Benzene

(1st Priority List)

CAS no. 71-43-2

EINECS no. 200-753-7

Summary Risk Assessment Report

FINAL APPROVED VERSION

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Preface

This document provides a short summary with conclusions of the Risk Assessment Report of the substance **Benzene** that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances.

For detailed information on the risk assessment principles and the procedures followed, the underlying data and the literature references the reader is referred to the original Risk Assessment Report.

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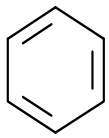
1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS No.:	71-43-2
EINECS No.:	200-753-7
IUPAC Name:	Benzene
Synonyma:	Cyclohexatriene; Benzol
Empirical formula:	C_6H_6
Structural formula:	



Molecular weight: 78.11 g/mol

Purity/impurities, additives

Purity:	> 99.9 %
Impurities:	0.04 % non-aromatics
	0.015 % toluene
	0.02 % methylcyclohexane + toluene

Physico-chemical properties

Benzene is a clear colourless liquid. Data on the physical and chemical properties are given in the following table:

Table 1.1: Physico-chemical properties of benzene

Melting point	5.5 °C
Boiling point	80.1 °C at 1013 hPa
Relative density	0.879 at 20 °C
Surface tension	28.9 mN/m (substance as such)
Vapour pressure	99.7 hPa at 20 °C
Partition coefficient	log Pow 2.13 (HPLC method)
Water solubility	1.8 g/l at 25 °C
Flash point	- 11 °C (DIN 51755)
Auto flammability	555 °C (DIN 51794)
Flammability	highly flammable [1)]
Explosive properties	not explosive [2)]
Oxidising properties	no oxidising properties [2)]

[1)] A.12 not conducted because of structural reasons
[2)] no test conducted because of structural reasons

Classification

- (Classification according to Annex I)

The current classification and labelling according to Directive 67/548/EEC, 29th ATP (Annex I, Index-No. 601-020-00-8) is:

Classification:

F; R11

Carc.Cat. 1; R45

Muta. Cat. 2; R46

T; R48/23/24/25

Xn; R65

Xi; R36/38

Labelling:

F, T

R: 45-46-11-36/38-48/23/24/25-65

S: 53-45

Concentration limits: none

In Germany, a limit immission value exists for air in cities under the Air Immission Law (§ 40 Section 2 BImSchG and 23. BImSchV) of 15 µg/m^3 (1 July 1995) and 10 µg/m^3 (from 1 July 1998), measured as annual average concentration. [Pfeffer et al. 1995]

In Germany, precautionary limit values of BTX substances, including benzene, are considered to protect soil and ground water from airborne deposits within the Soil Protection Law [Bachmann 1997].

2 GENERAL INFORMATION ON EXPOSURE

The natural sources of benzene are crude oil and, to a lesser extent, condensate from natural gas production. Benzene is produced by different petroleum conversion processes in petroleum refinery and chemical plant processes, primarily by catalytic reforming, steam cracking and dealkylation. Benzene is recovered during production of coal-derived chemicals, primarily from coke oven by-products. Benzene is extracted from these sources and purified for industrial use.

Based on the available information the estimated annual production of benzene as a chemical intermediate in the European Union (EU) is 7,247 kt/a. These figures, however, can overestimate production, because for some companies IUCLID figures were used.

In the EU benzene is produced or imported by 14 companies, 22 sites were identified at which both production and processing take place, and 12 sites where benzene is only processed.

The site specific information covers the production of 7,246.8 kt/a benzene and processing of 5,838 kt/a benzene. Taking into account exports of 130 kt/a and imports of 590 kt/a a quantity processed of approximately 1,868.8 kt/a is not covered by the exposure calculations based on data from 48 companies. A generic scenario is calculated for this quantity.

The major uses of benzene in the EU are the production of ethylbenzene (52 %), cumene (20 %), cyclohexane (13 %), nitrobenzene (9 %), alkylbenzene (3 %), maleic anhydride and other (2 %) and chlorobenzene (1 %). Benzene used in petrol is in addition to the benzene of chemical intermediate production. The quantity of benzene present in petrol may be estimated at 1.41 million tonnes for the EU in 2000.

Very small quantities are also used as a laboratory reagent and solvent.

Since benzene is a natural component of crude oil, it is an intrinsic constituent of certain refinery fractions, or it is formed during the refining process in use today. As a result, benzene as a component of refinery products also ends up in consumer products.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

a) Releases into the environment

Benzene is released from a number of man-made sources. The primary sources of environmental benzene are automobile exhaust emissions, evaporative losses and refuelling emissions. Benzene in automotive exhaust is a mixture of incompletely burned benzene and benzene produced in the motor during combustion through dealkylation of toluene and xylenes. From industrial sources, it primarily enters the environment as fugitive emissions from industrial intermediate production and processing operations and through air emissions from waste water treatment plants.

Natural sources of benzene emissions such as vulcanos and forest fires exist.

Benzene is used and emitted in large quantities. Because benzene is a volatile organic compound, it is mainly emitted to the air and emissions to soil and water partly lead to emission to the air. As a result the emission most of the benzene is found in the air compartment.

Based on the available and traceable exposure data and the default values used, an emission to waste water treatment plants (WWTP) of 25,821 t/a and an emission to air (direct) of 60,787 t/a is calculated for the industrial production and processing sites.

In addition, further environmental point source releases occur from oil refineries, coking plants, stationary combustion of fossil fuels for energy production, offshore platforms, road traffic. Disperse source releases include evaporative losses from petrol distribution, combustion of fossil fuels for commercial and residential heating, WWTP, laboratory reagent and solvent at laboratories, landfill sites, accidental releases (not considered in this report), natural sources and environmental tobacco smoke (ETS). A total emission to air of 193,909 t/a is estimated for the releases from all these sources, including industrial production and processing.

b) Degradation

From the results of standard biodegradation tests it can be concluded that benzene is readily biodegradable. For surface waters a half-life of 15 days can be derived for readily biodegradable substances. In soils and sediments benzene is biodegraded with estimated half-lives of 30 d and 300 d, respectively.

In biological treatment plants, benzene is estimated to be removed by 93.9 % by biodegradation and volatilisation. From site-specific influent and effluent concentrations elimination rates in the range of 90 to > 99 % can be calculated.

Hydrolysis at environmental conditions is not likely due to the lack of reactive functional groups in the molecule. Direct photolysis is also of minor importance due to low absorbance of UV light.

For the degradation of benzene in air by reactions with hydroxyl radicals, a half-life of 13.4 d is calculated.

Benzene contributes to ozone formation in the surface near atmosphere. However, the photochemical formation of ozone and other harmful substances in polluted air depends on emission of all VOCs and other compounds in a complex interaction with other factors. Therefore, a more in-depth evaluation of the contribution of benzene to the complex issue of air quality should more appropriately be dealt with by authorities regulating air quality rather than as a part of this substance specific risk assessment.

c) Distribution

When benzene is released to water, volatilisation will result in a substantial loss to the atmosphere. A Henry constant of 432.6 Pa m^3/mol at 20 ^oC was calculated.

On the basis of the log Pow value (2.13) and according to the TGD the Koc value is calculated as 134.1 l/kg. This value does not indicate a significant potential for geoaccumulation.

With a Mackay I fugacity model the atmosphere was identified as target compartment (98.8 %).

d) Accumulation

Different tests indicate that benzene has a low bioaccumulation potential. From the log Kow of 2.13 a BCF of 13 is estimated.

3.1.2 Aquatic compartment

3.1.2.1 Release during production and processing of pure benzene

For the calculation of the $Clocal_{water}$ for the 48 known production and/or processing sites site-specific data were used as far as they were available. In cases where exposure data was absent or not traceable, the “default values” from the TGD were applied. The quantity of approximately 1,868.8kt/a is not covered by the known processing sites. Therefore, a generic exposure scenario was calculated. A typical company, involved in the processing of pure benzene, with a processing quantity of 100 kt/a (mean value of processing sites) was used for the calculation.

The calculated PEClocal values for all production and/or processing sites, including the generic processing sites, are in the range of 0.29 to 4,732 µg/l.

3.1.2.2 Release from the use of benzene

Benzene is used as a laboratory reagent. Benzene occurs in small quantities in various solvents on a hydrocarbon basis. In the case of such uses release to municipal waste water can be assumed. An accurate estimate of the quantities involved is difficult, especially because it often concerns small concentrations in large volume flows. It is not possible to undertake an estimation of the $Clocal_{water}$ for these areas of use, because the quantities are not known.

3.1.2.3 Release from other areas

Releases into the aquatic compartment may occur from refinery processes. For 5 German refineries $Clocal_{water}$ between < 0.02 µg/l and 0.19 µg/l were estimated based on measured effluent concentrations.

Releases from German service stations and fuel depots resulted in estimated $Clocal_{water}$ of between 0.014 µg/l and 7.88 µg/l based on measured benzene concentration in the waste-water.

The prediction of absolute emission from service stations and bulk plants is not possible on the basis of the available data.

3.1.2.4 Sediments

Because of the low partitioning coefficients, no accumulation in sediments will take place. Thus an assessment of this sub-compartment is not necessary.

3.1.2.5 Aquatic monitoring data

Measured concentrations of benzene in surface waters are in the range of <0.1 – 31.7 µg/l. For seawater the range is <0.005 – 0.02 µg/l and for estuaries <1 – 89.4 µg/l. The monitoring data show regional differences in pollution levels.

3.1.3 Atmosphere

3.1.3.1 Release during production and processing of pure benzene

Direct releases into the atmosphere occur during production and processing. Indirect releases come from stripping processes in WWTPs. According to the SimpleTreat calculations 42.6 % of the releases to WWTP is distributed to the air compartment. The $PEClocal_{air}$ was calculated for the individual sites by using the currently available emission data of individual production and/or processing companies. Where no site-specific data was available, the $PEClocal_{air}$ calculation was performed using the “default values” of the TGD. In calculating the $PEClocal_{air}$ both the emission from a direct point source as well as the indirect emissions from WWTPs were taken into account. The maximum emission from these two sources was used for the calculation of $PEClocal_{air.}$

The quantity of approximately 1,868.8kt/a is not covered by the known processing sites. Therefore, a generic exposure scenario was calculated. A typical company involved in the

processing of pure benzene with a processing quantity of 100 kt/a (mean value of processing sites) was used for the calculation.

The calculated $PEClocal_{air\text{-}annual}$ for all production and/or processing sites, including the generic processing sites, were in the range of 1.48 µg/m³ to 4,084 µg/m³.

