European Union Risk Assessment Report

BENZENE

CAS No: 71-43-2
EINECS No: 200-753-7

RISK ASSESSMENT

GENERAL NOTE

This report contains different documents:

- Environment and Human Health
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RISK ASSESSMENT

Benzene

CAS-No.: 71-43-2

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FINAL APPROVED VERSION

Information on the rapporteur

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The first draft of the Comprehensive Risk Assessment Report of **Benzene**, a substance chosen from the EU 1st priority list in 1994 was discussed preliminarily at the Technical Meeting III / 2000 (19.-22. September 2000).

The Environment Section of the Risk Assessment Report was discussed "in-depth" at the Technical Meeting in June 2001 and as "2nd in-depth" at the Technical Meeting in March 2002. Furthermore, the Environment Section was distributed for the final written procedure in May 2002.

The Human Health Section of the Risk Assessment Report was discussed "in-depth" at the Technical Meeting in September 2001, as "2nd in-depth" at the Technical Meeting in June 2002 and as "last visit" at the Technical Meeting in September 2002. Furthermore, the Human Health Section was distributed for the final written procedure in March 2003.

After the OECD discussion at SIAM 21 the Human Health Section of the RAR Benzene was distributed for a 2nd final written procedure in December 2006 followed by a second OECD consultation in written procedure in July 2007.

This document is the final version of the Risk Assessment Report of Benzene which is submitted for publication.

CONTENTS

0 OVERALL CONCLUSIONS/RESULTS OF THE RISK ASSESSMENT

CAS No. 71-43-2

EINECS No. 200-753-7

IUPAC Name Benzene

Overall results of the risk assessment:

( ) i) There is need for further information and/or testing

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

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

Summary of conclusions:

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 for effects

- on microorganisms in industrial *Waste-water treatment plants*

$Clocal_{eff}/PNEC_{microorganism}$ ratios are > 1 for 23 out of 48 production and/or processing sites of the substance. 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).

- to the local *Aquatic ecosystems*

For two production and processing sites of the substance, the PEClocal/PNECaqua ratio is > 1. It has to be noted that the PEC calculations for these sites are partly based on default values.

- to the *Atmosphere*

Concerns arise as isolated benzene contributes to the formation of ozone and other harmful substances i.e. smog formation. 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.

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

This conclusion applies to

Atmosphere (direct effects of benzene on plants)

Terrestrial compartment

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

Human Health

The conclusion of the assessment of the risks to
Workers

is that there is a need for specific measures to limit the risks. **Conclusion (iii)**
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.

The conclusion of the assessment of the risks to
Consumers

is that there is a need for specific measures to limit the risks. **Conclusion (iii)**
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.

For exposure to benzene arising from exposures to gasoline at filling stations no formal risk characterisation has been performed since benzene exposures arising from handling gasoline are not formally a part of this risk assessment. Any conclusions regarding risk reduction measures for gasoline have to wait for the risk assessment of gasoline.

The conclusion of the assessment of the risks to
Humans exposed via the environment

is that there is a need for specific measures to limit the risks. **Conclusion (iii)**
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.

For exposure to benzene from traffic no formal risk characterisation has been performed since benzene exposures arising from gasoline are not formally a part of this risk assessment.

1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS No.: 71-43-2

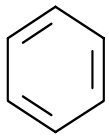
EINECS No.: 200-753-7

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	Römpp, 1995
Boiling point	80.1 °C at 1013 hPa	Römpp, 1995
Relative density	0.879 at 20 °C	Römpp, 1995
Surface tension	28.9 mN/m (substance as such)	Weast et al, 1988
Vapour pressure	99.7 hPa at 20 °C	Folkins, 1985
Partition coefficient	log Pow 2.13 (HPLC method)	Sangster, 1989
Water solubility	1.8 g/l at 25 °C	Freier, 1976
Flash point	- 11 °C (DIN 51755)	Chemsafe, 1995
Auto flammability	555 °C (DIN 51794)	Chemsafe, 1995
Flammability	highly flammable [1)]	Chemsafe, 1995
Explosive properties	not explosive [2)]	Chemsafe, 1995
Oxidising properties	no oxidising properties [2)]	Chemsafe, 1995

[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

2.1 PRODUCTION OF PURE BENZENE

The natural sources of benzene are crude oil and, to a lesser extent, condensate from natural gas production. It 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.

Production of pure benzene

Pure benzene can be isolated from coal tar oil and by refining crude oil. Over half of the benzene demand is covered by means of extractive distillation of naphtha.

Naphtha is a by-product of ethylene recovery by means of steam cracking (straight-run gasoline). Naphtha is rich in aromatics; its benzene content varies between 31 and 40 percent by volume. Extractive distillation produces a high benzene yield. After distillation, the benzene content of naphtha is reduced to only about 0.5 percent by volume. Extractive distillation, which is the most important benzene recovery process in terms of volume covers about 53.8 percent of the benzene used in Germany. (German Enquete Commission 1994).

The recovery of benzene from catalytic reformates, which are also rich in aromatics, involves two steps: the separation of aromatics and non-aromatics, and the separation of the aromatics mixture. The recovery of pure benzene from catalytic reformate invariably involves the recovery of toluene and xylene. This process covers 14.7 percent of the annual demand in Germany (German Enquete Commission 1994).

By means of a special washing process, benzene can also be isolated from coke oven gas which occurs during the coking of hard coal. This process covers 9.8 percent of the annual demand in Germany (German Enquete Commission 1994).

Catalytic dealkylation of toluene involving the addition of hydrogen is a relatively costly and energy-intensive process, which is only used if there is sufficient demand for pure benzene. Currently, this process accounts for about 21.7 percent of the annual demand in Germany (German Enquete Commission 1994).

Pure benzene (CAS No 71-43-2) demand is dominated by the production of three derivatives - ethylbenzene, cumene and cyclohexane - which together account for about 85% of benzene consumption in 1994. Table 2.1 presents available data on the benzene production in the main regions of the world.

Table 2.1 Production Volumes of Pure Benzene

Area	Annual Production [kt/a] (year)		Source
EU (from oil sources)	5 150	1991 - 1993	CEFIC 1996
EU (from coal sources)	400	1991 - 1993	CEFIC 1996
EU production	7 500	2000	prognosis SRI 1996
Japan	4 950	1994	SRI 1996
	3 620	1994	UN ECE 1996a
	> 4 000	2000	prognosis SRI 1996
USA	6 640	1993	C&EN 1995
	6 917	1994	C&EN 1996
	7 234	1995	C&EN 1996
	ca. 10 000	2000	prognosis SRI 1996
World	22 300	1992	VCI 1995
	> 32 000	2000	prognosis SRI 1996

Production in the European Union

IUCLID data on the production volumes are presented in ranges and distinguish between production and processing. Upper IUCLID figures overestimate production volumes. Recognizing this fact, the Aromatic Producers Association (APA) circulated a questionnaire in 1995 and 1999 whose results were made available to the German rapporteur. The survey yielded the following confidential data of 25 benzene production and processing sites:

- Production and processing volumes [t] in a given year, mostly 1993 and 1994 or 1999
- direct air emissions [t/a]
- direct water emissions to surface water or Waste Water Treatment Plant (WWTP) [t/a]

and in a few cases

- Waste Water Treatment Plant (WWTP) influent and effluent concentrations [µg/l].

A summary of the APA 1995 and 1999 data is presented in table 2.2. Where APA data were missing, IUCLID data or data communicated to the German rapporteur were used.

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.

Table 2.2 Production Figures of Pure Benzene in EU countries [kt/a] (1)

Region	Production process	CEFIC 1996	This report 1994 – 2001 (2)	1985 capacity (3)
EU	from oil and coal	5 550	7 247	7 304
Austria	from coal	10	0	16
Belgium	from oil from coal	124 41	373	150
Finland	from oil	83	110	220
France	from oil from coal	691 41	881.45	980
Germany (4)	from oil from coal	1 433 202	2 134.39	2 094 (5)
Italy	from oil from coal	532 12	680	865
Netherlands	from oil	1 297	1 697	1 315
Portugal	from oil	42	64	80
Spain	from oil	252	285	235
Sweden (6)		no data	10	3
United Kingdom	from oil from coal	696 92	1 012	1 346

(1) Data do not include benzene in petrol.
(2) Based upon IUCLID Data Sets (1992/93), APA Questionnaire 1995 and 1999, and additional information.
(3) Nielsen et al. 1991
(4) Other sources: 1944 kt (1994) [VCI 1995]; Statistisches Bundesamt 1995: 1518 kt (1993); 1944 kt (1994); 2546 kt (1995); 2578 kt (1996); from coal 103 kt (1995)
(5) West Germany
(6) Swedish Product Register (1995): 3348 t/a.

Data on imports to and exports from the European Union are published by the UN Economic Commission for Europe: import 576 128 t/a (1994); export 128 902 t/a (1994) (UN ECE 1996a).

Benzene demand in the year 2000

World benzene demand is projected to grow at an average annual rate of 4.7% from 1994 to 2000, amounting to over 32 million tonnes in 2000. Substantial production also takes place in Eastern Europe. Production in Asia except Japan and in the Middle East will grow by yearly rates of 10% resp. 8.5% from 1994 to 2000. [SRI 1996].

The benzene consuming facilities are being expanded more rapidly than production facilities. The routes of supply will also change over the coming years. One possibility is that there will be greater utilisation of dealkylation units around the world. The units will be needed on a more regular basis to meet the demand, rather than on a short-term/temporary basis as it presently the case. Around the mid-1990s three new or expanded benzene sources have come onto the scene:

- benzene produced as a by-product of p-xylene production.

- cyclar technology based on the cyclisation of propane / butane feedstocks; intended for motor spirit blending as a BTX product, unless market demands change significantly to merit production of benzene as the sole product.

- The greatest potential for „new“ benzene supply is thought to result from environmental regulations restricting the amount of benzene used in petrol [Nielsen et al. 1991]. Based on the “new” benzene source less synthesis will be needed.

Reliability of Production Data

The IUCLID data and the APA 1995 and 1999 data provide the basis for exposure assessment of pure benzene from industrial sources. For better transparency of the conclusions drawn, the following remarks on the reliability of these data are made:

- 39 companies provided a IUCLID data set, 25 companies provided data by way of the exposure questionnaire [APA 1995 and 1999], and some companies sent additional information to the German rapporteur including production data. Data from 48 companies are presented in this report

- For companies that did not report production volumes the IUCLID data ranges were used to calculate emissions rates [kg/d] and PECs.

- Some companies did not report the reference year of production. Figures could not be related to a specific year.

- Coking plants produce crude benzene from coal processing. The production is in the order of about 10% of oil based benzene production. Austria, Belgium, France, Germany (the pre-unification Federal Republic of Germany had twelve production sites [GDCh 1992]), Italy and the UK have coking plants. Since these facilities did not report under EU Regulation 793/93 of 23 March 1993 only limited information concerning the exposure situation of coking plants are available. These exposure data are only taken into consideration in the risk assessment of workers.

