	435 mg/m^3	100 ml/m^3	435 mg/m^3	100 ml/m^3
Ireland (2007), Greece (2001), USA:OSHA (2005), ACGIH (2008)	435 mg/m^3	100 ml/m^3	545 mg/m^3	125 ml/m^3
Germany (2008), Austria (2007)	440 mg/m^3	100 ml/m^3	880 mg/m^3	200 ml/m^3
United Kingdom (2007)	441 mg/m^3	100 ml/m^3	552 mg/m^3	125 ml/m^3
Spain (2008)	441 mg/m^3	100 ml/m^3	884 mg/m^3	200 ml/m^3
Belgium (2007)	442 mg/m^3	100 ml/m^3	551 mg/m^3	125 ml/m^3
Italy (2008), Luxembourg (2002), Portugal (2001), Hungary, **EU (Directive 2000/39/EC)**	442 mg/m^3	100 ml/m^3	884 mg/m^3	200 ml/m^3

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 ethyl benzene 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. Concern was expressed for dermal and combined exposure in scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) for repeated dose toxicity and developmental toxicity. In this scenario exposure was assesed to be 28,5 mg/kg/day or 2000mg/p/day (worst case), which is about 15 fold higher than the level to which dermal exposure should be

controlled (1.7 mg/kg/day or 120 mg/person/day (critical exposure level for systemic effects of repeated dose toxicity)).

Concerning inhalation exposure no concern was derived for the scenarios assessed. The critical exposure level is 9.3 mg/m^3. The exposure values of scenario 1 (production and processing) and scenario 2 (use of paints, lacquers, inks containing 20% ethylbenzene) are below this value. However, existing OELs are significatntly higher than the critical exposure level. These OELs should be revised in order to give possible future developments of new processes using ethylbenzene a proper benchmark for process design.

3.2 Consumers

Ethyl benzene 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 3:

Liquid substances or preparations, which are regarded as dangerous according to the definitions in Article 2 (2) and the criteria in Annex VI, Part 2, 3 and 4, to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (1), as adapted to technical progress by Commission Directives 93/21/EEC (2) and 96/54/EC (3)

1. May not be used in

— ornamental objects, intended to produce light or colour effects my means of different phases, for example in ornamental lamps and ashtrays,

— tricks and jokes,

— games for one or more participants, or any object intended to be used as such, even with ornamental aspects.

2. Without prejudice to the above, substances and preparations which:

— present an aspiration hazard and are labelled with R65, and

— can be used as fuel in decorative lamps, and

— are placed on the market in packaging of a capacity of 15 litres or less,

may not contain a colouring agent, unless required for fiscal reasons, or perfume or both. Without prejudice to the implementation of other Community provisions relating to the classification, packaging and labelling of dangerous substances and preparations, the packaging of substances and preparations covered by paragraph 2, where intended for use in

lamps, must be marked legibly and indelibly as follows: ‘ Keep lamps filled with this liquid out of the reach of children’ .

Appendix to Directive 76/769/EEC, Point 41:

Substances either

— appearing in Annex I to Directive 67/548/EEC which are classified as flammable or extremely flammable and labelled as such, or

— not yet appearing in Annex I to Directive 67/458/EEC but conforming to the criteria of flammability of Annex VI to Directive 67/458/EEC and being provisionally classified and labelled as flammable, highly flammable or extremely flammable according to Article 5 (2) of Directive 67/458/EEC

1. May not be used as such or in the form of preparations in aerosol generators marketed and intended for sale to the general public for entertainment and decorative purposes such as the following:

— metallic glitter intended mainly for decorations,

— artificial snow and frost,

— ‘ whoopee’ cushions,

— silly string, aerosols,

— imitation excrement,

— horn for parties,

— decorative flakes and foams,

— artificial cobwebs,

— stink bombs,

— etc.

2. Without prejudice to the application of other Community provisions on the classification, packaging and labelling of dangerous substances, the following words must appear legibly and indelibly on the packaging of aerosol generators referred to above; ‘ For professional users only’ .

3. By way of derogation, paragraphs 1 and 2 shall not apply to the aerosol generators referred to in Article 9a of Directive 75/324/EEC.

4. The products referred to above may not be placed on the market unless they conform to the requirements indicated.

Ethyl benzene is also regulated as follows:

Regulation **1907/2006/EC** (REACH), Annex XVII, Marketing and Use Restrictions, as modified by Directive 2007/51/EC, **Point no(s):3 and 40.**

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 "Highly Flammable liquids" substances in Part 2 of Directive 82/501/EEC. The qualifying quantities are 5000 tonnes (Articles 6 and 7) and 50000 tonnes (Article 9).

EU. Directive 2002/96/EC on waste electrical and electronic equipment (WEEE), Annex II, as amended by Directive 2008/34/EC, OJ (L 81) 65, 20 March 2008

EU. Commission Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products (INCI), as amended by Decision 2006/257/EC (OJ (L 97) 1, 5 Apr 2006)

EU. Toy Safety: Limits of Organic Chemical Compounds. European Norm EN 71-9, Tables 2(A-I) (February 2005)

(Source: Ariel WebInsight 5.1, 2008)

4 Possible Further Risk Reduction Measures

4.1 Workers

The following further Risk Reduction Measures are considered to be probably effective to reduce risks from dermal exposure and to properly adress potential risks from inhalative exposure in uses and processes not assessed in this risk assessment

- information on the need of technical and organisational measures, specific training, and occupational hygiene on company level in the framework of Directive 98/24

- o revise the occupational exposure limit value established at community level according to Directive 98/24/EEC .