3.1.3.2 Atmospheric monitoring data

There is an extensive database of benzene immission concentrations in air. For eight scenarios concentration ranges and typical values are summarised:

Category	**Concentration Range [µg/m³]**	**Typical Value $PEC_{air\text{-}monit.}$ [µg/m³]**
Ambient city air	1 - 275	10 – 20
Urban industrial areas	6 - 63	5
Rural and pristine areas	0.5 - 4.4	1.5
Oceanic air masses	0.03 - 0.5	0.3
Fuel service stations	2 – 27,000	120
Inside vehicles in cities	3 - 139	40
City indoor air	1 - 90	15
Smoker exposure indoor air	0.7 - 90	11

3.1.3.3 Creation of tropospheric ozone due to non-isolated benzene in car exhaust

It is known that benzene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone. The photochemical formation of ozone and other compounds depends on emission of all VOCs and other compounds in a complex interaction with other factors.

On the basis of monitoring of NMVOCs in street air there is indication that non-isolated benzene may contribute with about 2.5 to 7.5 % to the overall ozone formation due to NMVOCs.

3.1.3.4 Creation of ozone due to isolated benzene

It is known that benzene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone. The photochemical formation of ozone and other compounds depends on emission of all VOCs and other compounds in a complex interaction with other factors.

Utilising the availale information, it can roughly be estimated that emission of benzene from production and use of the commercial product benzene may be in the order of 0.5 % of total NMVOC emission.

3.1.4 Terrestrial compartment

Releases of benzene into the terrestrial compartment are to be expected as a result of deposition from the atmosphere. The deposition rate results from the calculations for three typical companies which produce and/or processe pure benzene. Based on the deposition fluxes of 50, 500 and 5,400 µg/m^2 · d the resulting soil concentration are 1.2, 11.9 and 129 µg/kg.

3.1.5 Non-compartment specific exposure relevant to the food chain

As there is no bioaccumulation, a biomagnification via the food chain is not expected.

3.1.6 Regional Exposure

All releases, from point sources and diffuse sources, were considered in the determination of a regional background concentration. The summarised local emissions for the production and processing of benzene as well as the diffuse releases of benzene, for instance vehicle exhaust fumes and further combustion processes, were distributed between the regional and continental area at a ratio of 10% to 90%.

The following regional environmental concentrations result from the calculations:

$PEC_{regional\ aquatic}$	0.275 µg/l
$PEC_{regional\ air}$	1.54 µg/m^3
$PEC_{regional\ agr.soil}$	0.017 µg/kg
$PEC_{regional\ natural\ soil}$	0.02 µg/kg

3.2 EFFECTS ASSESSMENT

3.2.1 Aquatic compartment

A lot of toxicity tests with aquatic organisms were conducted using benzene as test substance. For the risk assessment those tests are preferred that were conducted in flow-through systems with analytical monitoring of the benzene concentration because of the high volatility of the substance. If nominal concentrations are reported it has to be considered that the effect values may be significantly lower due to volatilization.

Short- and long-term tests are available with fish, invertebrates and algae.

With regard to short-term exposure of animals and algae the available valid LC/EC_{50} values point to similar susceptibility of sensitive taxa in fish and invertebrates (crustaceae), compared to a somewhat lower overall sensitivity of algae.

The lowest valid effect value was found in a fish early life stage test with *Pimephales promelas* performed in a flow-through system with analytical monitoring of the benzene concentration. The 32d-LOEC of 1.6 mg/l obtained in this study for the endpoints wet weight and total length was converted to a 32d-NOEC of 0.8 mg/l. In a reproductive toxicity test with the invertebrate *Ceriodaphnia dubia* a 7d-NOEC of 3 mg/l was found in a semi-static closed system. The NOEC is based on measured concentrations. For the green alga *Selenastrum capricornutum* a 72h-ErC_{50} of 100 mg/l and a 72h-ErC_{10} of 34 mg/l was determined. The test system was closed and the benzene concentration was monitored analytically.

With an assessment factor of 10 a **P**redicted **N**o **E**ffect **C**oncentration (PNEC) of 80 µg/l was derived from the NOEC for *Pimephales promelas*.

3.2.1.1 Effects on Microorganisms

The derivation of a PNEC for microorganisms is based on the result from a test on nitrification inhibition, as this was the most sensitive endpoint. With an assessment factor of 10 a PNEC of 1.3 mg/l was derived from the 24h-EC50 of 13 mg/l for *Nitrosomonas* spec..

3.2.1.2 Effects assessment for the sediment

There are no results from sediment tests with benthic organisms available. According to the physico-chemical properties currently known, there is nothing indicating that benzene accumulates in sediment. Therefore a quantitative risk assessment seems not to be necessary for this compartment.

3.2.2 Atmosphere

Direct effects

From the available data about effects of benzene on higher plants via the atmosphere it can be concluded that benzene seems not to be of concern for plants with regard to exposure via the

atmosphere except at very high concentrations (g/m³). No formal PNEC is established because of lack of appropriate long-term studies.

Indirect effects

Benzene contributes to ozone formation in the surface near atmosphere. However, the photochemically formation of ozone and other harmful substances in polluted air depends on emission of all VOCs and other compounds in a complex interaction with other factors. Therefore, a more in-depth evaluation of the contribution of benzene to the complex issue of air quality should more appropriately be dealt with by authorities regulating air quality rather than as a part of this substance specific risk assessment.

3.2.3 Terrestrial compartment

Concerning the terrestrial compartment, there are no effect values available that can be used for the effect assessment. Therefore, the PNECsoil is derived from the PNECaqua using the equilibrium partitioning method:

$$PNEC_{soil} = \frac{K_{soil-water}}{RHO_{soil}} \cdot PNEC_{aqua} \cdot 1000\ l/m^3$$

Using a $K_{soil\text{-}water}$ of 4.26 m^3/m^3 and a RHO_{soil} of 1700 kg/m^{-3} results in a $PNEC_{soil}$ of 0.2 mg/kg ww.

3.2.4 Non compartment specific effects relevant to the food chain

As benzene has only a low bioaccumulation potential, it is not required to carry out a risk characterization for secondary poisoning.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic Compartment

The risk assessment for aquatic organisms resulted in a $PNEC_{aqua}$ of 80 µg/l. The $PNEC_{microorganism}$ was determined to 1.3 mg/l.

Waste-water treatment plants

The benzene concentration in the effluent of municipal waste water treatment plants are between 0.2 and < 6 µg/l. Based on the available exposure informations for refineries, service stations and fuel depots the $Clocal_{effl}$ are between 0.14 and 788 µg/l.

Taking into consideration the $PNEC_{microorganism}$ of 1.3 mg/l, the ratios of $Clocal_{effl}$ /$PNEC_{microorganism}$ are below 1 and there is currently no indication of a risk to the microorganism population of these WWTPs.

The reported monitoring data of benzene in the effluent of industrial waste water treatment plants are between < 0.2 µg/l and 78,000 µg/l. The calculated effluent concentrations in chapter 3.1.2.3 are between 1 and 101,700 µg/l. It should be noted that the highest values are based on the use of TGD default values.

Taking into consideration the $PNEC_{microorganism}$ of 1.3 mg/l, the ratios of $Clocal_{effl}$ /$PNEC_{microorganism}$ are > 1 for a great part of the production and processing sites and there is currently an indication of a risk to the microorganism population of industrial waste water treatment plants (23 sites of all 48 sites).

Result:

conclusion (ii) There is at present no need for further information and/or testing.

This conclusion applies to all sites with $Clocal_{effl}$ /$PNEC_{microorganism}$ ratio is < 1 and also to municipal waste water treatment plants.

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

For 23 out of 48 sites the $Clocal_{eff}$/$PNEC_{microorganism}$ ratio is > 1. For all these sites the $Clocal_{eff}$ is based on default values and could possibly be lowered by site-specific and traceable exposure data. However, it is not expected to obtain exposure data for all these sites with reasonable efforts and time expenditure. Also the performance of further tests is not expected to result in a $Clocal_{eff}$/$PNEC_{microorganism}$ ratio below 1 for all sites due to the partly very high effluent concentrations of benzene (up to 102 mg/l).

Surface water

As production sites, 14 sites were identified. The calculated $PEClocal_{water}$ are ranging from 0.3 µg/l to 50.28 µg/l. As sites at which production and processing takes place on the same site, 22 sites were identified. The calculated $PEClocal_{water}$ are ranging from 0.3 µg/l to 4,732 µg/l. 12 processing sites were identified. The calculated $PEClocal_{water}$ are ranging from 0.29 µg/l to 19.49 µg/l. It should be noted that the highest values are based on the use of TGD default values.

Site specific calculations of the $PEClocal_{water}$ could be performed for all benzene production sites. Site specific data was absent only for the processed quantity of approximately 1,868.8 kt/a. For these sites a generic exposure scenario was used. A typical company, involved in the processing of pure benzene, with a processing quantity of 100,000 t/a was used for the calculation. A $PEClocal_{water}$ of 28 µg/l is obtained for an individual site.

Taking into consideration the $PNEC_{aqua}$ of 80 µg/l, a $PEClocal_{water}/PNEC_{aqua}$ ratio > 1 result for 2 sites of all 48 sites involved in the production and/or processing of benzene. The currently available data indicate a risk to the aquatic biocenosis for these sites.

Result:

conclusion (ii) There is at present no need for further information and/or testing.

This conclusion applies to sites with PEClocal/PNEC ratios < 1 and also to the aquatic compartment at the regional level.

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

For 2 sites the PEClocal/PNEC ratio is > 1. As the PEC calculations for these sites are partly based on default values, improvement of the data basis would be possible. However, the 2 sites were repeatedly asked for site-specific exposure data but did not react. Therefore, it is assumed that it is not possible to gather traceable exposure data for these sites with reasonable effort.

3.3.2 Atmosphere

On account of the atmospheric half-life ($t_{1/2}$ = approx. 13.4 days), abiotic effects on the atmosphere, such as global warming and ozone depletion in the stratosphere, are not to be expected in the case of benzene.

The calculated $Clocal_{air\text{-}annual}$ range from 1.48µg/m^3 to 4,084 µg/m^3. The 90 percentil of all 48 sites for the production and/or processing of pure benzene is 553 µg/m^3 and the mean $Clocal_{air\text{-}annual}$ is 297 µg/m^3.

A $Clocal_{air\text{-}annual}$ of 1,906 µg/m^3 is obtained based on a relevant processing quantity of 100,000 t/a benzene for a generic scenario.

The available effect data are very scanty and insufficient for the derivation of a distinct PNEC. However, they allow the statement that benzene seems not to be of concern for plants with regard to exposure via the atmosphere except at very high concentrations (g/m^3). Therefore, only a quantitative risk characterization for the atmospheric compartment is conducted using selected measured or calculated environmental concentrations. As highest benzene concentrations in air the PEC_{local} (100 m distance from point source) of 4.08 mg/m^3 is chosen. This value is a factor of more than 1000 below the concentration range at which effects on plants were observed. In view of these ratios it should be concluded that in the present immission situation no harmful effects on outdoor vegetation resulting from exposure to benzene in air are to be expected.