- Benzene in Petrol

Petroleum refinery streams containing benzene are blended with other petroleum streams to formulate petrol. This benzene is not isolated in the refinery process. Until the year 2000 in Europe benzene in petrol was limited to a maximum of 5 % by volume. The average was in the range of 3 - 3.5 % [CONCAWE 1994a]. The ARAL company (1997) reported that the benzene content in brand petrol in Germany declined from 4 % in 1980 to 1.8 % in 1996. The new European petrol quality requirements limit benzene in petrol to a maximum of 1.0 % by volume from 01.01.2000 [Directive 98/70/EC]. Annual consumption of petrol in Western Europe at present is 120 million tons (see RAR on toluene). The quantity of benzene present in petrol may be estimated at 1.41 million tonnes for the year 2000 (density of petrol 750 kg/m^3 and 880 kg/m^3 for benzene). This benzene used in petrol is in addition to the benzene of chemical intermediate production.

A 1 % by volume limit on the content of benzene in petrol has been discussed for both the United States and the European Union. A calculation based on the petrol consumption in these two major regions shows that such a reduction would lead to another 5 - 6 million tonnes of benzene per year theoretically being released onto the market. This production volume could theoretically replace the industrial benzene production worldwide. In practice however, there is scope for reducing benzene production within existing refining operations [Nielsen et al. 1991].

2.2 USES OF PURE BENZENE

Processing

In the chemical industry, benzene is industrially the most important of the so-called BTX aromatics (benzene, toluene, xylene). In industrial chemistry, benzene forms the basis for a great variety of aromatic intermediates and for the group of cycloaliphatic compounds. Benzene is used as the basis for the manufacture of plastics, synthetic rubber, dyestuffs, resins, raw materials for detergents, and plant protection agents. The most important secondary products manufactured from benzene in Western Europe in 1994 were [Chem-system 1994, German Enquete Commission 1994, GDCh 1992, Nielsen et al. 1991, Boehncke et al. 1997]:

Ethyl Benzene (52%)

About half of the benzene produced is consumed in the manufacture of ethylbenzene, which is then processed to styrene and polystyrene. Polystyrene is a quantitatively very important plastic, which is used in large volumes in the automobile industry (replacing metal parts), in the building industry and for packaging. Furthermore, styrene is a raw material for the manufacture of synthetic rubber.

Cumene (20%)

Oxidation of cumene (isopropylbenzene) is the most important method for producing phenol. Phenol is a raw material for the synthetic-fibres and synthetic-resins industry and is used in the manufacture of veneer glues, car brake linings and resins for the paints industry.

Cyclohexane (13%)

Benzene is the starting material for the production of cyclohexane, an intermediate in the manufacture of nylon. Nylon plays an important part as synthetic fibre in the manufacture of textiles, tyres, packing material etc., but is also an important thermoplastic.

Nitrobenzene (9%)

Nitrobenzenes are produced exclusively from benzene and are the basis for the manufacture of aniline dyes and polyurethane foams.

Alkylbenzene (3%)

Alkylbenzenes are used in the manufacture of surfactants.

Maleic Anhydride and others (2%)

Benzene is oxidized catalytically to maleic anhydride. This is the basis for manufacture of unsaturated polyester resins and some plant protection agents. It is also used in the manufacture of lubricating oil additives and antioxidants for oils and greases.

Chlorobenzene (1%)

Chlorobenzenes are obtained from benzene and are used *inter alia* as intermediates for the manufacture of plant protection agents, pharmaceuticals, dyestuffs, rubber auxiliaries, textile auxiliaries, disinfectants and air deodorizers. They are also used in the chemical industry as solvents and oils, greases, resins, rubber, ethylcellulose, etc.

Benzene as a laboratory reagent and solvent at laboratories

Very small quantities are also used as a laboratory reagent and solvent. This use is declining. However, benzene does occur in small quantities in various solvents on a hydrocarbon basis. An accurate estimate of the quantities involved is difficult, especially because it often concerns small concentrations in large volume flows. Data on the concentrations and used quantities of the solvents on a hydrocarbon basis are not available.

2.3 BENZENE IN CONSUMER PRODUCTS

Table 2.3 Categories of used benzene according to the Technical Guidance Document

Main category (MC)	Industrial category (IC)	Use category (UC)
Used in closed systems (I) - isolated intermediate stored onsite - isolated intermediate with controlled transport - non-dispersive use - non dispersive use (III)	Chemical industry (3)	Intermediate (33)
Wide dispersive use (IV)	Mineral oil and fuel industry (9)	Fuels (27)
Non-dispersive use (III)	Others (0)	Solvents (48)
Wide dispersive use (IV)	Others (0)	Laboratory chemicals (34)

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.

In Denmark the maximal concentration of benzene allowed in chemical products is 0.1 %. For more than 3500 chemicals with a potential pollution of benzene, the registration in the Danish product register is “concentration of benzene is < 0.1 %”. This number is not suitable for any calculation of the use of this substance.

In 7 products benzene is registered with a concentration of 0.1 – 1 %. Most of this is three coal tar products mainly for export. Some of this is wood impregnation products used in shipbuilding and private household (< 40 kg/year of benzene). In the remaining 4 products used in different areas the total amount of benzene is < 3 kg/year.

The most significant amount of benzene is found in motor fuel with concentrations of 1 - 5 %. As not all motor fuel in Denmark is registered, the total amount of benzene in this area cannot be calculated.

Besides the products containing benzene the substance is used as such (94 – 100 clean %) as a laboratory chemical in research / development and hospitals. The total amount registered in this area is < 75 kg/year (Danish Product Register, August 2001).

Table 2.4 Benzene in Consumer products (Swedish Product Register 2000)

Percent by weight benzene in product	Number of products
Max 0.1	18
Max. 1	4
1 – 10	3
10 – 80	-
80 - 100	-

All products in table 2.4 are motor fuels. There are also 3 other products that may contain benzene in concentrations below 0.1 %.

Sack et al. 1991, 1992 examined 1 159 common household products for 31 volatile organic compounds (VOCs) as potential sources of indoor air pollution. The products were distributed among 65 product categories within 8 category classes: automotive products (14.4 %), household cleaners/polishes (9.6 %), paint-related products (39.9 %), fabric and leather treatments (7.9 %), cleaners for electric equipment (6 %), oils, greases and lubricants (9.6 %), adhesive-related products (6.6 %), and miscellaneous products (6.1 %). Benzene occurred in 6 of the products, which is 0.6 %.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

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.

Focus of this Report

32 critical reviews on benzene have been written and two more are planned [ECETOC/UNEP 1996]. The purpose of this chapter is to describe quantitatively the exposure situation in the EU that results from industrial sources of pure benzene (CAS No 71-43-2) production and processing. The road traffic emissions are higher than the industrial emissions. An attempt was made to quantify these sources as best as possible, in order to provide an overall picture of all benzene emissions in EU countries.

Environmental models were used to predict the distribution and fate of benzene in air, water and soil. The large amount of benzene monitoring data provide an excellent basis for comparing the calculated exposure data with measured ones.

3.1.1.1 Release into the environment

3.1.1.1.1 Releases of benzene from production and processing of pure benzene

39 companies provided a IUCLID data set, 25 companies provided data by way of the exposure questionnaire [APA 1995 and 1999], and some companies sent additional information to the German rapporteur in the form of production, processing and exposure data. Data from 48 of 50 companies are presented in this report.

Site specific information from benzene production and processing sites was collected by the main manufacturers by way of a questionnaire circulated to the industrial sites concerned. The environmental exposure assessment should be based on site specific data. These site specific data have been taken into account. TGD default values were used where such data were unavailable. The results cover production sites, combined production and processing on the same site, and a few processing sites (see table 3.2).

Because of differences in production and processing methods and in the exposure situation exposure information from one company cannot be applied to another.

Some of the companies did not transmit exposure information for the production and/or processing of benzene or did not provide clear explanations as to the parameters that have been taken into account. For these companies the default values from the TGD were used to estimate the emission of benzene to air and water. In the following table these data are summarised.

Table 3.1 Default emission factors [Commission of the European Union 1996a]

	waste water		air	
	production	processing	production	processing
emission factors [t/t]	0.003	0.007	0.001/0.01	0.0001/0.025
main category	---	---	1b/1c	1b/3
source in TGD	ESD IC - 3	ESD IC - 3	A-table 1.2	A-table 3.3
vapour pressure [Pa]	---	---	1000-10000	1000-10000

The following exposure calculation is based on the assumption that every company involved in the production and/or processing of benzene discharges its wastewater to a WWTP.

Table 3.2 Site specific data for production, production and on-site processing and processing sites (IUCLID, APA 1995 and 1999), release fractions and emissions.

Site	Production (kt/a)	Processed (kt/a)	Sold for processing elsewhere (kt/a)	Release fraction to WWTP (t/t)	Release fraction to air (direct) (t/t)	Release to WWTP (kg/d)	Release to air (direct) (kg/d)	Release to air from WWTP[1] (kg/d)
Production								
P1	63	0	63	2.41E-06	6.26E-04	0.51	108.05	0.22
P2	172.05	0	172.05	2.86E-05	0.000061	16.42	34.98	7
P3	77	0	77	0.000995	0.00078	255.38	200.20	108.79
P4	135	0	135	0.003[2]	0.01[2]	1350.00	4500.00	575.10
P5	170	0	170	2.65E-12	0.0000277	0.0000015	15.70	0.00
P6	63.59	0	63.59	1.79E-06	0.0000113	0.38	2.40	0.16
P7	142.1	0	142.1	1.08E-06	0.0000167	0.51	7.91	0.22
P8	506	0	506	1.92E-07	0.0000143	0.32	24.12	0.14
P9	250	0	250	0.003[2]	0.0000084	2500.00	7.00	1065.00
P10	61	0	61	0.003[2]	0.000059	610.00	12.00	259.86
P11	64	0	64	0.0007	0.00017	149.33	36.72	63.62
P12closed 1999								
P13	160	0	160	0.000013	0.0011	7	580.00	no wwtp
P14	127	0	127	0.003[2]	0.000638	1270.00	270.09	541.02
Sum:	**1990.74**	**0**	**1990.74**	/	/	**6159.85**	**5798.70**	**2621.11**
Prod. And Proc.								
PP1	140	70	70	0.003/0.007[2]	/	3033.33	833.33	1292.20
PP2	170	170	0	0.01	6.83E-06	5666.67	3.87	2414.00
PP3	110	110	0	0.000021	0.0011[2]	7.68	403.33	3.27
PP4	497.4	377.5	119.9	2.47E-6 /6.04E-4	2.59E-4/1.35E-4	764.13	599.43	325.52
PP5	296	355	0	/	/	84.84	33.33	36.14
PP6	120	120	0	3.28E-06	0.0011[2]	1.31	440.00	0.56
PP7	400	400	0	0.0000505	0.00007	55.34	93.33	23.58
PP8	53.7	53.7	0	0.01[2]	0.0011[2]	1790.00	196.90	762.54
PP9	72	72	0	0.01[2]	0.0001042	2400.00	25.01	1022.40
PP10	580	640	0	/	/	1093.00	510.00	465.62