- to apply the following revised classification**:**

R11	Highly flammable
R20	Harmful by inhalation
R 36/37/38	Irritating to eyes, respiratory tract and to skin
R 48/20	Harmful: Danger of serious damage to health by prolonged exposure through inhalation
R 65	Harmful: May cause lung damage if swallowed

The options are assessed in section 5.

4.2 Consumers

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

Technical and organisational measures, specific training, and occupational hygiene on company level in the framework of Directive 98/24

The risk assessment has resulted in concern because of dermal exposure in scenario 2. (use of paints, lacquers, inks containing 20% ethylbenzene). Dermal exposure can in principle be reduced by technical measures (e.g.closing systems) and organisational measures that reduce the frequency, duration and area of exposure, by training to work cleanly, by personal hygiene and by appropriate use of PPE. Training, information and hygienic measures are foreseen in the framework of workplace legislation.

Organisational measures and training are practical and of low or moderate economic impact. Documentation on company level makes them monitorable, but enforcement is on behalf of the Member States. The proof of efficiency of measures to control dermal exposure is generally difficult.

Dermal exposure was assessed under the prerequisites that for the use of paints, lacquers, inks containing ethyl benzene in small and medium sized enterprises and the skilled-trade area it gloves are not regularly worn. Dermal contact is supposed to occur during activities like spraying, brushing, rolling of paints. Even for spray application of paints in the industrial and skilled-trade area it was assumed that protective gloves are not regularly worn (Voullaire, 1995). So the estimation of dermal exposure levels was performed for the unprotected worker.

In the Technical Guidance Document (TGD, 2003) dermal exposure estimates for specific exposure scenarios are described. The estimates for a) spray painting of large areas and brushing and b) rolling of liquids were taken to assess the daily dermal exposure during painting works.

a) Application of paint by airless spraying to relatively large areas

On the basis of the 90^{th} percentile respectively the 95^{th} percentile of two studies a reasonable worst case (RWC) of 10.000 mg on an exposed area of 840 cm^2 was derived. For the typical case an exposure value of 2.500 mg is described. In consideration of ethyl benzene content of 20 % dermal exposure through direct skin contact during spraying of the formulations is estimated to 2000 mg/person/day (RWC) and 500 mg/person/day (typical value).

b) Application of liquids by brushing and rolling

From a field study of consumers applying anti-fouling paints by roller and brush on their boats without gloves a RWC estimate (10.000 mg on an exposed area of 840 cm^2) was derived. From values for amateurs painting boats without gloves a typical value (1.700 mg) was derived. In consideration of ethyl benzene content of 20 % dermal exposure through direct skin contact during brushing and rolling of the formulations is estimated to 2000 mg/person/day (RWC) and 340 mg/person/day (typical value).

Concluding from these scenarios an exposure level of 2000 mg/person/day (reasonable worst case) and a typical value of 340 - 500 mg/person/day for daily dermal exposure during painting works (spraying, brushing and rolling) was taken forward for risk assessment.

Taking into account, that the exposures that were taken forward for risk assessment were worst case values, it seems that the measures foreseen in the framework of workplace legislation are sufficiently effective to reduce the risks of dermal exposure. Startig form the typical exposure of 500 mg/person/day instead of 2000 mg/person/day (reasonable worst case) and supposing that gloves with an efficiency of 90% are worn, remaining exposures would be 50 mg/person/day which is clearly below 120 mg/person/day (critical exposure level for systemic effects of repeated dose toxicity)).

However, it should be born in mind, that the efficacy of gloves depends on organisational measures like training and instruction and that dermal contact should also be reduced by organisational measures and occupational hygiene.

Occupational Exposure Limit

An occupational exposure limit is not required to limit the risks in the scenarios assessed in the risk assessment.

However, existing OELs are significantly higher than the critical exposure level that has been identified. Existing OELs should therefore be revised in order to give a proper benchmark for future developments concerning the use and concerning new processes using ethylbenzene. A revised OEL would also support the risk assessment for scenarios that already exist but are not assessed in the risk assessment under EU Regulation 793/93.

Effectiveness, practicality , economic impact, monitorability will not to be analysed in depth in this strategy. The competent committees might easily use the data and assesssments provided in the risk assessment report.

Application of revised classification

The revised classification draws attention to systemic effects upon repeated exposure. The risk phrase R 48/20 (Harmful: Danger of serious damage to health by prolonged exposure through inhalation) will rise awareness to the risks of ethylbenzene and induce appropriate risk management mersures on company level. Application of the rewised classification is an effective and practical measure within the framework of workplace legislation as well as in the context of classification and labelling provisions. The economic impact is negligible and it can easily be monitored on the label and in the safety data sheet.

5.2 Consumers

6 Further Risk Reduction Measures Recommended

6.1 Workers

The risk reduction strategy recommends the following measures:

- information on the need of technical and organisational measures, specific training, and occupational hygiene on company level in the framework of Directive 98/24

- to revise the occupational exposure limit value established at community level according to Directive 98/24/EEC .
-

- to apply the following revised classification**:**
  R 36/37/38 Irritating to eyes, respiratory tract and to skin
  R 48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation
  R 65 Harmful: May cause lung damage if swallowed

6.2 Consumers

7 Marketing And Use Restrictions

Not applicable to ethylbenzene.

8 Possible Monitoring Arrangements

9 Organisations consulted