It is assumed that the risk for terrestrial organisms exposed to benzene via inhalation is covered by the risk assessment for human health.

Result:

conclusion (ii) There is at present no need for further information and/or testing.

It is known that benzene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone. The photochemical formation of ozone and other compounds depends on emission of all VOCs and other compounds in a complex interaction with other factors. Based on a rough estimation utilising available information, the current risk assessment indicates that emission of benzene from the use and production of the commercial product benzene may be in the order of 0.5 % of total NMVOC emissions. Locally and regionally this proportion may vary substantially due to differences between regions in the VOC emission pattern from industrial sectors using benzene. Even a simple evaluation of the photochemical ozone creation potential of the emission of isolated benzene is difficult to perform, when the emission pattern of individual NMVOCs is not available.

Effects of ozone exposure on plants, animals and humans are documented. The severity of exceedance of the EU threshold level for health protection (110 µg/m³, 8h average) has been estimated by WHO. The 1995 summer ozone incidence is estimated to have caused 1500 – 3700 deaths and further 300 – 1000 extra emergency hospital admissions due to respiratory deseases. If these figures are used to estimate the impact of emission from production and use of the commercial product benzene through formation of ozone then this emission may have caused around 15 deaths in summer 1995 if a linear relatioship exists between the emission of benzene, the emission of NMVOCs and the creation of ozone. Similarly, the vegetation and wildlife may be severely affected by ozone incidences and benzene is likely to contribute to these effects.

However, no simple relationship has been established between the proportion of benzene to total NMVOC emitted – and thus also between emissions arising from the use of the commercial product benzene – and the creation of troposheric ozone.

Result:

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

This conclusion applies to the contribution of the commercial product benzene to the formation of ozone. Although only a rough estimation with considerable uncertainties behind it could be performed, the information available is regarded as sufficient to draw this conclusion. In the context of the consideration of which risk reduction measures that would the most appropriate, it is recommended that under the relevant air quality Directives a specific in-depth evaluation be performed. Such an evaluation should focus on the contribution of isolated as well as non-isolated benzene to the complex issue of ozone and smog formation and the resulting impact on air quality.

3.3.3 Terrestrial compartment

Releases of benzene into the terrestrial compartment are to be expected as a result of deposition from the atmosphere. The deposition rate results from the calculations for three typical companies which produce and/or processe pure benzene. Based on the deposition fluxes of 50, 500 and 5,400 µg/m^2 · d the resulting soil concentration are 1.2, 11.9 and 129 µg/kg.

A comparison between the highest calculated PEC_{soil} of 129 µg/kg and the PNECsoil of 200 µg/kg leads to a ratio of 0.65. Consequently, the actual benzene exposure level presents no risk to the terrestrial compartment.

Result:

conclusion (ii) There is at present no need for further information and/or testing.

3.3.4 Non compartment specific effects relevant to the food chain

As benzene has only a low bioaccumulation potential it is not required to carry out a risk characterization for secondary poisoning.

3.3.5 Unintentional releases

Aquatic compartment

Benzene is a naturally occurring substance. From e.g. offshore platforms, oil refineries, cooking plants, road traffic unintentional releases into the environment occur. These releases

have been quantified as far as possible in the RAR and have been considered for the calculation of the continental and regional background concentrations.

To establish representative release data for the whole EU from these unintentional sources is not within the scope of this programme. Based on the available exposure information the $PEClocal_{water}$ for refineries are 0.5 µg/l, for service stations 1.01 µg/l and for fuel depots 8.19 µg/l. Taking into consideration the PNECaqua of 80 µg/l, the ratio of $PEClocal_{water}$/PNECaqua are below 1 and there is currently no risk to the aquatic biocenosis for these sites.

Result:

conclusion (ii) There is at present no need for further information and/or testing.

Air compartment

The major releases of benzene to the atmosphere are automotive exhaust emissions, evaporative losses and combustion of fossil materials. These disperse releases must be taken into account in the evaluation of the monitoring data and in the calculation of the regional PEC. This emission path is not however the subject of this risk assessment.

The typical benzene concentration in ambient city air is between 10 and 20 µg/m^3 with a maximun of 348 µg/m^3. In rural and pristine areas benzene concentrations are measured between 1 and 3 µg/m^3.

A regional background concentration of 1.54 µg/m^3 for benzene in the atmosphere is calculated from all of the releases of benzene into the environment.

The maximum measured benzene concentration in streets of 0.348 mg/m^3 is a factor of 10 lower than the highest $PEClocal_{air}$ calculated for production / processing of benzene and a factor of 10,000 below the concentration range at which effects on plants were observed. In view of these ratios it can be concluded that in the present immission situation no harmful effects on outdoor vegetation resulting from exposure to benzene in air can be expected.

It is assumed that the risk for terrestrial organisms exposed to benzene via inhalation is covered by the risk assessment for human health.

Result

conclusion (ii) There is at present no need for further information and/or testing.

It is known that benzene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone. The photochemical formation of ozone and other compounds depends on emission of all VOCs and other compounds in a complex interaction with other factors.

The industrial use of the commercial product benzene contributes significantly to the overall emission of benzene, however, emission of benzene in exhaust gases expelled from motor vehicles seem to be the largest single source.

On the basis of monitoring of NMVOCs in street air there is indication that non-isolated benzene can contribute with about 2.5 – 7.5 % to the overall ozone formation due to NMVOCs.

Result:

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

This conclusion applies to the contribution of non-isolated benzene to the formation of ozone. Although only a rough estimation with considerable uncertainties behind it could be performed, the information available is regarded as sufficient to draw this conclusion. In the context of the consideration of which risk reduction measures that would the most appropriate, it is recommended that under the relevant air quality Directives a specific in-depth evaluation be performed. Such an evaluation should focus on the contribution of isolated as well as non-isolated benzene to the complex issue of ozone and smog formation and the resulting impact on air quality.

4 HUMAN HEALTH

4.1 EXPOSURE

4.1.1 Occupational Exposure

The potential of benzene exposure to workers occurs in numerous of industries, e.g. in the chemical industry, in the petroleum refinery and in coking plants.

Since benzene is a natural component of crude oil, it is an intrinsic constituent of certain refinery fractions, or it is formed during the refining process in use today. As a result, benzene as a component of refinery products also ends up in products used at the workplace.

Detailed information on the production volumes is given in chapter 2.

Based on the available information the following relevant occupational exposure scenarios are to be expected:

- production of benzene, further processing in the chemical industry, refinery - scenario 1
- coking plant, by-product recovery - scenario 2
- formulation of perfumes (use of pure benzene) -scenario 3
- production of formulations (use of solvents, benzene content 5%, assumption) - scenario 4
- distribution of gasoline (benzene content 1%) - scenario 5
- automobile industry, mechanic engineering, car repair and car recycling (use of solvents, benzene content 1% – scenario 6
- handling of gasoline at service stations (benzene content 1 %) – scenario 7
- cleaning of tanks (crude benzene, gasoline and heating oil tanks) – scenario 8
- use of formulations with residual benzene (< 0.1 %), e.g. adhesives, paints – scenario 9
- tire retreading, inter alia using adhesives (benzene content limited to 0.1 %) – scenario 10
- foundries (benzene as a decomposition product) – scenario 11

The results for the different scenarios are summarised in table 4.1.1.

Legal conditions

According to the Council Directive 97/42/EC (27.06.1997, amending Directive 90/394/EEC) the overall occupational exposure limit of benzene is laid down to 3.2 mg/m^3 (1 ml/m³) from 27. June 2003 onwards. Until 27. June 2003 a transitional occupational exposure limit of 9.6 mg/m^3 (3 ml/m³) is valid. The member states are obliged to implement this regulation in national legislation. In the past, different OELs (Occupational Exposure Limits) were established, up to 16 mg/m³. In part, the member states have splitted OELs with higher OELs for the area of coking plants, works at gasoline or benzene conduction parts in the chemical or petroleum industry.

Benzene may be a minor component in solvents which are applied e. g. in paints, paint strippers, degreasing agents and rubber cements. Since 1989, the concentration of benzene in preparations is limited to 0.1 % (w/w) within the EU.

An exception is gasoline, which contains up to 1 % (v/v) benzene (European Directive 98/70/EC, from 01.01.2000). Until 31.12.1999, the maximum content of benzene in gasoline was 5 % (v/v).

According to the European Directive 94/63/EC, the conditions of the storage of gasoline and its distribution from terminals to service stations are changing. There are new technical standards which are obligatory for all devices built later then 31.12.1995. Transition periods of three to nine years are established for existing devices depending on the throughput (European Directive 94/63/EC).

Exposure assessment

The exposure assessment is based on measured data and literature data, expert judgement and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure assessment generally aims at assessing exposure levels representing the reasonable worst case situation. The reasonable worst case is regarded as the level of exposure which is exceeded in a small percentage of cases over the whole spectrum of likely circumstances of use for a specific scenario.

Dermal exposure is exclusively assessed according to the EASE model.

In the case of benzene and gasoline, the predominant effect reducing dermal exposure is the high volatility of the substances (vapour pressure of benzene: 99.7 hPa and of gasoline: 50 - 900 hPa.) which leads to considerable low retention times of the substances on the skin or on the protective gloves. An evaporation time of up to 10 seconds (order of magnitude) is calculated and given in addition to the EASE estimates. This exposure reducing effect cannot be considered if workers have continuous direct contact with the substances, e.g. dipping hands into the substances. In case of occlusive conditions the retention time may be prolonged to a few minutes. Non-occlusive exposure is regarded as predominant.

The assessment of occupational exposure of benzene is difficult because the legal conditions have changed recently and will change in the near future (see above: *Legal conditions*).

Therefore, for many scenarios, exposure could not be assessed for the current situation at the workplace but for past conditions, e.g. based on data from the 90ies, when other OELs were valid and higher benzene concentrations in gasoline were permitted. In part, the old data are taken together with model estimate in order to conclude to the actual exposure level. Taking into account the past and future changes of the legal conditions, the exposure assessment is made on the basis of the most actual measurement data, although they are limited in some cases. In accordance with DOC.ECB4/23/98 internationally reviews are partially used and for a detailed description reference is made to the reviews.

The vapour phase of a gasoline with 1 % (v/v) benzene contains approx. 0.5 % (v/v) benzene. This relationship was derived by measurements and model calculations and is used for the prediction.

Based on the information available within the frame work of this exposure assessment it is concluded, that relevant exposure levels of benzene are mainly to be excepted in the production of benzene and its further processing as a chemical intermediate, in the refinery and distribution of gasoline, by cleaning of gasoline tanks as well as in foundries.

Further detailed information see in the Comprehensive Risk Assessment Report.

Summary of exposure data

Table 4.1.1: Summary of exposure data

All values are seen to represent the reasonable worst case situation (RWC: reasonable worst case).