Site	Production (kt/a)	Processed (kt/a)	Sold for processing elsewhere (kt/a)	Release fraction to WWTP (t/t)	Release fraction to air (direct) (t/t)	Release to WWTP (kg/d)	Release to air (direct) (kg/d)	Release to air from WWTP[(1)] (kg/d)
PP11	100	100	0	0.01	0.0011[(2)]	3333.33	366.67	1420.00
PP12	990	990	0	7.63E-06	1.50E-05	25.18	49.50	10.73
PP13	200	400	0	/	/	183.33	266.67	78.10
PP14	450	180	270	/	/	30.84	55.00	13.14
PP15	57	57	0	0.01[(2)]	0.0011[(2)]	1900.00	209.00	809.40
PP16	128	128	0	0.01[(2)]	0.0011[(2)]	4266.67	469.33	1817.60
PP17	107	107	0	0.01[(2)]	0.0011[(2)]	3566.67	392.33	1519.40
PP18	50	50	0	0.01[(2)]	0.0011[(2)]	1666.67	183.33	710.00
PP19	10	10	0	0.01[(2)]	0.0011[(2)]	333.33	36.67	142.00
PP20	450	162	288	/	/	14.16	800.00	6
PP21 closed								
PP22	275	129	146	/	/	56.4	79.00	no wwtp
sum:	**5256.1**	**4681.2**	**893.9**	**/**	**/**	**30272.88**	**6046.04**	**12872.19**
Processing								
Pc1	0	10	0	0.007[(2)]	0.025[(2)]	233.33	833.33	99.40
Pc2	0	128	0	0.0000244	5.63E-07	8.56	0.20	3.65
Pc3	0	48	0	0.007[(2)]	0.025[(2)]	1120.00	4000.00	477.12
Pc4	0	108	0	0.007[(2)]	0.025[(2)]	2520.00	9000.00	1073.52
Pc5	0	5	0	0.007	0.025[(2)]	116.67	416.67	49.70
Pc6	0	214.404	0	0.0000018	0.025[(2)]	1.21	17867.00	0.52
Pc7import only								
Pc8	0	6.4	0	0.0000043	0.000064	0.08	1.14	0.03
Pc9	0	70	0	0.007[(2)]	0.0004715	1633.33	110.02	695.80
Pc10	0	7	0	0.007[(2)]	0.025[(2)]	163.33	583.33	69.58
Pc11	0	10	0	0.007[(2)]	0.025[(2)]	233.33	833.33	99.40
Pc12	0	550	0	7.30E-07	7.30E-06	1.34	13.38	0.57
sum:	**0**	**1156.804**	**0**	**/**	**/**	**6031.18**	**33658.40**	**2569.29**
Total	**7246.84**	**5838**	**2884.64**			**42464**	**45503**	**18062.6**

[(1)] Indirect releases come from stripping processes in waste water treatment plants. According to the SimpleTreat calculations (see table 3.26; 42.6% of the releases are to the air and 6.1% to the water pathway). [(2)] based on TGD default values (see table 3.1)

Production sites

As production sites, 14 sites with a total benzene production volume of approximately 1 990.7 kt/a were identified. Emissions to waste water vary from approximately 0.32 to 2 500 kg/day and emissions to air vary from 2.4 to almost 4 500 kg/day. It should be noted that the highest values are based on the use of TGD default values.

Production and processing sites

As sites at which production and processing takes place on the same site, 22 sites were identified covering 5 256.1 kt/a of benzene production and processing of 4 681.2 kt/a of benzene. Emissions to waste water vary from 1.3 to 5 667 kg/day and emissions to air vary from 3.9 to almost 833.3 kg/day. It should be noted that the highest values are based on the use of TGD default values.

Processing sites

Of processing sites, 12 sites were identified covering the processing of approximately 1 156.8 kt/a of benzene. Emissions to waste water vary from 0.08 to 2 520 kg/day and emissions to air vary from 0.2 to almost 17 867 kg/day. It should be noted that the highest values are based on the use of TGD default values.

The site specific information covers the production of 1 990.7 kt/a + 5 256.1 kt/a = 7 246.8 kt/a benzene and processing of 4 681.2 kt/a + 1 156.8kt/a = 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 these exposure calculations based on data from 48 companies presented in table 3.2.

For this quantity of 1 868.8kt/a of benzene processed at unknown sites the default values from the TGD were used to estimate the emission of benzene to air and water. The emission to waste water is 43 605 kg/day and the emission to air is 155 733 kg/day.

Summary of emissions from the production and processing of pure benzene in the EU

Based on the available and traceable exposure data and the default values used, the following emissions are identified:

- **Emission to WWTP's:** **86 t/d**
  (volatilisation from WWTP to air 36.64 t/d; 42.6 % of the WWTP emission)

- **Emission to air (direct):** **201.24 t/d**

3.1.1.1.2 Emission of benzene from different sources

In this chapter all the emissions of benzene to the environment are identified and quantified on a country basis. The emissions from the production and processing of benzene (not only pure but also crude benzene) are included for some point sources (oil refineries and industrial production and processing of benzene). The main releases are to the atmosphere.

Point source releases from

1. oil refineries
2. industrial production and processing of benzene
3. coking plants
4. stationary combustion of fossil fuels: energy production
5. offshore platforms

Disperse source releases from

6. road traffic
7. petrol distribution: evaporative losses
8. combustion of fossil fuels: commercial and residential heating
9. waste water treatment plant (WWTP)
10. laboratory reagent and solvent at laboratories
11. waste disposal: landfill sites
12. accidental releases (not considered in this report)
13. natural sources
14. environmental tobacco smoke (ETS).

Several EU countries maintain emission inventories (Pollution Release and Transfer Registers, PRTR) of environmental benzene releases and follow the emission trends. The following three tables present unpublished emission estimates from Germany (1995) and published emissions from the UK (1990) and the Netherlands (1994). Unfortunately, these inventories use different classification systems and relate to different years. Emission amounts therefore cannot be compared. As shown in the German table benzene emissions decreased drastically over the years.

Table 3.3 Unpublished estimates for benzene air emissions in Germany 1985 to 2010 [UBA Air Division 2000]

Source	1985 [t]	1990 [t]	1995 [t]	1996 [t]	1997 [t]	1998 [t]	1999 [t]	2000 [t]	2005 [t]	2010 [t]
traffic	***63 570***	***71 531***	***28 862***	***25 770***	***21 746***	***18 031***	***14 225***	***11 936***	***6 927***	***5 374***
exhaust[(1)]	60 275	68 133	27 056	24 204	20 485	17 162	13 705	11 659	6 816	5 308
• passenger cars	51 295	59 861	22 293	19 622	16 074	12 961	9 740	7 935	3 735	2 582
• light professional cars <3.5 t	2 218	1 994	600	531	432	358	281	220	87	51
• heavy professional cars >3.5 t	932	1 088	1 304	1 203	1 159	1 127	1 065	1 011	774	655
• buses	175	171	133	129	123	122	117	110	87	72
• motor cycles	3 455	3 319	1 476	1 469	1 447	1 344	1 252	1 133	883	698
• construction, agriculture, military	2 200	1 700	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
evaporation: passenger cars (Otto) [(1)]	3 295	3 398	1 806	1 566	1 261	869	520	277	111	66
• petrol distribution [(2)]	***1 500***	***1 700***	***750***	***650***	***450***	***400***	***330***	***180***	***110***	***85***
combustion of fossil fuels (commercial and residential heating)	***5 100***	***4 300***	***1 150***	***1 150***	***1 150***	***1 150***	***1 150***	***1 150***	***1 150***	***1 150***
industry (without energy production) [(3)]	***2 850***	***1 630***	***1 275***	***1 252***	***1 222***	***1 186***	***1 184***	***1 183***	***1 142***	***1 105***
processes										
• chemical industry	450	450	450	*450*	*450*	*450*	*450*	*450*	*450*	*450*
• oil-refineries	170	170	170	*170*	*170*	*170*	*170*	*170*	*170*	*170*
• coking plants	1370	280	55	*52*	*52*	*51*	*49*	*48*	*42*	*35*
• others	610	480	350	*330*	*300*	*265*	*265*	*265*	*230*	*200*
• laboratory chemicals	250	250	250	*250*	*250*	*250*	*250*	*250*	*250*	*250*
Total	***73 020***	***79 161***	***32 037***	***28 822***	***24 568***	***20 767***	***16 889***	***14 449***	***9 329***	***7 714***

(1) Based on calculations with the TREMOD (see chapter 3.1.1.1.3)
(2) From 1985 to 1990 only the old Federal States, from 1995 Federal States including the new 5 Federal States.
(3) Emissions from energy production are considered to be rather small (see page 32). Therefore, they are not listed in this table.

Dutch emission rates from all known sources for 1994 are presented in table 3.4. The Dutch chemical industry and refineries account for 2.5 % and 1.6 %, respectively, of these emissions

Table 3.4 Benzene emissions reported in the Dutch emission inventory - 1994 [Berdowski et al. 1996]

Source of Emission	to Air [t/a]	to Water [t/a]	Total [t/a]
Refineries	127	4.06	131
Energy sector (1)	1 850	0	1850
Chemical industry	200	6.50	206
Other industry	234	0.691	235
Waste disposal	9.1	1.69	11
Agriculture	46.5	0	46
Traffic and transport	4 310	149	4 459
Buildings	14.0	0	14
Consumers	1 050	98.7	1 149
Trade and public services	310	1.75	312
Drinking water works	0.113	0	--
Canalisation of water supply installations	0.0688	0	--
Natural	0	0	0
Other	0	0	0
Total	8 151	262	8 413

(1) Personal communication from van der Auweaert, TNO Delft; 9 September 1997: Emissions from power plant combustion are small (9 t/a); emissions from gas exploitation and distribution account for the rest (1841 t/a).

Table 3.5 1991 Atmospheric benzene emissions inventory for the UK [Legget 1996]

Source	Emission to Air [t/a]	Percent [%]
Petrol exhaust	39251	78.8
Diesel exhaust	4550	9.1
Petrol evaporation	3346	6.7
Static combustion	943	1.9
Solvent use	0	0
Petrol refinery/distillation	1367	2.7
Gas leaks	377	0.8
Industry/ residue waste	0	0
Total	49834	100

Estimated emissions from Norwegian offshore platforms

Benzene is a natural component of crude oil. During the production of petroleum i.e. at offshore platforms releases of benzene into the marine environement occur. Petroleum is a heterogeneous mixture of organic substances with significant differences depending on e.g. geological conditions in the reservoirs and technical solutions on the platforms. Additionally, the content and fraction of the substances in the petroleum will change during the production period or life period of the oilfield. In general the fraction of water in the petroleum will increase when the oilfields get older. When the petroleum reaches the platform, different mechanical and chemical methods are used for separating the water from the petroleum. In this process naturally occurring benzene will follow the discharged water to the sea. This discharge of water is called “produced water”. Quantitative information is available from Norway (SFT report 1762/2000). The total annual release of benzene from the petroleum production on the Norwegian Continental Shelf in 1999 was estimated to approximately 400 tons. The Norwegian discharge of “produced water” is about 25% of the total release to the North Sea. It has to be noted that the discharge of “produced water” is not necessarily linear with the release of benzene, and therefore extrapolation for calculation of the total release of benzene to the North Sea would be highly uncertain. Therefore, the total EU emissions from offshore platforms are not quantified and these unintentional releases are not taken into account for the continental / regional exposure assessment.

3.1.1.1.3 Estimated air emissions of benzene in the EU

The summarised air emission of benzene in the EU presented in the following chapter is based on the data for 1995, because only for this year a calculation for all identified sources of benzene is possible. Where more recent data were available these data are discussed in addition to the data from 1995.

Emission trends for Germany were reported by the Umweltbundesamt [UBA Traffic Division (2000):]. These computations (release of benzene from the use of gasoline in Germany) cover the period between 1985 and 2010 and are based on the TREMOD[1)] model. Where possible, this forecast takes into account emission reduction measures already adopted or to be expected as well as the anticipated trends in traffic. The parameters for the TREMOD model are described in (ifeu 1999) and are also taken into account in the new petrol quality requirements of Directive 98/70/EC.

[1)] TREMOD (Transport Emission Estimation Modell) developed on behalf of the Umweltbundesamt, Berlin (UFOPLAN 293 45 057) UBA FB 99-017, by "ifeu" Institut für Energie- und Umweltforschung Heidelberg GmbH; December 1997

Table 3.6 Traffic-related benzene emissions calculated with theTREMOD model for Germany

Emission (t/a)	1985	1990	1995	1996	1997	1998	1999	2000	2005	2010
Buses	175	171	133	129	123	122	117	110	87	72
Light-duty trucks <3.5 t	2 218	1 994	600	531	432	358	281	220	87	51
Heavy-duty trucks >3.5 t	932	1 088	1 304	1 203	1 159	1 127	1 065	1 011	774	655
Passenger cars	51 295	59 861	22 293	19 622	16 074	12 961	9 740	7 935	3 735	2 582
Motor cycles	3 455	3 319	1 476	1 469	1 447	1 344	1 252	1 133	883	698
Evaporative losses	3 295	3 398	1 806	1 566	1 261	869	520	277	111	66
Total:	**61 370**	**69 831**	**27 612**	**24 520**	**20 496**	**16 681**	**12 975**	**10 686**	**5 677**	**4 124**

The emission figures of Germany, Denmark and United Kingdom show that motor vehicle traffic is the major source (Germany 82 %for 1995, Netherlands 53 % for 1994, UK 95% for 1991). However, the European inventory of all benzene emissions into air (see table 3.16) indicates that air emissions from WWTP are a non-negligible component that is not taken into account in these national emission inventories. Benzene emissions in Germany fell from 79 161 t/a in 1990 to 16 889 t/a in 1999 (see table 3.3). This trend is confirmed by immission measurements in a Frankfurt/Main residential area (see table 3.43) as well as by the decrease of the benzene content in petrol in Germany and by the introduction of the catalytic converter.

The emissions resulting from industrial and commercial activities, as well as storage, transhipment and transport, are relatively small and have also declined considerably in Germany in the past few years due to the sealing of storage tanks, gas recovery and vapour recycling during loading and unloading, and during petrol deliveries to service stations.

Studies conducted by *TÜV Rheinland* (Rhineland Technical Inspectorate) have shown that benzene emissions in the exhaust gas of spark-ignition engines (motor cars not equipped with catalytic converters) decrease in proportion with declining benzene content. However, if the benzene content theoretically approached a value of zero percent by volume, emissions would still amount to about 60 percent of the volume released at a content of three percent by volume. This is due to the secondary formation of benzene by means of thermal dealkylation of the aromatics contained in the motor fuel (mainly toluene and xylene) and by trimerisation of ethylene [Nielsen et al. 1991]. About 50 percent of the benzene emissions in the exhaust gas of spark-ignition engines is due to this *de-novo* synthesis [German Enquete Commission 1994,]. Taking into consideration this secondary formation of benzene from other aromatics, the net effect of the reduction of the benzene content from three percent by volume in 1982 to 1.7 to 2.5 percent by volume in 1991 probably meant a reduction of benzene emissions by ten percent [German Enquete Commission 1994].

The level of benzene emissions also depends on the individual driving habits, e.g. „full throttle“, the driving cycles (short trips -- long trips), and the specific engine-related parameters. With the current level of knowledge, it is not possible to quantify exactly the relative weights of these variables.

There is consensus about the efficacy of catalytic converters in reducing benzene emissions. For this reason, emissions are expected to fall sharply as more and more spark-ignition engine motor cars are fitted with catalytic converters. In 1994, about 40 percent of all spark-ignition engine motor cars were equipped with catalytic converters. In Germany, about 95 to 98 percent of all new cars registered since 1990, and all new cars registered since 1993, have been fitted with catalytic converters. The latter has been due to the exhaust gas emission limits laid down in Directive 91/441/EEC. Every year, between 5 and 10 percent of motor vehicles without catalytic converters are replaced by vehicles equipped with such converters. However, given the current status of catalytic converter technology, it must be assumed that, under certain conditions, these converters do not operate at optimum efficiency.

Future emission trends will depend to a large extent on future traffic volumes. Between 1982 and 1991, the total distance driven in Germany increased to 126.7 billion kilometres. Correspondingly, motor fuel consumption in absolute terms went up by 39 percent during the same period of time. Emission reductions due to the increasing use of catalytic converters and the reduction of the benzene content to one percent by volume would be partly offset by the expected increase in total distance [German Enquete Commission 1994, Boehnke et al. 1997].

Estimated emissions in EU Member countries (EU-15)

The critical figure for the continental SimpleBox estimation is the total amount of all continental air emissions in the EU countries. This figure is not known but can be estimated in the main emission categories of subchapter 3.1.1.1.2. The estimated EU air emissions are calculated from the most recent German emission figures by using related reference values.

Estimated emissions from oil refineries

For the EU only processing capacities for crude oil are available (MWV 1999). The usage of processing capacities in Germany was over 92 % since 1995 and nearly 100 % since 1996. Assuming similar usage of processing capacities in the whole EU, processed amounts of crude oil can be estimated from processing capacities without too big an error.

Table 3.7 Estimated air emissions from oil refineries

Country	Year	Benzene emission [t/a]	Crude oil processed (t/a)	Emission factor [t/t]
Germany	1995	170	103 090 000	0.00000165
Netherlands	1994	131	---	---
UK	1991	1367	---	---
West Europe	1995	985 (1)	597 180 000	0.00000165

(1) Predicted from German emission factor.

Estimated emissions from industrial production and processing

The estimated benzene production volume comes to 7 247 kt/a, 130 kt/a are exported out of and 590 kt/a benzene are imported to the EU. Based on these quantities 7 707 kt/a are used in the EU as intermediate. This figure may be overestimated, because it contains upper limit ranges of IUCLID production data. The following table presents emissions projected using the air and waste water emissions data from individual sites (see chapter 3.1.1.1.1) as submitted by companies through the APA questionnaire (1995 and 1999). However, in this approach the TGD emission factors were used for companies that did not submit site specific data or did not provide explanations as to the parameters taken into account.

Table 3.8 Estimated emissions to air from industrial production and processing of pure benzene

Compartment	TGD emission factor	Emissions calculated using data from individual sites [t/a](1)
Air direct production processing	 0.001 or 0.01 0.0001 or 0.025	**Σ = 60 787**
Air via WWTP(2)	-	**11 000**

(1) Emission from Chapter 3.1.3
(2) Volatilisation from WWTPs to air 42.6 % (see SIMPLETREAT calculation)

There is only one study that presents quantitative data on atmospheric emissions of benzene from waste water treatment plants. California legislation required the city of Los Angeles to prepare air toxic emission inventories for its four waste water treatment plants [Mayer et al. 1994]. Being one of the major industrial releases this pathway should be examined in more detail.

Estimated emissions from coking plants

Table 3.9 Estimated air emissions from coking plants in the EU

Country	year	Benzene emission [t/a]	Production coke [t/a]	Emission factor [g/t coke]
Germany	1995	55 (1)	11 102 000 (2)	5 (3)
EU	1995	615	41 039 000 (2)	15 (3,4)

(1) Taken from table 3.3.
(2) Klatt Ed H.-J. et al. 1996
(3) Umweltbundesamt, Section III 2.3, R. Albert, personal communication.
(4) Assumed emission factor for the EU. This was the emission factor for Germany in 1988.

Estimated EU emissions from stationary combustion of fossil fuels (power plants)

In Germany these sources are considered to have low benzene emissions. Based on a quantity of 44.9 million t of hard coal burnt in power plants in Germany in 1995 (DIW 1998), a flue gas volume of 10 000 m^3/t coal (Greim, 1990) and a benzene concentration of 3.1 – 20 µg/m^3 (Garcia et al. 1992), benzene emissions from coal-fired power plants in Germany are calculated at 9 t/a. Compared to the amounts of benzene emitted by commercial and residential heating, this amount can in deed be neglected. The same assumption can be made for the EU.

Estimated EU emissions from road traffic

It is generally agreed that road traffic accounts for a relevant proportion of benzene air emissions. Several projections of EU air emissions are presented below. These projected figures range between 73 000 and 244 600 t/a, if the two extreme estimations of the Commission and of CEFIC are disregarded. The most reliable - worst case - figure is the one of 114 817 t/a (1995) that was projected via the petrol consumption.

- *Estimationn of the EU Commission (1996b)*

The Commission of the European Communities (1996b) estimated the traffic-related air emissions of benzene for the European Union to be 13 900 t/a (1995). This figure seems to be too low, because it is less than the German estimated road traffic emissions for 1995 (see table 3.3).

- *Estimation of Umweltbundesamt - Traffic Division 1997*

The German Umweltbundesamt [UBA Traffic Division 1997] estimated a value of 73 000 t/a (1995) for road traffic emissions in European cities using the „Pollutant Emissions of Road Traffic“ model.

- *Estimation by Müller (1996)*

Müller (1996) estimated the annual emission rate E [t/a] of benzene in the air mass over a given territory by using the area F, the mixing height H (1000 m), the measured background immission concentration c (1 µg/m^3), and the mean atmospheric residence time t [d] (half-life of the photo-oxidative degradation: $t_{1/2}$ = 13.4 d): $E = (c \cdot F \cdot H)/t_{1/2}$. Applying this formula to the area of Europe $3.56 \cdot 10^6$ km^2 an annual emission rate of 96 970 t/a is obtained.

Table 3.10 Estimated EU Air Emissions via the car fleet [UBA Chemicals Division 1997a]

Country	Year	Benzene emission [t/a]	Number of cars	Emission factor [t/car/a]
Germany	1995	28 862 (1)	47 267 000 (2)	0.0006106
EU	1990 1995	98 273 (4)	146 309 000 (3) 160 939 900 (3) (projected)	0.0006106

(1) from table 3.3.
(2) Umweltbundesamt (Federal German Environmental Agency - Traffic Division) 1997.
(3) Euro Stat 1995
(4) Projected with German emission factor.

- *Estimation by Umweltbundesamt via petrol consumption [UBA Chemicals Division 1997b]*

Based on the traffic-related air emissions of Germany (table 3.3), the Netherlands (table 3.4), and the UK (table 3.5), and the petrol consumption in these countries and the EU, the following emission factors were calculated respectively. These figures include automotive evaporative losses. They show a reasonable agreement.

Table 3.11 Estimated EU air emissions by road traffic

Country	Year	Benzene emission (1) [t/a]	Petrol consumption (2) [t/a]	Emission factor [t/t]
Germany	1995	28 862	30 165 000	0.0009568
Netherlands	1994	4 459	4 036 000	0.001105
United Kingdom	1990	39 251	22 935 000	0.001711
EU	1995	114 817 (3)	120 000 000	0.0009568

(1) Data from tables 3.3, 3.4, 3.5 respectively.
(2) MWV 1996 and RAR for toluene
(3) Predicted using German emission factor, the reduction of the emissions by road traffic in Germany from 1990 to 1995 is approximately 55 %.