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m^3]	Dermal exposure Shift average [mg/person/day]
Production and further processing of benzene			
1) Production, further processing, refinery	shift length, daily	**3.5** (1) (95th percentile) before 1995	**low** (2) (expert judgement) **420** (3) (EASE)
2) Coking plants, by-product recovery	shift length, daily	**15.5** (1) (highest result) 1990-1991	**420** (4) (EASE)
Formulation of preparations			
3) Production of perfumes, use of benzene	shift length (assumed), daily	**84** (1) (90th percentile) 1987-1995	**420** (4) (EASE)
4) Production of formulations, use of solvents, benzene content unknown, assumption: 1 %	shift length (assumed), daily	**0.15** (1) (highest result) 1987-1999	**4.2** (4) (EASE)
Use of gasoline			
5) Distribution of gasoline (marine, road, rail), 1 % benzene, a)without VR, b) with VR	shift length (assumed), daily	**a) 6.8** (5) (90th percentile) 1999-2000 **b) 1.26** (5) (90th percentile) 1999-2000	**4.2** (4) (EASE)
6) Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	4 hours (assumed), daily	**2.25** (6) (results obtained before 1995, modified using EASE estimates)	**8.4** (4) (EASE)

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m³]	Dermal exposure Shift average [mg/person/day]
7) Service stations, handling of gasoline (1 % benzene), a) without VR, b) with VR	4 hours (assumed), daily	**a) 0.5** (5) (90th percentile) 1999-2000 **b) 0.1** (5) (90th percentile) 1999-2000	**0.4** (4) (EASE)
Other			
8) Cleaning of tanks: a) crude benzene tanks, gasoline tanks (75% benzene) b) heating oil tanks	8 hours (assumed), daily	**a) 67.7** (1) (95th percentile) before 2000 **b) 0.44** (5) (highest result) 2000	**a) 1575** (4) (EASE) **b) negligible** (7) (expert judgement)
9) Use of formulations with residual benzene, e.g. adhesives, paints containing <0.1 % benzene	shift length, daily	**1** (8) (95th percentile) 1991-1995	**6.5** (4) (EASE)
10) Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1 %	4 hours (assumed), daily	**2.7** (1) (highest result) before 1991	**0.4** (4) (EASE)
11) Foundries a) without LEV b) with LEV	shift length, daily	**a) 5.4** (1) (95th percentile) 1991-1995 **b) 1.6** (1) (95th percentile) 1991-1995	**low** (9) (expert judgement)

(1) Exposure levels are assessed based on data from before 1995. Therefore, the data possibly do not reflect the current workplace situation
(2) expert judgement of dermal exposure for the proper use of suitable gloves
(3) unsuitable gloves, worst-case estimation for unprotected workers
(4) dermal exposure is predicted assuming that gloves are not worn
(5) measurement results are regarded to represent the current exposure situation
(6) measured data relating to gasoline containing up to 5 % benzene were modified using EASE estimates for 1 % benzene. The exposure level is regarded to represent the current exposure situation
(7) expert judgement based on the low concentration of benzene in heating oil (< 1 mg/person/day)
(8) limited number of measurement results from one company, supported by EASE estimates
(9) rough estimation; benzene is released as a decomposition product, secondary contact with contaminated surfaces (< 1 mg/person/day)

EASE: Estimation using the EASE model (Estimation and Assessment of Substance Exposure)
LEV: Local Exhaust Ventilation
VR: vapour recovery

4.1.2 Consumer Exposure

Consumer exposure to benzene results from tobacco smoking, filling gasoline at a filling station and driving cars. Additionally, there are data that benzene may be present as a contaminant in consumer products. Paints may contain a maximum content of 390 ppm (1.24 mg/l), lubricants and adhesives of 410 ppm (1.3 mg/l), and model and hobby glues of 780 ppm (2.48 mg/l). From these data as a worst case assumption the maximum content of benzene in consumer products was estimated to be 2.5 mg/l.

Inhalation exposure

Cigarette smoke contains high amounts of benzene thus resulting in human exposure due to smoking (scenario 1). The amounts of benzene are between 10 and 100 µg per cigarette respective 150 to 240 µg/m³ in the mainstream. Thus, smokers will be exposed to a large amount of benzene during smoking since they inhale the mainstream and sidestream directly. The uptake of benzene per cigarette is estimated to account up to 30 µg. Hence, a smoker who smokes 20 cigarettes per day will inhale up to 600 µg of benzene.

Air concentrations of benzene in homes of smokers and non-smokers have been measured during fall and winter. Mean benzene air levels were 16 and 9.2 µg/m³ in homes of smokers and non-smokers, respectively. The difference between both values (about 7 µg/m³) can be considered as contribution of smoking to the air concentration of benzene in a non-smoker house. Thus, this concentration resulting from smoking has been taken into account for exposure estimates for non-smoking people (passive smokers). In spring and summer, the respective concentrations were 4.8 µg/m³ (smokers) and 4.4 µg/m³ (non-smokers).

Exposure to benzene from paints (scenario 2) was estimated taking the CONSEXPO Scenario "painting" and the model "painting". Use of this model reveals an average concentration of benzene during use for the user of 17 µg/m³, for the bystander (non-user) of ~ 3 µg/m³.

The average benzene concentration during a three minutes car refuelling is 0.8-1.0 mg/m³ at filling stations (scenario 3). According to measured exposure data during gasoline refuelling the overall arithmetic mean concentrations for benzene in the integrated samples (n = 8) were 0.90 mg/m³ with gasoline containing less than 1% benzene. This data set consisted of 8 integrated samples covering each approximately 20 refuellings for a total of 167 operations (Vainiotalo et al., 1999; addendum September 11, 2002). The maximum value of 1.3 mg/m³ is selected for risk characterisation purposes.

Concentrations of benzene of 4.3 mg/m³ have been published in a previous study for the years 1984-1985 in which the average benzene content of gasoline was reported to be 4% (w/w). Higher concentrations of 50 mg/m³ have been measured at filling stations directly nearby the filling tube. These values are not used for exposure estimations, because this can be considered as an extreme situation, and concentrations of benzene will be normally lower.

Consumers may be exposed to benzene from car interior accessories when driving by car (scenario 4). Average concentrations of benzene levels inside cars vary between 10 and 120 µg/m³. The benzene concentration declines within a period of 10 weeks to less than 10% of this concentration. Thus an air concentration of 12 µg/m³ can be assumed as worst case exposure. Driving an old car, the internal concentrations will be even lower. Benzene exposure will increase considerably if the driving duration is increased extensively. Moreover, there exists a high variability of benzene concentrations in the car interior air due to different

releases in the variety of car types. Furthermore the release from car interior equipment is dependent on temperature. Higher temperature results in a higher release.

The following exposure estimates for the different scenarios will be taken forward to the risk characterisation of consumers:

1. Exposure of passive smokers from smoking (scenario 1) 0.007 mg/m³
2. Exposure from painting (scenario 2) 0.017 mg/m³
3. Filling gasoline (scenario 3) 1.3 mg/m³
4. Exposure from car interior accessories (scenario 4) 0.012 mg/m³

Oral and dermal exposure

For the identified consumer exposure scenarios, exposure to benzene via the oral route is not considered to be relevant for the risk assessment. Dermal exposure to benzene may occur when a person is filling the tank of a car at a filling station and gasoline splashes. This dermal exposure in the order of 0.6 µg/kg bw will be neglected for risk characterisation purposes.

4.1.3 Humans exposed via the environment

For benzene it can be assumed that the predominant exposure pathway is via air.

For the calcuation estimated local air concentrations are used. Different values representing relevant scenarios for indirect exposure are selected. Resulting doses for the different scenarios are:

Scenario	**Estimated range of emission**	**Selected value**	**PEClocal$_{air-annual}$**	**Resulting DOSEtot**
Default emission to air direct (10 sites)	403.33– 9,000 kg/d	Mean : 3,888 kg/d	890 µg/m³	192 µg/kg bw d
Default emission to air via wwtp (17 sites)	3.65 – 2414 kg/d	Mean : 857 kg/d	197 µg/m³	43.7 µg/kg bw d
Site-specific emission to air direct (18 sites)	1.14 – 800 kg/d	Max : 800 kg/d 90%il : 586 kg/d	184 µg/m³ 136 µg/m³	41 µg/kg bw d 30.7 µg/kg bw d

In addition to the scenarios described above, unintentional releases from road traffic are considered relevant for indirect exposure. Measured concentrations in ambient city air are in the range of 1 to 275 µg/m³, with typical values between 10 and 20 µg/m³. Current European ambient air levels are in the range of < 5 µg/m³ to 20 µg/m³ dependent upon location. Using an air concentration of 20 µg/m³ as a realistic worst-case and the regional concentrations for all other compartments gives a total daily dose of 4.3 µg/kg body weight day

4.2 EFFECTS ASSESSMENT

Toxicokinetics, metabolism and distribution

The toxicokinetics of benzene have been studied in both animals and humans. The key findings suggest that benzene is absorbed by all routes (inhalation, dermal and oral) with inhalation as the most important route of exposure. Benzene is rapidly distributed in the body and higher concentrations are found in fat and in lipid rich tissues compared to blood. After absorption via inhalation, the dermal or the oral route, most of benzene is metabolized and the metabolites are excreted after phase-II-conjugation mainly in the urine. Oxidative metabolism of benzene is a prerequisite to toxicity in animals and follows similar pathways in humans and animals. The liver is the major site of benzene metabolism, but metabolism in the bone marrow may be associated with the haematotoxic and leukaemogenic effects of benzene.

There is considerable support for the idea that benzene works via a multiple metabolite type of mechanism, that not just one metabolite is responsible for benzene toxicity but multiple metabolites are involved. These multiple metabolites of benzene are capable of interacting to induce cytotoxic and cytogenetic responses particularly in bone marrow myeloid and stromal cells. There are apparent species differences in the rate of benzene metabolism, in Vmax at higher exposure to benzene, and in the proportion of toxification (oxidative) versus detoxification (conjugation) metabolic pathways. At present it is unclear whether the observed species differences in developing haematotoxicity and leukaemia may be explained by species differences in metabolism. As it is poorly understood what metabolite is relevant for toxic effects such as leukemia or haematotoxic effects, the different PBPK models are not suited to support positions in the risk characterisation nor can they be used for the choice of the most appropriate species. An integrative PKPD modeling approach using animal and human benzene data is confounded by the fact that the type of leukaemia in animals is different from the type of leukaemia in man. Hence all the conclusions from PKPD modeling using animal data are not applicable to man.