- ***CEFIC Extrapolation via benzene content of VOCs [CEFIC 1996]***

Monitoring data on VOC (Volatile Organic Compounds) emissions are generally total hydrocarbons emissions. However, with a known benzene content within the different emission sources, CEFIC used this relationship to project the continental EU benzene air emissions for 1995. The 1983 figures were corrected for a higher current production of petrol and a lower benzene content. These data are presented in table 3.12.

Table 3.12 Estimated emissions to air from petrol sources (Western Europe) [CEFIC 1996]

Source	Benzene emission in 1983 [t/a]	Benzene emission projected to 1995 [t/a]
Automotive Exhaust	212 000	222 400
Automotive Evaporative	10 800	11 300
Petrol Distribution	5 600	5 900
Refining	4 800	5 000
Totals	233 200	244 600

Estimated EU emissions from petrol distribution

Table 3.13 Estimated EU air emissions from petrol distribution:

Country	Year	Benzene emission [1] [t/a]	Petrol consumption [2] [t/a]	Emission factor [t/t]
Germany	1995	750	30 165 000	0.00002486
Netherlands	1994	310	3 906 000	0.00007936
United Kingdom	1990	3 346	24 338 000	0.0001374
EU	1995	2 984 [3]	120 000 000	0.00002486

[1] Data taken from tables 3.3, 3.4, 3.5 respectively.
[2] MWV 1996 and RAR for toluene
[3] Predicted using the emission factors of Germany.

Estimated EU emissions from combustion of fossil fuels

Table 3.14 Estimated EU air emissions from combustion of fossil fuels: commercial and residential heating

Country	Year	Benzene emission [t/a]	Energy consumption [10^{15} J]	Emission factor [kg/10^{12} J]
Germany				
hard coal [1]	1995	152.5	25 [5]	6.1 [6]
brown coal [2]		455	70 [5]	6.5 [6]
Total coal		607.5		
Netherlands	1994	1374 [3]	---	---
United Kingdom	1990	943 [4]	---	---
EU				
hard coal [1]	1995	915	150 [5]	6.1 [6]
brown coal [2]		585	90 [5]	6.5 [6]
total coal		1500		

[1] Hard coal, patent fuel, coke
[2] lignite, brown coal briquettes.
[3] See table 3.4: the sum of 14 t/a (buildings) + 1050 t/a (consumers) + 310 t/a (trade and public services)
[4] See table 3.5: static combustion.
[5] EUROSTAT Energy Balances 1995, proportion Germany/EU from 1994.
[6] Personal communication F. Pfeiffer, University of Stuttgart (IVD), 15 October 1996.

Estimated EU emissions from Waste Water Treatment Plants (WWTPs)

Air stripping of benzene in WWTPs is a known process that releases considerable amounts of benzene to the air. SimpleTreat calculations (table 3.26) predict that 42.6 % is released to air. Thus, WWTPs are a major source of environmental benzene. This fact led the United States EPA to issue legislation under the Clean Air Act Amendments of 1990 in order to contain volatile organic compounds (VOCs) in benzene waste operations (National Emissions Standards for Hazardous Air Pollutants (NESHAP)). [Jagiella 1994, Mayer et al. 1994).

The emissions of benzene from WWTPs from the production and processing of pure benzene are calculated in chapter 3.1.3.

Waste water from 5 German refineries was analysed before and after biological treatment for individual hydrocarbons, among them benzene. The average benzene concentration in the influent was 251.7 µg/l, the average concentration in the effluent 0.7 µg/l (DGMK, 1991).

With a waste water volume of 0.12 – 0.23 m^3/t crude oil (DGMK, 1991) (average: 0.175 m^3/t), this results in an input of benzene of 44 mg/t crude oil into the waste water influent.

According to the SimpleTreat model, 42.6 % of the benzene entering the waste water treatment plant enters the air and 6.1 % passes on to the hydrosphere. Division of the influent concentration into the above mentioned fractions and multiplication with the amount of crude oil processed provides estimates of the total amounts entering the different environmental compartments.

As for the EU, only processing capacities for crude oil are available (MWV 1999). The usage of processing capacities in Germany was over 92 % since 1995 and nearly 100 % since 1996. Assuming similar usage of processing capacities in the whole EU, processed amounts of crude oil could be estimated from processing capacities without too big an error. Releases of benzene into the environment can then be estimated using the same waste water volume per ton crude oil processed and the same benzene concentration as used for Germany.

Table 3.15 Estimated EU emissions from WWTPs of refineries in 1995

Year	**1995**			
Processing capacity in EU(t/a)	648 400 000			
Capacity usage in Germany	92.1 %			
Estimated amount of processed crude oil in EU(t/a)	597 180 000			
Benzene in inflowing waste water (t/a)	26.3			
Benzene release into the atmosphere (t/a)	11.2			
Benzene release into the hydrosphere (t/a)	1.6			

Estimated EU emissions from solvent uses

It is assumed that benzene is no longer used as a solvent in non industrial uses. However, it cannot be excluded that benzene is used as solvent or reagent in laboratories. Other source can be the use of solvents like white spirits because of the possible presents of benzene (concentrations not known). The German emission inventory estimates air emissions of 250 t/a (see table 3.3).

Based on the population in Germany and the EU, air emission of approximately 1100 t/a can be calculated for the emission of benzene from solvent use or educt in research laboratories in the EU.

Estimated EU emissions from landfill sites

Landfill sites are a potential, however small, source of benzene releases into the local environment. Föst et al. (1989) reported the presence of benzene in 5 leachate samples from German hazardous waste landfill sites at levels of 20 to 1180 µg/l and in the leachate from sanitary landfill at lower levels of 1.1 to 572 µg/l. Young and Parker (1983) analysed the gaseous emissions from 6 UK landfill sites for a variety of organic compounds. Benzene was found to be present at a concentration of 4.2 mg/m^3 within a landfill containing 7 months old domestic waste, and at a concentration of 23 mg/m^3 within a landfill containing 5 years old industrial waste. A high level of 114 mg/m^3 benzene was found at one point within a landfill containing domestic and industrial wastes.

The U.S. EPA identified at least twelve pollutants such as benzene, chloroform, and ethylene dichloride contained in municipal solid waste landfill emissions to have the potential to produce health effects [Lehman 1996]. Assmuth and Kalevi (1992) measured more than 30 aromatic and halogenated aliphatic trace compounds in gas samples from wells in three old and one active municipal solid waste landfill emissions in southern Finland: average range 1.4 to 9, maximum 11 mg/m^3.

The Dutch emission inventory quantifies this source as 11 t/a in 1994 (see table 3.4). A reasonable projected EU air emission rate for all 15 Member states may be a tenfold projected value of 110 t/a.

EU emissions from natural sources

Benzene is a naturally occurring organic substance. Crude oil always contains benzene in concentrations of up to 4 g/l. Benzene is also formed during incomplete combustion of organic matter, for example in heath and forest fires [GDCh 1992]. Biomass burning [Blake et al. 1994 and 1996; Hurst et al. 1994] contributes to the worldwide natural burden of benzene. Natural emissions are not of great importance and the amount of emission is not quantified.

Estimated EU emissions from Environmental Tobacco Smoke (ETS)

Benzene in environmental tobacco smoke is a major component of indoor air pollution. ETS accounts in the United States of America for about 5% of total nation-wide exposure to benzene. Another 20% is contributed by various personal activities, such as driving [Wallace, 1989]. The airborne yield per cigarette included particulate matter (10 mg) and its mutagenic activity in a *Salmonella* bioassay, carbon monoxide (67 mg), nitrogen oxides (2 mg), nicotine (0.8 – 3.3 mg), formaldehyde (2 mg) acetaldehyde (2.4 mg), acrolein (0.56 mg), benzene (0.5 mg), and several unsaturated aliphatic hydrocarbons [Löfroth et al, 1989]. C2-C8 substances, including benzene, were quantified in indoor smoky air and in air inside a private car [Barrefors and Petersson, 1993]. The concentrations of ETS constituents including benzene were measured in the living rooms of ten non-smoking and 20 smoker households in the suburb of Munich. The median benzene levels during the evening hours were 8.1 in the non-smoker's and 10.4 µg/m^3 in the smoker's homes. The corresponding outdoor levels were considerably lower: 3.5 and 4.6 µg/m^3 [Scherer et al., 1995]. Tables 11 and 12 of appendix A II present a detailed overview of indoor air concentrations in homes of smokers and non-smokers. The amount of emission is not quantified.

3.1.1.1.4 Summary of estimated EU air emissions and trends

The following table summarises the emissions of the previous subchapter. It is emphasised that these EU emission figures are rough estimates which should indicate the order of magnitude and their relative proportions.

Table 3.16 Estimated EU air emissions by different sources

Source	Predicted air emissions for 1995 [t/a]	Comments and trends
1. oil refineries direct via WWTP	985 11	may stay constant
2. industrial production and processing direct via WWTP	60 787 11 000	worst case situation
3. coking plants	615	declining
4. stationary combustion of fossil fuels: energy production	---	considered negligibly small
5. road traffic	114 817	declining, because of lower benzene content in petrol and catalytic converters; however, this effect may be weakened by the increasing number of cars
6. petrol distribution (evaporation losses)	2 984	declining, because of new pollution abatement equipment, e.g gas recovery in filling operations
7. combustion of fossil fuels: commercial and residential heating	1 500	declining, because of less consumption
8. solvent use	1 100	benzene is no longer used as solvent in non-industrial operations; however, benzene is released in research laboratories
9. waste disposal: landfill sites	110	rough estimate, may stay constant
10. natural sources	---	cannot be quantified
11. environmental tobacco smoking	---	cannot be quantified
Total	193 909	

3.1.1.2 Benzene air emissions projected from CORINAIR and TNO

Except for Germany, the Netherlands and the United Kingdom, there are no known emission inventory benzene emissions by country. However, these figures are of interest. They can be calculated from the CORINAIR emission inventory data by the proportion of 2 % of benzene in non-methan volatile organic compounds (NMVOCs) [European Topic Centre on Air Emissions 1997; Eurostat, European Commission, European Environment Agency et al. 1995 (The Dobrís Assessment)]. The proportion of 2 % is a mean value of the values reported by Loibl et al. 1993: 1.667 %, Andersson-Sköld et al. 1992: 2.37 %, and Derwent and Jenkins 1991: 1.7 %.

Table 3.17 Air emissions of benzene in EU states

Country	TNO 1984 [t/a] (1)	CORINAIR 1990 [t/a] (2)	CORINAIR 1994 [t/a] (2)
Austria	8 670	13 120	5792
Belgium	6 740	7 880	6748
Denmark	4 400	3 560	3088
Finland	5 200	9 140	3542
France	50 200	57 320	46 159
Germany, D.R.	20 200	---	---
Germayn, F.R.	45 500	66 460	42 905
Greece	4 590	14 360	7 238
Ireland	3 980	3 940	1 862
Italy	28 400	50 960	44 770
Luxemburg	no data	400	353
Netherlands	10.300	9 200	7 561
Portugal	3 820	12 880	4 509
Spain	16 300	37 880	22 401
Sweden	16 200	14 440	7 628
United Kingdom	47 600	53 640	47 013
EU-15	272 100	355 180	251 469
Reference	Warmenhoven et al., 1989	Eurostat et al., 1995	European Topic Centre on Air Emissions, 1997

(1) Calculated from consumption and emission factors
(2) Calculated from NMVOC emissions using a proportion of 2% benzene.