Acute toxicity

An oral uptake of about 15 ml benzene by humans (176 mg/kg bw) can cause collapse, bronchitis and pneumonia. The direct aspiration of liquid benzene into the lungs causes immediate pulmonary oedema and haemorrhage at the site of contact with the pulmonary tissue. Very high concentrations of benzene vapours produce narcotic effects and can lead to death by respiratory arrest. Fatal effects can occur after inhaling a benzene concentration of 65 mg/l for 5-10 minutes. Exposure of 30 minutes to benzene concentrations of 25 mg/l can be dangerous to life threatening. After inhalation exposure to 0.16-0.48 mg/l for 6 hours headache and lassitude occur while after inhalation of 0.08 mg/l for 6 hours no acute toxic effects were documented. The odor threshold is reported to be 4.8 mg/m³ (1.5 ppm). In a report on three fatalities of acute benzene poisoning by acute dermal and inhalation exposure second degree chemical burns to face, trunk and limbs, haemorrhagic lungs and pulmonary oedema were documented. A relationship between chemical burns and death was not mentioned.

Acute oral toxicity for rats ranges from 810 mg/kg bw to 10000 mg/kg bw. Experiments using high numbers of rats suggest that the oral LD50 is above 2000 mg/kg bw. Depending on the dose the main clinical signs are sedation and narcosis. Pathological findings include among others hyperaemic and haemorrhagic lungs, adrenals and spine. Acute inhalation toxicity is

low with a LC50 value of 44.5 mg/l after a 4-hour exposure to rats. Depression of the central nervous system appeared to be related to death. The main pathological findings were congestion of the lungs and liver. A dermal LD50 value of >8260 mg/kg bw for rabbits and guinea pigs has been reported.

Irritation/Corrosivity

In humans, high concentrations of benzene vapour are irritant to mucous membranes of the eyes, nose and respiratory tract. Second degree chemical burns of the face, trunk and limbs after acute benzene vapour poisoning are reported.

In rabbits benzene is irritant to the skin and may cause serious damage to eyes. Inflammation and slight swelling of the eyelids, and questionable or just perceptible transient superficial necrosis of the cornea involving an area of less than 50% were documented.

SensitisationSensitisation

There are no reports on skin sensitisation or respiratory allergy due to workplace exposure to benzene. Data on animal test are not available. Taking into account long lasting human experience and the chemical structure of benzene no sensitisation of the skin and/or by inhalation is expected.

Repeated dose toxicity

Irrespective of the exposure route the main and sensitive targets of toxicity in animals and humans after repeated dose application of benzene are the cells of the bone marrow and haematopoietic system. The rapidly proliferating stem cells, myeloid progenitor cells and stromal cells are sensitive targets. Chronic benzene exposure can result in bone marrow depression expressed as leucopenia, anaemia and/or thrombocytopenia, leading to pancytopenia. and aplastic anaemia.

The effective vapour concentration inducing haematotoxicity is comparable in man and mouse, conclusively, the susceptibility to toxic benzene effects seems to be comparable. As there are only few data from rats exposed repeatedly, the interspecies comparison should be focussed on the mice and humans. Related to the benzene effects on the bone marrow and peripheral blood the mouse seemed to be more sensitive than the rat. There is evidence from several studies that benzene exposure resulted in disparate toxic responses among various strains of mice indicating that some strains are more susceptible than others. Whereas one study could not demonstrate haematotoxicity at 10 ppm (32 mg/m^3) benzene, others found significant effects at this concentration. It is postulated that strain-dependent differences in metabolic activity were correlated to the toxic effects of benzene.

Repeated inhalation exposure in mice was effective at concentrations from 32 mg/m³ benzene (10 ppm, LOAEC), the lowest observed effect level in chronic oral studies was 25 mg/kg bw/d (LOAEL). In repeated dose studies, benzene dose-dependently caused lymphocytopenia, anemia and pancytopenia characterized by a decrease in all peripheral blood cell types, and a marked reduction in marrow progenitor cells. Bone marrow showed hypocellularity or hypercellularity, but failed to deliver normal numbers of cellular elements or normal formed elements. Reduction of precursor cells was obvious at different stages of cell differentiation:

the haematopoietic multipotential stem cells, early progenitor cells and intermediate stages of differentiation. Morphologically, anaemia in mice, the species with the most extended database, can be classified as macrocytic and hypochromic.

Various studies have reported that prolonged exposure to benzene in vivo depresses the number of haemopoietic progenitor cells as quantified in functional tests of colony formation. Marrow progenitor cells seemed to be a more sensitive parameter of benzene effects than the bone marrow cellularity. In two studies the number of transplantable coloning forming units (CFU) were able to identify early effects of benzene treatment whereas the cellularity of the bone marrow did not or effects were only visible at high dose (e.g. 200 ppm benzene).

Whereas polychromatic erythrocytes (reticulocytes) were transiently or persistently decreased, premature stages of erythrocytes (MN-PCE and MN-NCE) increased reflecting the cytotoxicity of benzene to the maturing erythropoietic cells. Increased extramedullary haemopoiesis confirmed that there is an increased demand for erythrocyte production. No morphologic signs of scavenger of degenerated erythrocytes were reported in most animal studies on benzene effects. Splenic hemosiderin deposits were reported in exposed animals without giving exact data on a dose response. Anaemia is not primarily caused by peripheral loss or destruction of mature erythrocytes but it results due to a reduced bone marrow production.

Benzene-induced immunological effects are probably a reflection of bone marrow toxicity. Besides of leukocytopenia and other effects on the lymphocyte cellularity also several studies on the immune response revealed that benzene is suppressive on the cellular and humoral immunity of mice at doses from 10 ppm (6 hr/d, 6 d, inhalation) or from 40 mg/kg bw/d, 4 weeks, given orally. Occasionally, immune stimulatory responses were seen at a low dose of 8 mg/kg bw/d, 4 weeks, in a mouse study. Short-term treatment with high doses of benzene (800 mg/kg bw/d, 3 d) activated non-specific immune response of bone marrow derived monocytic cells.

Repeated dose toxicity / Human epidemiological data

Chronic benzene exposure in humans leads to depression of white and red blood cells. This effect is reversible after long time exposures (years) with low concentrations (reported concentration range: > 32-64 mg/m³, 10-20 ppm). Exposure to 192 mg/m³ (60 ppm) benzene for about one week may be associated with an increased proportion of large granular lymphocytes, and not severe narrow effects nor specific cytopenias. At higher concentrations, benzene may lead to aplastic anaemia which can be fatal. A review suggests a fatal outcome in 13% of the cases (as opposed to 85% for idiopathic aplastic anaemia).

The prevalence of leucopenia correlates with the exposure concentration of benzene. Drawn from these data, the LOAEC for leucopenia is in the range between 40 mg/m³ (12.5 ppm) and 64 mg/m³. A higher prevalence for leucopenia is given at concentrations higher than 320 mg/m³ (100 ppm). The LOAEC for red blood depression may be somewhat lower than 32 mg/m³ (10 ppm). Thus, for blood cell depression an overall LOAEC is suggested to be 32 mg/m³ (10 ppm).

Recent case control studies showed that the most sensitive reaction in humans to chronic benzene exposure is lymphopenia. A collective of workers exposed to benzene concentrations in a range between 1.6 and 31 ppm had significantly reduced lymphocyte counts as compared

to a cohort of non-exposed workers. A NOAEC for that effect of 3.2 mg/m³ (1 ppm) is derived from these studies.

Mutagenicity

Benzene is an in vivo mutagen in mammals, especially chromosomal aberrations and micronuclei are induced. After oral application the lowest dose with observed mutagenic effect was about 25 mg/kg bw for acute as well as for long-term exposure (micronucleus tests in mice). According to one report a single low dose of 3.2 mg/m³ (1 ppm) induced micronuclei in bone marrow cells of rats after inhalation exposure. However, in investigations on chromosomal aberrations in rats positive effects were obtained only at concentrations of 320 mg/m³ (100 ppm) and higher (single exposure) or 32 mg/m³ (10 ppm) and higher (repeated exposure). In mice, the lowest effective concentration is reported to be 32 mg/m³ (micronuclei after a single exposure).

Although only intraperitoneal studies are available, it seems that benzene has the potential for induction of transplacental genetic effects. Only few valid data on germ cell mutagenicity in mammals are available. In mice chromosomal aberrations are induced in spermatogonia by oral doses ranging from 220 to 880 mg/kg bw. Negative results on dominant lethal mutations in mice and rats are reported from invalid studies.

Concerning human data it is reported in a number of publications that benzene exposure induces genotoxic effects in human lymphocytes in vivo. A fully reliable conclusion, however, cannot be drawn due to poor exposure data and methodological insufficiencies. Therefore, it is not possible to deduce a dose-effect relationship. It is unlikely that exposure levels up to 64 mg/m³ (20 ppm) induce observable genotoxic effects in humans.

Overall, benzene obviously is an in vivo somatic cell mutagen for mammals and man. Data on germ cell effects are inconsistent. However, due to the clastogenicity to spermatogonia and the toxicokinetic properties it is concluded that benzene has the potential to reach the gonads and induce germ cell mutations.

Carcinogenicity/Animal data

Benzene induced neoplasms in both sexes of different strains of mice and rats on multiple sites by several routes of administration. Target organs of benzene induced carcinogenic effects in animals included the haematopoietic system and a spectrum of tissues of epithelial origin indicating that benzene is a multipotential animal carcinogen. The predominant tumors induced in the inhalations studies were of the haematopoietic system, particularly lymphomas have been found.

The main target cell for carcinogenesis in the mouse appears to be the lymphocyte. Lymphomas were induced in several mouse studies, however not all studies demonstrated clearly increased lymphatic tumour rates. Additionally, the tumour responses were not homogeneous in different mouse strains. Only few data existed which described the induction of myelogenous leukaemias. An increased rate of leukaemias without specification of the predominant cell type was found in long-term treated RF/J mice.

Some of the mice studies also demonstrated leukaemia of granulocytic cell lineage. However, these studies positive for myelogenous/granulocytic leukaemia revealed no significance of

tumour response or the positive findings were not reproducible. Even, lower rates of myelogenous leukaemia were seen after benzene treatment.

In contrast to the benzene induced lymphomas in mice, no clear effect on the rate of lymphoma formation was observed in long term studies in the rat. Increased frequencies of leukaemia in comparison to controls were found in benzene exposed Sprague-Dawley rats and Wistar rats of the Maltoni study and in a rat study on the metabolite hydroquinone.

It has to be taken into account that many animal studies do not include a complete registration of different tumour types of the haematopoietic system. Commonly, tumours were simply reported as malignant lymphomas or leukaemia without further data on the classification of the predominant cell type or cell lineage affected. The interpretation of heterogeneous tumour response from earlier animal studies with respect to the biological significance to humans remains difficult.

Differences in the organ spectrum of benzene-induced tumors were suspected to the evidence of specific cellular enzymes. It was assumed that chronic target organ toxicity is restricted to peroxidase-rich tissues such as the bone marrow, Zymbal, Harderian, and mammary glands. This hypothesis was confirmed by investigations on the tissue-specific benzene metabolism in rat organ homogenates finding high levels of peroxidase activity in the Zymbal gland, nasal and oral cavities, mammary gland, and bone marrow (Harderian gland was not examined in this study).

Animal models were able to identify the carcinogenic potential of benzene. However, the tumour response is different between animals and humans e.g. humans have no Zymbal or Harderian glands. Possible explanations not to identify the leukaemia of myeloid origin observed in humans may be that mice show differences in their spectrum of haematopoietic tumours spontaneously occurring with respect to the tumour spectrum seen in humans. Tumour spectrum also differs to other animals including the rat. It is assumed that the tissue-specific benzene metabolism is likely to contribute to target tissue tumour susceptibility.

Human epidemiological data

There is sufficient scientific evidence from the numerous human epidemiological studies to assume a causal relationship between benzene exposure and acute non-lymphatic leukaemia. It is unclear, however, if there exists a threshold level of benzene exposure above which the risk of leukaemia significantly increases.

Recent data (Monash University, 2001) support the view that the risk of developing acute myeloic leukemia and chronic lymphocytic leukemia (but not non-Hodgkins lymphoma or multiple myeloma) is increased at very low benzene exposure without clear cut-off concentration.

Previous studies concluded that the leukaemic risk is increased at relatively low levels of benzene exposure. Using modeling techniques, which were based on revised estimates of the benzene exposures in the Pliofilm cohort with an update of the follow-up (until 1987) analyses assume a negligibly increased mortality attributable to benzene if the average exposure is < 3.2 mg/m³ (<1 ppm) over 40 years. The recently published cohort study from exposed Chinese workers adds to the findings of the Pliofilm data showing elevated risk for acute non-lymphotiac leukaemia and myelodysplastic syndrom at average benzene exposure levels of less than 32 mg/m³ (10 ppm).

From a theoretical point of view a threshold level might exist and in this context the data of the meta-analysis by Wong and Rabe (1995) have been used to define a NOAEC in misinterpreting the results as an indication that a benzene exposure related carcinogenic effect can be excluded at the mean exposure level (700 µg/m³) of the 19 different studies. However, the data do not allow to establish such a threshold level with the appropriate certainity.

Besides Wong and Rabe (1995) various publications have addressed the issue of linearity in the dose-response relation of benzene induced haematotoxicity and leukaemia (e.g. Lamm et al., 1989; Bailer and Hoel, 1989; Paxton, et al., 1996; Cox, 1996; EPA, 1997; Health Council, 1997; Goldstein, 2000; Snyder, 2001). Especially for extrapolation to low doses, arguments have been presented for a non-linear, a sub-linear, and a supra-linear dose relationship. In addition, arguments have been presented for epigenetic factors responsible for leukaemia induction which lead to the suggestion of a threshold approach. As pointed out in EPA 1997, the various arguments proposed for non-linearity can be counteracted by arguments supporting linearity. Nevertheless, present knowledge is insufficient to support any quantitative deviation from the linear dose-response curve, at least from a regulatory point of view (EPA, 1997; Health Council, 1997; Goldstein, 2000). Recent data (Monash University, 2001) support the view that the risk of developing acute myeloic leukaemia and chronic lymphocytic leukaemia (but not non-Hodgkins lymphoma or multiple myeloma) is increased at very low benzene exposure without clear cut-off concentration.

Toxicity for reproduction

Evidence from human data for an effect of benzene exposure on female reproduction is not sufficient to demonstrate a causal association due to poorly designed studies and inadequately quantified exposure to benzene as well as to other chemicals. Epidemiological studies in males on effects on fertility are not available. Likewise epidemiological studies implicating benzene as a developmental toxicant have many limitations thus not providing sufficient information to assess the effects on the human fetus. Thus, hazard identification and assessment is primarily based on the data from animal studies. Whereas no specific embryotoxic and teratogenic potential could be revealed in teratogenicity and developmental toxicity studies, fetal growth retardation was observed, often associated with maternal toxicity. A NOAEC developmental toxicity of 32 mg/m³ (10 ppm) has been derived. An available fertility study in rats is recognised from which it appears that female fertility is not affected at inhalation exposures of up to and including 300 ppm (960 mg/m^3), however, this study is not considered sufficient and adequate for overall assessment of an impairment of male/female fertility. Data from repeated dose toxicity studies revealed some effects of benzene to the organs of the reproductive system in mice (NOAEC 96 mg/m³, 30 ppm), but not in rats. The significance of these findings in relation to possible impairment of fertility remains unclear, since adequate functional studies are not available.

4.3 RISK CHARACTERISATION

4.3.1 Workers

Introduction to occupational risk assessment

Benzene is a colourless liquid with a vapour pressure of 9970 Pa at 20°C which is easily soluble in organic solvents and to some extent in water. The most prominent effects of benzene according to its toxicity profile are carcinogenicity, mutagenicity and chronic toxicity. The main targets of toxicity are the hematopoietic system and the cells of the bone marrow. Exposure routes to be considered at the workplace are inhalation against benzene vapour and skin contact with the liquid substance.

Benzene seems to be readily absorbed via all routes. For risk assessment purposes oral and inhalative absorption are assumed to be 100 % and 50 %, respectively. Problems arise in the determination of dermal absorption because of the fact that benzene evaporates very fast and the potential systemic availability of benzene will be essentially limited by the duration of skin contact. For the purpose of assessing the dermal and combined risks exposure values are therefore converted to internal body burdens, using the available information on absorption and exposure conditions. In general dermal contact time is too low to result in relevant internal body burdens. However in certain scenarios it cannot be excluded that inappropriate use of protective gloves or repeated initial contacts may increase evaporation time. As result (see table 4.3.1.B, footnote 3) internal body burdens of up to 14 mg/person/day might be reached. However, clearly higher values arise from inhalation exposures for which the maximum internal body burden calculates to 420 mg/person/day. (see table 4.3.1.A). Combination of both exposure routes only for scenario 6, “Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)” determines an additional risk component, which has not been identified by the route-specific assessment.

With the exception of carcinogenicity for toxicological endpoints with quantitative data available, MOS values for benzene are calculated as quotient of the relevant NOAEC from human or animal studies and workplace exposure assessments.

As decision mark for concern a minimal MOS is identified which takes into account all aspects relevant for adaptation of the toxicity data from study situations to real workplace conditions. Because for benzene toxicity data from inhalative studies are available, only few aspects of data adaptation have to be considered. In general, for workers a breathing volume of 10 m^3 is anticipated, assuming a shift length of 8 hours. In addition for each toxicological endpoint an uncertainty factor is introduced in the minimal MOS which takes into account the confidence of the database.

In a parallel procedure, which gives identical but more direct results, a “critical exposure level” is identified for each endpoint as quotient of the relevant NOAEC and the according minimal MOS. Concern is indicated if occupational exposure levels exceed this value.

In the following risks at the workplace are considered specifically for each toxicological endpoint. Summary tables containing all scenarios are given at the end of this section. Risk assessment for the occupational exposure scenarios 5, 6 and 7 refers to benzene in gasoline;

for these exposure scenarios no formal conclusion is drawn. These scenarios are included for illustrative purposes and are not a formal part of the present risk assessment.

Acute toxicity

Local effects: ***see Irritation, no further information available***

systemic effects

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

As starting point for worker risk assessment the air concentration of 80 mg/m^3 is chosen. This dose did not cause acute toxic symptoms in humans who inhaled benzene for 6 hours. The according internal NAEL calculates to 300 mg/person/day. Evaluation of inhalative exposure scenarios has to account for the difference in exposure duration (6 hours compared to shift length) and for uncertainty considerations. The minimal MOS is 2.7. For evaluation of the dermal and combined MOS values only uncertainty considerations need to be adressed, the minimal MOS is 2. The critical exposure level is identified as 30 mg/m^3 (9.2 ppm) or 150 mg/person/day as internal dose.

For the highest inhalative exposure scenarios concern is indicated (see table 4.3.1.A). Dermal exposure scenarios, however, do not fall in the concern range.

Irritation/Corrosivity

conclusion (ii) There is at present no need for further information and/or testing

Skin / Eyes

From animal studies and reports on humans it is assumed in accordance with the concentration limits for classification and labelling in the Preparations Directive, that preparations containing ≥ 20 % benzene will most probably be irritant to human skin and human eyes. According to the exposure assessment fluids containing high percentages of benzene are handled in the area of the chemical industry and during cleaning of crude benzene tanks.

On the grounds that control measures exist for benzene, which should be able to efficiently minimize exposure thereby similarly mitigating concern, conclusion ii is proposed. However, these control measures must be implemented and complied with to reduce the risk of skin/eye damage.

Respiratory irritation

As starting point the airborne concentrations of 972 mg/m^3 which did not reveal local effects in the respiratory tract of mice is taken for risk assessment. No special aspects concerning data extrapolation have to be accounted for during MOS evaluation, an uncertainty factor does not seem necessary. The minimal MOS is 1, the critical airborne concentration is 972 mg/m^3 (300 ppm).

All inhalative exposures at the workplace are well below this critical airborne concentration and irritating effects are not of concern for workers.

Sensitisation

conclusion (ii) There is at present no need for further information and/or testing

No data on animal skin sensitisation or information on respiratory sensitisation is available. Benzene is not suspected to be a potent skin or respiratory sensitizer in humans according to the fact that during all the years of use no notice of specific case reports has been given. No concern is expressed for workers

Repeated dose toxicity

Local effects: ***see Irritation, no further information available***

systemic effects

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

For risk assessment purposes the case control studies in chinese workers will be used which have shown decreased lymphocyte counts for a group of persons exposed to 1-20 ppm . The human NOAEC of less than 1 ppm resulting from this studies will be taken forward as starting point for the assessment of chronic effects. The according internal value calculates to 16 mg/person/d. No further factors need to be introduced for evaluation of the MOS values. The critical exposure level is 3.2 mg/m^3 (1 ppm) for inhalation or 16 mg/person/day as internal dose.

For some inhalative scenarios MOS values below 1 lead to conclusion iii whereas dermal MOS values generally are above the minimal MOS.

Mutagenicity

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

Risks caused by the genotoxic properties of benzene cannot be excluded for any of the working scenarios with exposure to benzene. There is no information available which would help to identify exposure levels for which assessment could indicate that risks are low. Concern is expressed for all inhalative and dermal exposure scenarios at the workplace.