Given the uncertainties of these estimations, the figures of table 3.17 show good agreement with other published emission data and predicted EU air emissions in chapter 3.1.1.1.4. Loibl et al (1993) published benzene emissions of 7 800 t/a in Austria for the year 1987 and Andersson-Sköld (1992) reported benzene emissions of 10 258 t/a in Sweden for the year 1989.

3.1.1.3 Degradation

3.1.1.3.1 Abiotic degradation

Hydrolysis

Hydrolysis at environmental conditions is not likely due to the lack of reactive functional groups in the molecule [Harris 1990; Howard 1990]. The rate constant in the following model calculations is set at $khydro_{water} = 6.93 \cdot 10^{-7}$ d^{-1}, $t_{1/2}$ = 2740 a (as a default value for irrelevant degradation processes).

Direct Photolysis

Direct photolysis is of minor importance due to low absorbance of UV light [Howard 1990, Bryce-Smith and Gilbert 1976]. The rate constant in the following model cacluations is set at $kdegr_{photo} = 6.93 \cdot 10^{-7}$ d^{-1}, $t_{1/2}$ = 2740 a (as a default value for irrelevant degradation processes).

Photooxidation in the Troposphere

Degradation of benzene in air occurs by reactions with hydroxyl [OH], nitrogen oxide radicals [NO_x], and ozone [O_3]. However, on the basis of the rate constants of the reaction and the concentrations, only the reaction with hydroxyl radicals is important for the tropospheric elimination of benzene (RIVM 1988; GDCh 1992). The rate constant for this reaction has been often measured (see table 3.18). The recommended values are presented in table 3.19.

Table 3.18 Benzene degradation in the atmosphere by the reaction with hydroxyl radicals

Rate constant [cm^3 $molecule^{-1}$ s^{-1}]	OH Concentr. [$molecules/cm^3$]	Half-life [d]	Note to the half-life estimation	Reference
1.15E-12 to 1.59E-12	-	-	OH concentration not provided	Atkinson, 1989
1.22E-12	5.00E+10	1.32E-03	OH concentration not realistic	Becker et al., 1983
1.02E-12	5.00E+10	1.57E-03	OH concentration not realistic	Becker et al., 1983
1.1E-12	4.00E+11	1.82E-04	OH concentration not realistic	Becker et al., 1983
1.2E-12	4.00E+11	1.67E-04	OH concentration not realistic	Becker et al., 1983
9.7E-13	1.00E+9	8.27E-02	OH concentration not realistic	Becker et al., 1983
1.1E-12	-	-	OH concentration not provided	Becker et al., 1983
1.2E-12	-	-	OH concentration not provided	Becker et al., 1983
1.04E-12	-	-	OH concentration not provided	Becker et al., 1983
1.2E-12			OH concentration not provided	Perry et al., 1977
0.91E-12 to 1.04E-12	-	-	OH concentration not provided	Rinke and Zetsch, 1984
1.20E-12	1.25E+06	5.3	OH concentration for polluted air	RIVM, 1988
1.04E-12 to 2.20E-12	-	-	k values as a function of temperature, 250 – 1017 K	Tully et al., 1981
1.11E-12 to 1.33E-12	-	-	k values as a function of temperature, 239 – 354 K	Witte et al., 1986
2.0417E-12	5.00E+5 (24 h/d)	7.8	Model calculation	AOPWIN, 1995

AOPWIN, 1995: model Atmospheric Oxidation Program for Windows ver. 1.75

Table 3.19 Recommended benzene degradation rate constants

Rate constant [cm^3 $molecule^{-1}$ s^{-1}]	Concentration [molecules/cm^3]	Half-life [d]	Note	Reference
k_{OH} = 1.2E-12	5.0 E+05 (1)	13.4	for OH – radicals	Perry et al., 1977
k_{O3} = 7E-23	3.0 E+12	38 200	for O_3	Atkinson and Carter 1984; Pate et al. 1976
k_{NO3} = < 3E-17	1.32 E+08 (2)	2 026	for NO_3 – radicals	Atkinson et al. 1984 Atkinson 1991

(1) this mean 24-hour OH radical concentration is used for this calculation of the half-life

(2) The atmospheric concentration of NO_3 radicals in a relatively uncontaminated atmosphere at night is given as $2.4 \cdot 10^8$ NO_3 /cm^3 by Sabljic and Güsten (1990). As they absorb light with a wavelength above 600 nm, the NO_3 radicals are, however, relatively quickly photolysed in daylight. Assuming a concentration of NO_3 radicals of $2.4 \cdot 10^8$ NO_3 /cm^3 at night and of approx. $2.4 \cdot 10^7$ NO_3 / cm^3 during the day (10% of the concentration at night), a mean 24 hours NO_3 radical concentration of $1.32 \cdot 10^8$ NO_3 /cm^3 is obtained.

The hydroxyl radical concentration is the decisive factor in calculating the tropospheric half-life of benzene according to a pseudo first order reaction. The OH radical concentrations published in the literature were submitted to a critical analysis in a survey published by GDCh (1993). Recent measurements confirmed the daytime summer (August) rural OH concentrations of 3-6 $\cdot 10^5$ in the early morning to $1.4 \cdot 10^7$ molecules/cm^3 at noon (Mount and Eisele 1992; Dorn et al. 1996; Hofzumahaus et al. 1996; Brauers et al. 1996; Goss Levi 1996). There are day and night variations (factor 10), daily variations (increase from morning to noon and decrease to evening), summer and winter variations (factor of 2 to 3 with the maximum in summer) and latitude variations of OH concentrations; concentrations at the equator are highest, concentrations at 30° North and South are about 70% of the equator concentration. Crutzen (1983) calculated the global, mean 24-hour OH radical concentration at $5 \cdot 10^5$ molecules/cm^3, with a probable range of $(0.3 – 1.0) \cdot 10^6$ molecules/cm^3. This value is now accepted by the TGD.

Rasmussen and Khalil (1983) measured the benzene and toluene concentrations at 9 locations dispersed over the globe in order to answer the question of the global fate of benzene. The sites span latitudes from inside the arctic circle to the south pole. Their findings are the following:

- Benzene concentrations increase from south to north and are highest in the northern hemisphere. The average northern hemisphere concentrations drops off rapidly at 44° N as one moves southward.
- The benzene concentrations at four North American sites are inversely proportional to the seasonal cycle of OH radical concentrations which are high in summer and low in winter according to solar radiation intensity, i.e. winter time benzene concentrations are highest and summer concentrations are lowe by about a factor of 3.
- The latitudinal profile of benzene is consistent with the expected locations and sources.

Rasmussen and Khalil (1983) concluded that the benzene atmospheric lifetime is expected to be around 10 to 20 days during summer at northern high latitudes and about 4 days in tropical regions.

Boudries et al. (1994) published benzene atmospheric air concentrations that originated in air masses from five directions around Porspoder which is situated at the most western point of Brittany/France. Four-day back-trajectories reaching Porsoder at 0 h and 12 h noon, supplied by the French National Meteorological Service, were analysed to identify the origin and direction of the air masses. This analysis provides an insight into the atmospheric transport of benzene over the European continent in space and time.

Table 3.20 Geographical origin and concentrations of benzene in European air masses [Boudries et al., 1994]

Origine of air masses	Concentration range [ng/m^3] (1)	Period
continental air masses coming from St. Petersburg over the European continent	713 – 1 879 582 - 615	April – July 1992 October – November 1992
North Sea air masses, coming from the North Sea via the English cannel	324 972 – 1 620	October 1992 April – June 1992
England air masses, coming from the British isles	91 - 152 454 – 1 296	Sept. – October 1992 April – August 1992
Stagnant oceanic air masses, staying one day or more near the coast before reaching Porspoder	123 - 421 680 - 842	July – December 1992 April – June 1992
Oceanic air masses, coming from the Atlantic ocean with fast wind speeds up to 90 km/h.	26 - 210 356 - 518	June 1992 – January 1993 April – May 1992

(1) calculated 1 pptv = 3.24 ng/m^3 at 25 °C.

These results allow the following conclusions:

- There are seasonal variations of benzene concentrations: August 1992- January 1993: 230 – 324; February – June 1992: 745 – 1 166 ng/m^3 (all directions). The maximum (spring) / minimum (autumn) ratio is about five. This ratio reflects the high OH concentration in summer and the low OH concentration in winter that scavenges benzene in the troposphere.
- The concentrations in air masses from continental Europe are higher by a factor of about 10 – 50 than those from oceanic origins, i.e. European anthropogenic benzene stays in Europe and is transported over long distances within Europe.
- High concentrations from the North Sea may result from oil drilling emissions.
- Anthropogenic benzene of North America is unlikely to reach Europe by long-range transport over the Atlantic Ocean.

Assuming an average global hydroxyl radical concentration of $5 \cdot 10^5$ molecules/cm^3 and a rate constant of $1.2 \cdot 10^{-12}$ cm^3/molecule s^{-1} , the benzene half-life is calculated at 13.4 days. The seasonal variation of benzene monitoring data [Boudries et al. 1994, see table 3.20; Rasmussen and Khalil, 1983], however, indicate that the scavenging power of OH radicals is two to three times lower in winter than in summer. This would mean a two to three times longer benzene half-life in winter than in summer. Results of similar seasonal considerations found a benzene summer half-life of 7 and a winter half-life of 22 days [GDCh 1992].

Degradation Products

Grosjean (1991) describes the photooxidation of benzene by the primary attack of OH radicals. The addition of OH to the benzene ring is followed by a reaction with oxygen to form phenol, with nitrogen dioxide to form nitrobenzene or by ring opening to form formaldehyde, formic acid, maleic anhydride and glyoxal. 80 % of the products are attributed to phenol and nitrobenzene, 20 % to the ring opening products. Phenol can react with nitrate radicals at night to form nitrophenol (Atkinson et al., 1984).

In smog chamber experiments Grosjean (1984, 1985) proved that benzene and toluene degrade photochemically in the troposphere in the presence of OH radicals and NO_x to phenols, nitrobenzene, nitrophenols, dinitrobenzene, and methylnitrophenols. Benzene is the most important source of these degradation products [Nojiama et al. 1975]. Herterich and Herrmann (1990) estimated an amount of photochemically produced nitrophenols in West-Germany of 20 000 t/a, based upon 400 000 t/a of emitted $C_6 - C_9$-aromatic compounds and a conversion factor of 5% that was derived from smog chamber experiments. Thus benzene is the major precursor of other air pollutants, i.e., nitrophenols [Schleyer et al. 1996].

Final photochemical reaction products of benzene are glyoxal, butenedial, acroleine, carbonmonoxide and formaldehyde [RIVM 1988].

Tropospheric ozone formation

The formation of troposheric ozone involves complicated chemical reactions between NO_x and VOC driven by the solar radiation. In order for these reactions to occur in substantial quantities, meterological conditions must prevail that prevents dispersion of NO_x and hydrocarbons. After a night time accumulation NO_x reacts with sunlight to produce NO and highly reactive atomic oxygen. The atomic oxygen may react with many compounds in the air, i.e. O_2 to produce O_3 or VOC to produce free radicals. The time scale of ozone production is such that ozone concentrations may build up over several days under suitable weather conditions, and that this pollutant and its precursors can be transported over considerable distances (European Commission, DGXI 1998).

There is as yet no consensus on the quantitative yield of these reactions, making modelling of these processes difficult. In addition to the VOC speciation and concentrations, VOC/NO_x ratio, solar radiation and meterological conditions vary from city to city within the EU. Since the environmental conditions differ considerably, a certain concentration of VOC may lead to very different ozone concentrations within the EU. For example European Commission, DGXI (1998) used a simplified EMEP model calculations and showed how a change in the VOC concentration may affect the ozone formation to a small extent in some parts of Europe (NO_x limited region), while in other parts of Europe a change in the VOC concentration will lead to a considerable change in the ozone formation (high NO_x regions). Thus there is no

simple relationship between the VOC and NO_x concentrations and the resulting tropospheric ozone creation. The ozone concentrations may at some places of Europe even be higher at the same VOC concentration and at lower NO_x concentrations than may be the case at other places. Likewise the time trends of the tropospheric ozone concentration for Europe in general cannot be forecasted by predicting the future concentrations of VOC and NO_x.

Nevertheless, the member countries in UNECE has agreed to use a Photochemical Ozone Creation Potential (POCP) factor system where the individual VOC's potential to create ozone is given as a relative equivalence factor expressed as g ethylene / g VOC (gas) (Hauschild and Wenzel, 1998). Here their relative importance has been evaluated against ethylene, which is given a value of 100. Two sets of factors exist corresponding to a low and high NO_x situation.

Hauschild and Wenzel (1998) proposed POCP equivalence factors for benzene of 0.4 g C_2H_4/g benzene gas in a low NO_x situation and 0.2 g C_2H_4/g benzene gas in a high NO_x situation.

To evaluate the relative importance of benzene for the creation of troposheric ozone using the POCP factor system the VOC composition within the region of concern has to be known. For a simple evaluation of the relative importance of the isolated commercial product benzene for the creation of ozone the VOC composition from industrial sources as well as the VOC composition from other sources e.g. traffic emissions has to be known. For a more in depth evaluation also the solar radiation and the NO_x concentrations has to be taken into account. These will of course vary considerably in Europe, between regions and between individual sites within the region as will also the VOC composition which depends on composition of the regional / local industrial sector and the traffic.

An attempt to evaluate the relative contribution of non-isolated benzene (traffic emissions) and isolated benzene to the ozone creation potential has been performed in section 3.1.3.3.

3.1.1.3.2 Biodegradation

Aerobic biodegradation in water

Many tests on the biological degradation of benzene are available. As benzene has a high volatility only closed tests are appropriate to determine the biological degradation. The most relevant test results for the risk assessment are presented below.

In a MITI-I test (OECD 301C) employing sludge from different sewage treatment plants, rivers, bays and a lake as inoculum a biodegradation of 39-41 % (on the upward trend) after 14 days was obtained. Biodegradation was measured as BOD (CITI 1992).

The biodegradation of benzene was measured with the OECD Manometric Respiration test (OECD 301 F). A benzene concentration of 17 mg/l was used in the test that is equivalent to a ThOD of 51 mg/l. The test guideline demands a ThOD concentration of 50 – 100 mg/l or a substance concentration of 100 mg/l. The employed inoculum was activated sludge from a sewage treatment plant treating predominantly domestic sewage in a concentration of 30 mg/l.

The test was run with three parallel vessels. Benzene in the tested concentration was inhibitory over the first week of incubation, with oxygen uptake in the test flasks being lower than in the blanks. The lag periods in the three test flasks ranged from 4 to 7 days. At the end of the 10-day window a degradation of 58 %, 72 % and 87 % was measured. After 28 days biodegradation of benzene (measured as ThOD) was 53 %, 80 % and 102 % in the three parallel vessels. As the biodegradation of the replicates differ by more than 20 % both at the end of the 10d window and at test end the test is regarded as not valid. (Shell, 1999).

The test was repeated with the same benzene concentration and the same inoculum. In this test no inhibitorty effects of the test substance were observed. After 28 days a biodegradation of 106 %, 82 % and 100 % was found. The lag phase of the three replicates was 3.5 and 4 days. At the end of the 10-day window a biodegradation of 93 %, 81 % and 90 % was measured (Shell, 2000).

A further biodegradation test according to OECD 301 F was conducted by Exxon Mobil (2000). The benzene concentration was 17 mg/l. Fresh activated sludge from a waste water treatment plant treating predominantly domestic sewage was used as inoculum. The test was run with three parallel vessels. After 28 days biodegradation of benzene (measured as ThOD) was 99 %, 103 % and 87 %. The lag phase was for all three vessels 4 days. At the end of the10-day window a degradation of 93 %, 104 % and 86 % was measured.

Astra Zeneca (2001) also performed a manometric respirometry test according to OECD 301 F using a benzene concentration of 17 mg/l. Activated sludge from a sewage treatment plant treating predominantly domestic sewage was used as inoculum. After 28 d a biodegradation of 63 %, 70 % and 62 % was found for the three replicates. The 10d window was reached.

Within a research and development project (GSF 1983) the biodegradation of benzene was determined by six different laboratories with the Closed Bottle test (OECD 301 D). According to the guideline a benzene concentration of 2 mg/l was used. The following biodegradation test results (measured as BOD) were found by the different labs:

Lab 1: 51 %

Lab 2: 5 % / 56 %

Lab 3: 10 %

Lab 4: 70 %

Lab 5: 88 %

Lab 6: 4 %

A Zahn-Wellens test (OECD 302B) conducted with industrial activated sludge resulted in a biodegradation of benzene of 90 % after 6 days. The test method was adapted to the high volatility of benzene by using a respirometric method to determine the biodegradation instead of DOC measurement. After a lag phase of 2 days 85 % biodegradation took place within 4 days (Wellens 1990).

Korte and Klein (1982) examined the biodegradation of ^{14}C-labelled benzene in a closed system. Activated sludge from a domestic sewage treatment plant (no information about adaptation) was used as inoculum. The benzene concentration was 50 µg/l. After 5 days a biodegradation of 29 % related to the formation of $^{14}CO_2$ was measured.

Price et al. (1974) tested the biodegradation of benzene with settled domestic wastewater as inoculum (3 ml/bottle). The benzene concentration was 3, 7 or 10 mg/l. After 20 days a BOD/TOD ratio of 29 % was achieved. The same test was then repeated with acclimated inoculum. An equal-volume mixture of 2 biologically treated petrochemical effluents, settled domestic wastewater, Kanawha river water (this river receives the waste effluent from numerous industrial and domestic sources) and soil in BOD dilution water was acclimated to benzene for 45 - 60 days. With this acclimated inoculum a BOD/TOD ratio of 80 % after 20 days was achieved.

The biodegradability of benzene in ground water, river water and harbour water by autochthonous microorganisms was examined by Vaishnav and Babeu (1987). Benzene concentrations of 0.8, 1.6 and 3.2 µl/l (equivalent to 0.7, 1.4 and 2.8 mg/l) were employed. Biodegradation was measured as BOD related to TOD. After 20 days biodegradation of about 42 % (river water), 22 % (ground water) and 10 % (harbour water) related to BOD was found. As the biodegradation of benzene followed a first-order kinetic the half-life could be determined from the first-order rate constant.

For ground water and river water rate constants of 0.025 d^{-1} and 0.044 d^{-1} respectively were found and half-lives of 28 resp. 16 days could be calculated.As benzene was resistant to biodegradation in harbour water the same experiment was conducted in harbour water being amended with nutrients (nitrogen and phosphorus) and/or acclimated microorganisms.

In samples that were either supplemented with nutrients or acclimated microbes no biodegradation of benzene occurred whereas in samples that were amended with nutrients and acclimated microorganisms a rate constant of 0.082 d^{-1} and a half-life of 8 days could be determined.

Delfino and Miles (1985) examined the primary degradation of benzene in untreated groundwater under aerobic and anaerobic conditions. Benzene concentration was measured by GC/MS. Under aerobic conditions after an acclimatization phase of 8 days and a period of slow degradation of 4 days a complete primary degradation of benzene (initial concentration: 1 mg/l) was achieved between day 12 and day 16. The sterile control showed no elimination during this time. Under anaerobic conditions no elimination was found within 96 days.

Biodegradability of several organic compounds in river and sea water was tested by Kondo et al. (1988). The test chemical was added to a mixture of river or sea water from an unpolluted area and an autoclaved solution of 0.2 % peptone (and 3 % NaCl for sea water) in a test tube with a tight plug. The test tubes were incubated in the dark at 30 °C. After 3 days of incubation a primary degradation of 15 – 30 % was found in both river and sea water for a benzene concentration of 10 mg/l, while for a benzene concentration of 20 mg/l a primary degradation of 100 % in river water and of 11 % in sea water was obtained.

Bridié et al. (1979) measured the BOD of benzene over 5 days with effluent from a sanitary waste treatment plant as inoculum (20 ml/l). A BOD/TOD ratio of 71 % was found.

Stover and Kincannon (1983) examined the elimination of benzene in a complete-mix, bench-scale, continuous-flow activated sludge reactor. The reactor was fitted with stainless steel covers to facilitate off-gas analysis. Benzene was added to a synthetic waste water containing ethylene glycol, ethyl alcohol, glucose, glutamic acid, acetic acid, phenol, ammonium sulphate, phosphoric acid and salts. Activated sludge from a municipial activated sludge

sewage treatment plant was acclimated to the benzene-containing waste water and then used as inoculum. The hydraulic retention time was 8 hours. Mean cell residence times of the activated sludge system were 2, 4 and 6 days. Over a period of 60 days elimination of benzene was measured by GC analysis. The benzene concentration was reduced by 99.9 % (influent concentration: 153 mg/l). 15 % of benzene was found to be stripped from the test system. BOD_5, COD and TOC of the synthetic waste water were also measured over a period of 60 days. With a sludge age of 6 days the BOD_5 was reduced by 99 %, COD and TOC by 94 %.

Other test results are available that are not regarded as relevant for the risk assessment as e.g. benzene was not the sole source of carbon or special bacteria strains were used for the experiments. Therefore, these results are only cited in the IUCLID data sheet. None of these test results is in contradiction to those results cited above.

Summary of the aerobic biodegradation in water

The available biodegradation tests show a great variation of the results. In some tests complete mineralization was found while in other tests nearly no degradation was observed.

Also the available standard screening tests on ready biodegradation show conflicting results: while in 3 newly conducted OECD manometric respirometric tests and in 2 closed bottle tests the pass level for ready biodegradation was fulfilled, in 4 closed bottle tests the pass level was not reached. If more than 1 screening test result is available, positive results should be considered for assessment purposes, irrespective of negative results, when the scientific quality is good and the test conditions are well documented. As this is the case for the studies that show ready biodegradation of benzene, benzene has consequently to be classified as readily biodegradable.

With this classification, for sewage treatment plants a rate constant of 1 h^{-1} can be derived according to the TGD. Although there are some tests available that were performed with surface waters the representativness of these tests for environmental conditions (benzene concentration, concentration of micro-organisms…) is questionable. Therefore, the half-life for surface waters is derived according to the TGD from the result of the screening tests. For a readily biodegradable substance a rate constant of 0.047 d^{-1} can be derived, resulting in a half-life of 15 days.