Carcinogenicity

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

From epidemiological studies there is sufficient scientific evidence to assume a causal relationship between high levels of cumulative benzene exposure and non-lymphatic leukaemia in humans. Different attempts to quantify the excess cancer risks of benzene expressed as additional benzene-attributable leukaemia mortality for an average exposure of 1 ppm over a working lifetime of 45 years resulted in estimations which span several orders of magnitude. Rinski (1987), for instance, estimated the additional benzene mortality to 1.6 – 3.1 cases per thousand exposed individuals whereas the analysis by Crump (1994) revealed a range of 0.02 – 0.036 cases per thousand. No decision can be drawn which analysis reveals the most reliable basis for risk assessment at the workplace. In addition in the different models the relationship between cumulative exposure and excess cancer risk is not linear. Thus cancer risks at the workplace cannot easily be quantified. From the Scientific Expert Group an occupational exposure limit of 1 ppm is recommended. For risk evaluation the inhalative exposure to 1 ppm which is equivalent to an internal body burden of 16 mg/person is used as reference exposure.

By general considerations it may be assumed that risks in a range of 1 case per 10^5 exposed individuals could possibly resemble a decision mark for low risk situations. It is recognized that for benzene not even the low end of the risk range calculated at the reference exposure of 1 ppm (0.02 cases per thousand) does meet this criterion. The exposure indicating low risk situations should at least be one order of magnitude lower. Thus the critical airborne concentration should be lower as 0.32 mg/m^3 (0.1 ppm) corresponding to an internal body burden of 1.6 mg/person/day.

Overall, conclusion iii is applied to all scenarios because an exposure level without cancer risk cannot be identified for benzene. Only in few scenarios the reported exposure values fall in a range below the anticipated critical airborne concentration.

Reproductive toxicity, fertility impairment

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

In an inhalation study with mice for 13 weeks histomorphologic changes in reproductive organs and decrease in testes weights have been observed at 300 ppm. The experimental NOAEC of 97 mg/m^3 in this study will be used as starting point for MOS calculation. The corresponding internal NAEL calculates to 485 mg/person/day. Evaluation of the MOS values accounts for adaptation of exposure conditions from experimental animals to workers and uncertainty considerations. Together the minimal MOS calculates to 10. The critical exposure level is identified as 9.7 mg/m^3 (3 ppm) for inhalation, or 49 mg/person/day as internal dose.

Some inhalative MOS values lead to conclusion iii, but none of the dermal scenarios is in the concern range.

Reproductive toxicity, developmental toxicity

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

From the results of inhalation experiments it has been shown that benzene may lead to fetal growth retardation as evidenced by decreased fetal body weight and body length, and/or

skeletal variation including delayed ossification from 50 ppm onwards. As starting point for MOS calculation the NOAEC in rats of 32 mg/m^3 will be used. The corresponding internal NAEL calculates to 160 mg/person/day. Evaluation of the MOS values has to account for adaptation of exposure conditions from experimental animals to workers and for uncertainty considerations. Together the minimal MOS calculates to 10. The identified critical exposure level of 3.2 mg/m^3 (1 ppm) for inhalation, or 16 mg/person/day as internal dose.

Some scenarios are identified to be of concern after inhalation exposure. Dermal exposure alone gives no rise to concern.

Summary tables

Tables 4.3.1.A and 4.3.1.B give a summary of the most critical exposure scenarios in the order of risk with respect to inhalation and dermal exposure, respectively. For mutagenicity conclusion iii applies for all scenarios (not shown).

Table 4.3.1.A: Ranking of the most critical inhalative exposure scenarios for benzene and associated health risks(1)

Scenario		shift average in mg/m^3	Internal body burden in mg/p/d (shift average x 10 m^3 x 0.5)	Carcinogenicity	Repeated dose toxicity / Developmental toxicity	Fertility	Acute toxicity
				critical exposure level in mg/m^3 (ppm)			
				0.32 (0.1)(2)	3.2 (1)	9.7 (3)	30 (9.2)
3	Production of perfumes, use of benzene	84	420	iii	iii	iii	iii
8a	Cleaning of tanks: crude benzene tanks, gasoline tanks	67.7	339	iii	iii	iii	iii
2	Recovery of benzene in coking plants by-product recovery	15.5	77.5	iii	iii	iii	
5a	Distribution of gasoline (marine, road, rail), 1% benzene (without VR)	6.8	34	(4)	(4)		
11a	Foundries (without LEV)	5.4	27	iii	iii		
1	Production , further processing, refinery	3.5	17.5	iii	iii		
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	14	iii			

Scenario		shift average in mg/m³	Internal body burden in mg/p/d (shift average x 10 m³ x 0.5)	Carcinogenicity	Repeated dose toxicity / Developmental toxicity	Fertility	Acute toxicity
				critical exposure level in mg/m³ (ppm)			
				0.32 (0.1)[2]	3.2 (1)	9.7 (3)	30 (9.2)
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	12.3	[4]			
11b	Foundries (with LEV)	1.6	8	iii			
5b	Distribution of gasoline (marine, road, rail), 1% benzene (with VR)	1.26	6.3	[4]			
9	Use of formulations with resudual benzene, e.g. adhesives, paints containing < 0.1% benzene	1	5	iii			
7a	Service stations, handling of gasoline (1% benzene) (without VR)	0.5	2.5	[4]			
8b	Cleaning of tanks: heating oil tanks	0.44	2.2	iii			
4	Production of formulations, use of solvents, benzene content unknown, assumption 5%	0.15	0.75	iii[3]			
7b	Service stations, handling of gasoline (1% benzene) (with VR)	0.1	0.5	[4]			

(1) blank fields: conclusion ii

(2) values derived on a preliminary basis only

(3) For discussion of the according risk levels see chapter 4.1.3.2.2/Carcinogenicity in the Comprehensive Risk Assessment Report

(4) A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

Table 4.3.1.B: Ranking of the most critical dermal exposure scenarios for benzene and associated health risks[1]

Scenario		Shift average in mg/p/d	Internal body burden in mg/p/d	Carcinogenicity	Repeated dose toxicity / Developmental toxicity	Fertility	Acute toxicity
				Critical internal dose in mg/p/d			
				1.6[2]	16	49	150
2	Recovery of benzene in coking plants by-product recovery	420	14[3]	iii			
8a	Cleaning of tanks: crude benzene tanks, gasoline tanks	1575	14[3]	iii			
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	8.4	8.4[3]	[5]			
5a	Distribution of gasoline (marine, road, rail), 1% benzene (without VR)	4.2	4.2[3]	[5]			
5b	Distribution of gasoline (marine, road, rail), 1% benzene (with VR)	4.2	4.2[3]	[5]			
9	Use of formulations with resudual benzene, e.g. adhesives, paints containing < 0.1% benzene	6.5	1.5	iii[4]			
other scenarios		< 1	< 1	iii(4)			

(1) blank fields: conclusion ii

(2) value derived on a preliminary basis only

(3) contact time of 5 minutes used for calculation of prolonged skin contact

(4) For discussion of the according risk levels see chapter 4.1.3.2.2/Carcinogenicity in the Comprehensive Risk Assessment Report

(5) A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

Table 4.1.3.C: Summary of exposure scenarios with concern for benzene(1)

Scenario		Acute tox.	Repeated dose tox. / Developmental tox.			Muta-genicity	Carcino-genicity		Ferti-lity
		Inhalation	Inhalation	Dermal	Combined	Inhalation / Dermal	Inhalation	Dermal	Inhalation
1	Production , further processing, refinery		iii		(2)	iii	iii	iii(3)	
2	Recovery of benzene in coking plants by-product recovery		iii		(2)	iii	iii	iii	iii
3	Production of perfumes, use of benzene	iii	iii		(2)	iii	iii	iii(3)	iii
4	Production of formulations, use of solvents, benzene content unknown, assumption: 5%					iii	iii(3)	iii(3)	
5a	Distribution of gasoline (marine, road, rail), 1% benzene (without VR)		(4)		(4)	(4)	(4)	(4)	
5b	Distribution of gasoline (marine, road, rail), 1% benzene (with VR)					(4)	(4)	(4)	
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)				(4)	(4)	(4)	(4)	
7a	Service stations, handling of gasoline (1 % benzene) (without VR)					(4)	(4)	(4)	
7b	Service stations, handling of gasoline (1 % benzene) (with VR)					(4)	(4)	(4)	
8a	Cleaning of tanks: crude benzene tanks, gasoline tanks (75% benzene)	iii	iii		(2)	iii	iii	iii	iii
8b	Cleaning of tanks: heating oil tanks (b)					iii	iii	iii(3)	
9	Use of formulations with resudual benzene, e.g. adhesives, paints containing < 0.1% benzene					iii	iii	iii(3)	

Scenario		Acute tox.	Repeated dose tox. / Developmental tox.			Muta-genicity	Carcino-genicity		Ferti-lity
		Inhalation	Inhalation	Dermal	Combined	Inhalation / Dermal	Inhalation	Dermal	Inhalation
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%					iii	iii	iii[3]	
11a	Foundries (without LEV)		iii		[2]	iii	iii	iii[3]	
11b	Foundries (with LEV)					iii	iii	iii[3]	

[1] Blank fields: conclusion ii
[2] Conclusion iii already results from inhalation and/or dermal exposure, therefore no specific concern for combined exposure scenarios is indicated
[3] For discussion of the according risk levels see see chapter 4.1.3.2.2/Carcinogenicity in the Comprehensive Risk Assessment Report
[4] A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

4.3.2 Consumers

Consumer exposure to benzene may result from active and passive smoking and from filling gasoline at a filling station and from use of contaminated paints. Moreover, data exist that benzene may be a contaminant in consumer products. Inhalation is the dominant pathway for benzene exposure in humans, whereas oral and dermal exposure can be neglected.

The following concentrations of benzene have been estimated for the different exposure scenarios:
1. Exposure of passive smokers from smoking (scenario 1) 0.007 mg/m³
2. Exposure from painting (scenario 2) 0.017 mg/m³
3. Filling gasoline (scenario 3) 1.3 mg/m³
4. Exposure from car interior accessories (scenario 4) 0.012 mg/m³

Benzene arises from combustion of tobacco and therefore occurs in tobacco smoke. Exposure to benzene due to smoking is included for illustrative purposes, however not considered in the risk characterisation. It is not supplied for use in tobacco. As a consequence, this source of potential exposure is not subject to consideration under EEC/793/93, thus no formal conclusion will be drawn for scenario 1. Moreover, during smoking humans are exposed to a variety of other toxic chemicals originating from combustion of tobacco.

No formal risk characterisation has been performed for filling gasoline at self service stations (scenario 3) since benzene exposures arising from handling gasoline are not formally a part of this risk assessment.

Acute Toxicity

Following the exposure assessment (scenarios 2 and 4), consumers are not expected to be exposed to benzene in the range of animal LC50 concentrations (~ 44 g/m³, 13700 ppm). In humans no acute toxic clinical symptoms were documented at 80 mg/m³ (25 ppm), inhaled for 6 hours. Therefore, benzene is considered to be of no concern for the consumer in relation to acute inhalation toxicity.

conclusion (ii) There is at present no need for further information and/or testing

Irritation /Corrosivity

High concentrations of benzene vapours are irritating to the mucous membranes of the eyes, nose, and respiratory tract. Following the exposure assessment, consumers are not exposed to such concentrations.

conclusion (ii) There is at present no need for further information and/or testing

Sensitisation

There are no data on animal tests. Taking into account the more than 100 years of human experience with this solvent which was commonly used in earlier times, it can be assumed that skin sensitisation or respiratory allergy is not a hazard that has to be expected when humans being exposed to benzene.

conclusion (ii) There is at present no need for further information and/or testing

Repeated dose toxicity / Non-neoplastic effects

Most relevant adverse effects in animals repeatedly exposed to benzene were observed in the haematopoietic system. Irrespective of the exposure route chronic benzene exposure can result in bone marrow depression expressed as leucopenia, anaemia and/or thrombocytopenia, leading to pancytopenia and aplastic anaemia. Decreases in haematological cell counts and in bone marrow cellularity have been demonstrated in mice after inhalation concentration as low as 32 mg/m^3 (10 ppm) for 25 weeks (LOAEC). This value characterises the most sensitive adverse effect after repeated exposure of animals to benzene.

In humans, haematological effects of varying severity have occurred in workers occupational exposed to high levels of benzene. The NOAEC (for depression of lymphocytes) of 3.2 mg/m³ (1 ppm) is considered as the most appropriate NOAEC for risk assessment procedures with regard to subchronic and chronic inhalation exposure scenarios.

The margin of safety between the estimated exposure levels in the scenarios painting and exposure from car interior accessories (< 0.017 mg/m^3, scenarios 2 and 4) and the NOAEC of 3.2 mg/m^3 is judged to be sufficient, even if special considerations on intraspecies variation, nature and severity of effects and possible human populations at risk are taken into consideration. Thus, there is no concern in relation to repeated inhalation exposure of consumers to benzene regarding non-neoplastic effects.

conclusion (ii) There is at present no need for further information and/or testing

Mutagenicity

Benzene is an in vivo mutagen in mammals, especially chromosomal aberrations and micronuclei are induced. Moreover, it is obviously an in vivo somatic cell mutagen for mammals and man. Data on germ cell effects are inconsistent. However, due to the clastogenicity to spermatogonia and the toxicokinetic properties of benzene, it is concluded that it has the potential to reach the gonads and induce germ cell mutations. Taking that into consideration, no safe level of exposure can be recommended.

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

Carcinogenicity

Long term experimental carcinogenicity bioassays have shown that benzene is a carcinogen which may produce a variety of tumours in animals (including lymphomas and leukaemia). There is sufficient scientific evidence from numerous human epidemiological studies to assume a causal relationship between benzene exposure and acute non-lymphatic leukaemia. Benzene is carcinogenic to humans and no safe level of exposure can be recommended.

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

Toxicity for reproduction / Fertility

The available chronic toxicity studies in mice showed that high benzene concentrations of 960 mg/m^3 led to clear-cut haematotoxicity in both sexes. Additionally, there were some indications for changes in reproductive organs which appeared to be more distinct for the males (testes weight and histopathology affected) than for the females (occasional ovarian cysts). No effects for either sex of rats had been observed in these studies at the same concentration. Also, no effects on female reproductive capacity and capability were found for rats at these concentration levels. Based on the effects in mice a NOAEC/reproductive organ toxicity of 96 mg/m^3 (30 ppm) was derived. The margin of safety for the scenarios painting as well as exposure from car interior accessories regarding reproductive organ effects is judged to be sufficient.

conclusion (ii) There is at present no need for further information and/or testing

Developmental toxicity

No specific embryotoxic and teratogenic potential of benzene could be revealed in teratogenicity and developmental studies. Fetal growth retardation was observed in animal studies often associated with maternal toxicity. None of these clinical findings of fetal growth retardation were observed at exposure levels of 128 mg/m^3 (40 ppm) or lower. From the available studies with rats the lowest NOAEC developmental toxicity of 32 mg/m^3 (10 ppm) will be used for quantitative risk assessment. For the scenarios painting as well as for

exposure from car interior accessories the margin of safety regarding developmental toxicity is judged to be sufficient.

conclusion (ii) There is at present no need for further information and/or testing

4.3.3 Humans exposed via the environment

Indirect exposure via the environment has been calculated for the uptake of benzene via ambient air, drinking water, vegetables, milk, and meat. For all scenarios the most relevant contribution to the total daily dose is the uptake via air (96 - > 99%). Drinking water and fish uptake vary in the range of 0.1 to 2% and all other sources of exposure (milk, meat and vegetables) can be regarded not significant. According to the TGD both a local and a regional scenario has to be considered.

Following the local scenario data (at a point source) a local air concentration of 890 µg/m³ has been calculated as highest emission. Following the data for the regional scenario, there is also the air concentration of 1.54 µg/m^3 the predominant indirect exposure way of man via the environment.

In addition to the scenarios described above, for benzene unintentional releases from road traffic are considered relevant for indirect exposure. Measured concentrations in ambient city air are in the range of 1 to 275 µg/m³ with typical values between 10 and 20 µg/m³. The air concentration of 20 µg/m³ is considered as realistic worst case to be used for the risk assessment of unintentional benzene releases from road traffic. However, no formal risk charakterisation has been performed for the road traffic scenario since benzene exposure arising from use of gasoline is not formally a part of this risk assessment.

Repeated dose toxicity / Non-neoplastic lesions

For details regarding the LOAEC used for the risk assessment discussion see 4.3.2.

Local scenario

The margin of safety for non-neoplastic effects between the calculated exposure level of 0.89 mg/m^3 and the NOAEC of 3.2 mg/m^3 is judged not to be sufficient.

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

Regional scenario

The margin of safety for non-neoplastic effects between the calculated regional exposure level of 1.54 µg/m^3 and the NOAEC of 3.2 mg/m^3 is judged to be sufficient.

conclusion (ii) There is at present no need for further information and/or testing

Mutagenicity

Benzene is an in vivo somatic cell mutagen for mammals and humans. Data on germ cell effects are inconsistent. However, due to the clastogenicity to spermatogonia and the toxicokinetic properties of benzene, it is concluded that it has the potential to reach the gonads and induce germ cell mutations. Taking that into consideration, no safe level of exposure can be recommended.

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

Carcinogenicity

From the numerous human epidemiological studies there is sufficient scientific evidence to assume a causal relationship between benzene exposure and acute non-lymphatic leukaemia. Benzene is carcinogenic to humans and no safe level of exposure can be recommended.

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

5 OVERALL RESULT OF THE RISK ASSESSMENT

Environment

Waste-water treatment plants

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

$Clocal_{eff}/PNEC_{microorganism}$ ratios are > 1 for 23 out of 48 sites. For all these sites the $Clocal_{eff}$ is based on default values. It is not expected to obtain site-specific exposure data with reasonable efforts and time expenditure. In addition, it is not likely that the performance of a test with industrial activated sludge will result in a $Clocal_{eff}/PNEC_{microorganism}$ ratio < 1 for all sites due to the partly very high benzene concentrations in wwtp effluents (up to 102 mg/l).

conclusion (ii) There is at present no need for further information and/or testing.

This conclusion applies to 25 out of 48 sites and also for municipal wwtps.

Aquatic environment

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

For two production and processing sites the PEClocal/PNECaqua ratio is > 1. As the PEC calculations for these sites are partly based on default values, improvement of the data basis would be possible. However, the 2 sites were repeatedly asked for site-specific exposure data, but did not react. Therefore, it is assumed that it is not possible to gather traceable exposure data for these sites with reasonable efforts.

conclusion (ii) There is at present no need for further information and/or testing.

This conclusion applies to 46 out of 48 sites as well as to the aquatic compartment at regional level.

Atmosphere

conclusion (ii) There is at present no need for further information and/or testing.

This conclusion applies for direct effects of benzene on plants exposed via the atmosphere.

It is assumed that the risk for terrestrial organisms exposed to benzene via inhalation is covered by the risk assessment for human health.

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

This conclusion applies to the contribution of benzene to the formation of ozone. Although only a rough estimation with considerable uncertainties behind it could be performed, the information available is regarded as sufficient to draw this conclusion. In the context of the consideration of which risk reduction measures that would the most appropriate, it is recommended that under the relevant air quality Directives a specific in-depth evaluation be performed. Such an evaluation should focus on the contribution of isolated as well as non-isolated benzene to the complex issue of ozone and smog formation and the resulting impact on air quality.

Terrestical compartment

conclusion (ii) There is at present no need for further information and/or testing.

Non compartment specific effects relevant to the food chain (secondary poisoning)

conclusion (ii) There is at present no need for further information and/or testing.

<u>Human Health</u>

Workers

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

This conclusion is reached because of:
— concerns for mutagenicity and carcinogenicity as a consequence of dermal and inhalation exposure arising from all worker scenarios,
— concerns for acute toxicity as a consequence of inhalation exposure during production of perfumes (use of benzene) and cleaning of crude benzene and gasoline tanks,
— concerns for repeated dose toxicity and developmental toxicity as a consequence of inhalation exposure during production of perfumes (use of benzene), cleaning of crude benzene and gasoline tanks, recovery of benzene in coking plants, distribution of gasoline

(without vapour recovery) foundries (without local exhaust ventialtion) and production, further processing and refinery,
— concerns for fertility as a consequence of inhalation exposure during production of perfumes (use of benzene), cleaning of crude benzene and gasoline tanks and recovery of benzene in coking plants.

Benzene is easily absorbed after inhalation and skin contact. Internal body burdens after demal exposure are generally low because of rapid evaporation of benzene and only prolonged exposure might pose a risk. For prolonged dermal exposure and inhalation exposure at levels below 1 ppm (3,2 mg/m3) the only concerns are for mutagenicity and carcinogenicity.
Occupational exposure scenarios 5, 6 and 7 refering to benzene in gasoline are included only for illustrative purposes and are not a formal part of the present risk assessment. According to Council Regulation 793/93 risk reduction measures concerning benzene in gasoline should await a special risk assessment of gasoline.

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Consumers

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

This conclusion is reached because of:
— concerns due to mutagenic and carcinogenic effects by inhalation exposure from use of contaminated paints and from car interior accessories.

Humans exposed via the environment

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

This conclusion is reached because of:
— concerns due to repeated dose toxicity, mutagenicity and carcinogenicity.
The predominant indirect exposure of humans via the environment occurs via the air. Due to the genotoxic and carcinogenic effects of benzene no safe level of exposure can be recommended.

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

Part I - Environment
This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.
The environmental risk assessment concludes that there is concern for the atmosphere, for the aquatic system and for the sewage treatment plants.
There is no concern for the terrestrial compartment.

Part II – Human Health
This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.
The human health risk assessment concludes that there is concern for workers, consumers and humans exposed via the environment.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.