Anaerobic biodegradation

Several authors examined the biodegradation of benzene under anaerobic conditions (e.g. Delfino and Miles (1985), Battersby and Wilson 1989, Van Beelen and Van Keulen 1990, Grbic-Galic and Vogel 1987). They found negligible biodegradation or the biodegradation took place only after long adaptation phases of several month.

Therefore, for the biodegradation of benzene under anaerobic conditions a rate constant of 0 is appropriate.

Biodegradation in soil

Haider et al. (1974) examined the biodegradation of ^{14}C-labelled benzene in soil. 2 mg of the labelled substance were mixed with 100 g of a parabrownish soil and the formation of $^{14}CO_2$ was measured for up to 10 weeks. After 3 days, 1, 2, 5 and 10 weeks mineralization of 7.5 %, 24 %, 37 %, 44 % and 47 % respectively was measured. Due to the incomplete mineralization within the test duration and the unknown further course of the degradation curve no half-life for the biodegradation of benzene in soil can be derived from these data. Therefore the biodegradation in soil is estimated based on the tests conducted in the water phase and the partition behaviour of benzene.

The biodegradation of chemicals in soils is dependent on the Kp_{soil} of the substance. For a Kp_{soil} of 2.68 l/kg and the classification "readily biodegradable" the TGD proposes a half-life of 30 days for the biodegradation in soils. With this value a rate constant of $2.3 \cdot 10^{-2}$ d^{-1} can be calculated.

Table 3.21 Biodegradation Rate Constants and Half-lives

Compartment	Rate Constant	k-value	Half-life	Source
Wastewater	$kbio_{STP}$	1 h^{-1}	0.69 h	SimpleTreat
Surface water	$kbio_{water}$	0.047 d^{-1}	15 d	TGD
Bulk soil	$kbio_{soil}$	0.023 d^{-1}	30 d	TGD
Bulk sediment	$kbio_{sed}$	0.0023 d^{-1}	300 d	TGD
Bulk surface water	$kdeg_{water}$	0.047 d^{-1}	15 d	TGD
Anaerobic degradation	$kbio_{anaerobic}$	0	---	experimental (see above)

3.1.1.3.3 Distribution

Air/Water Partitioning

When benzene is released to water, volatilisation will result in a substantial loss to the atmosphere. This loss is evident from Henry's law constant of 270.5 Pa m^3/mol at 10 °C and 557.1 Pa m^3/mol at 25 °C calculated by Mackay and Leinonen (1975).

A Henry constant of 432.6 Pa m^3/mol at 20 °C was calculated from data given in chapter 1.3 (see appendix A I) and used in all model calculations of this report. The substance is rapidly volatilised from an aqueous solution, according to Thomas [Thomas 1982]. A volatilisation half-life of 11.5 days was calculated using the EQC model (see below)), which is in good

agreement with experimental data: $t_{1/2}$ = 23 d (spring 8-16 °C), 3.1 d (summer 20-22 °C), and 13 d (winter 3-7 °C) in sea water [Wakeham et al., 1983].

The volatilisation rate depends on flow depth, flow velocity, temperature, and less on the wind conditions. Pankow et al. (1996) used established theory to calculate the volatilisation half-life from flowing surface waters.

Table 3.22 Calculated Volatilisation Half-Life of Benzene from River Waters (Pankow et al. 1996)

Flow depth [m] Flow velocity [m/s]	Winter $t_{1/2}$ [d] temperature 5 °C	Summer $t_{1/2}$ [d] temperature 25 °C
10 m 0.032 m/s	68.2	42.3
10 m 3.16 m/s	7.13	4.39
0.3 m 0.032 m/s	0.39	0.24
0.3 m 3.162 m/s	0.049	0.029

Table 3.23 Air/Water Partition Coeffients[(1)]

Compartments	Partition Coefficient	Value
Henry's law constant	H	432.64 Pa m^3 mol^{-1}
Henry's law constant	log H	2.63
Air/Water partitioning	$K_{air/water}$	0.178 m^3/m^3

(1) for the calculation see appendix A I

Air/Aerosol Partitioning

Air/aerosol partitioning was calculated according to the Jung equation: $Fass_{aer} = 10^{-8}$, i.e. there is no relevant adsorption of benzene to the aerosol solid phase.

Soil/Water Partitioning

A chemical's ability to bind or sorb to soils is characterised by its organic-carbon partition coefficient Koc. The soil sorption coefficients Koc that are reported in the literature range between 18.2 l/kg for a silt loam soil [Chiou et al. 1983], 42-759 l/kg for three Dutch soils [Larsen at al. 1992a], 100 – 900 l/kg for 20 Dutch aquifer materials [Larsen et al. 1992b] and 1,023 l/kg [Uchrin and Mangels 1987] depending on the test conditions and the soil characteristics.

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 (see appendix A I). This calculated Koc value is located within the

range of the experimentally determined values and is used in all model calculations of this report. Likewise, this calculated Koc value of 134.1 l/kg does not indicate a significant geoaccumulation. If benzene is released or deposited to soil, the substance will rapidly re-volatilise to the atmosphere. The half-life of this intermedia transfer soil to air is a result of the EQC model calculations: 1.4 h.

Solid-specific partition coefficients Kp may be estimated for soils, sediments, suspended matter based on the Koc value. The equation is:

$$Kp = Koc \times f_{oc.}$$

Where f_{oc} is the fraction of organic carbon in the solid. The TGD recommends values for f_{oc}: soil 0.02, sediment 0.05, suspended matter 0.1. table 3.24 presents the calculated soil/water partition coefficients of these compartments based on the Koc value.

Table 3.24 Soil/Water Partition Coefficients

Compartments	Partition Coefficient	Value	Source
Soil sorption	Koc	18.2 l/kg	experimental Chiou et al. 1983
Soil sorption	Koc	1 023 l/kg	experimental Uchrin, Mangels 1987
Soil sorption	Koc	134.15 l/kg	TGD calculation(1)
Soil	Kp_{soil}	2.683 l/kg	TGD calculation(1)
Soil/water	$K_{soil\text{-}water}$	4.26 m^3/m^3	TGD calculation(1)
Sediment	$Kp_{sediment}$	13.415 l/kg	TGD calculation(1)
Sediment/water	$K_{sediment/water}$	7.51 m^3/m^3	TGD calculation(1)
Suspended matter	Kp_{susp}	13.415 l/kg	TGD calculation(1)
Susp. Matter/water	$K_{susp/water}$	4.254 m^3/m^3	TGD calculation(1)

(1) for the calculation see appendix A I

Plant/Air Partitioning

Binding of benzene in a plant occurs through the exchange at the air/leaf interface. A transfer from soil to the plant via the roots seems not likely because of the very low concentration in soil. The air/leaf partitioning was calculated by Behrendt and Brüggemann (1994) to be $K_{air\text{-}leaf}$ 10.6. The volume related concentration in the leaf is one order of magnitude higher in the leaf compared to air. Given an air concentration of 1 µg/m^3 the concentration in the leaf is calculated to be 21 ng/kg wet weight (density of the leaf = 0.5 g/cm^3).

Benzene vapour penetrates into leaves through the stomata and is then metabolised in the plant. The intensity of the absorption depends on the number of stomata and the structure of the cuticle [Ugrekhelidze et al. 1997].

Behaviour in Waste Water Treatment Plants (WWTPs)

Representatives of sixteen benzene producing companies supplied data to CEFIC on benzene influent and effluent concentrations in waste water treatment plants before dilution in receiving water [CEFIC 1996]. Some of the companies reported summarised data while others supplied individual sample values. These data are summarised in table 3.25. The majority of the data are reported as less than the detection limit, which ranged from <1 to 100 µg/l. Influent/effluent monitoring data were also reported under the APA questionnaire (1995) and are presented in appendix A II table 6. These data range for influent concentrations between 100 (minimum) to 10 000 µg/l and for effluent concentrations between <0.2 and 78 000 µg/l. The elimination in the WWTP can be calculated only for 6 sites in the range of 90 to > 99 %.

Effluent concentrations of 0.1 – 10 µg/l were measured in four German facilities in 1995 [Fooken et al. 1997]. This data base is not sufficient to express the elimination capacity of an industrial WWTP.

Concentrations calculated from the production volume and site specific exposure information or the TGD default emission factors (chapter 3.1.2) range from 43 µg/l to 2 500 000 µg/l for influent and from 1 µg/l to 101 700 µg/l for effluent concentrations.

Table 3.25 Benzene Concentrations in industrial WWTP's

Effluent Concentration Range [µg/l]	Number of Reported Measurements
non-detected (<1)	269
non-detected (<100)	702
1 - 100	21
101 – 1000	66
> 1000	9

Where no site specific traceable exposure data for the elimination in the WWTP or the effluent concentration of benzene in the waste water are available, the elimination of benzene in the waste water is calculated with the Simpletreat model in accordance with the TGD.

Based on the physico-chemical properties of benzene and the rate constant for biodegradation of 1 h^{-1} (for ready biodegradation) the elimination in industrial WWTPs is determined as follows.

Table 3.26 Behaviour of Benzene in WWTP's according to the SimpleTreat Model

Distribution	SimpleTreat in [%]
to air	42.6
to water (effluent)	6.1
to sewage slugde	1.2
degradation	50.1
elimination	93.9

It may be expected that the aerobic biodegradation rates achieved in industrial WWTPs exceed those derived from standard biodegradation tests and therefore a higher degree of biodegradation than predicted above may be reached [Parkerton, 2001]. However, the elimination of 93.9 % estimated by Simpletreat is in the same order of magnitude with elimination rated calculated from site-specific influent and effluent concentrations that are in the range of 90 to > 99 %. Therefore, the elimination calculated by Simpletreat is used for the exposure assessment for all those sites that did not deliver site-specific data about elimination in their WWTP.

3.1.1.4 Fugacity Model Calculations: Equilibrium Criterion Model (EQC)

Benzene environmental distribution and fate were calculated with the Equilibrium Criterion Model (EQC) Model [Mackay et al. 1996] based on the following input values (see chapter 1 and chapter 3.1.1.3).

Table 3.27 Input Values for EQC Model

Input parameters	Input values
Temperature	20 ^{o}C
Molecular mass	78.11 g/mol
Melting point	5.5 ^{o}C
Vapour pressure	9970 Pa
Water solubility	1800 mg/l
octanol/water partition coefficient	log Pow: 2.13
Half-life in air	321 h = 13.4 d
Half-life in Water	360 h = 15 d
Half-life in Soil	720 h = 30 d
Half-life in Sediment	7 200 h = 300 d

Level I Model: steady-state, equilibrium, closed system, no degradation

Level I is a six-compartment closed system environment with steady-state and equilibrium conditions. The results are presented in table 3.28.

Table 3.28 Results of Level I Model

Compartment	Distribution [%]
Air	98.8
Water	1.115
Soil	0.099
Sediment	0.002
Suspended sediment	0.00007
Fish	0.000006

The model predicts that benzene is practically exclusively an airborne pollutant. No geo- or bioaccumulation occurs.

Level II Model: steady state, equilibrium with degradation and advection

The level II model is the same as model I and allows for degradation and advection. The results of the environmental distribution are the same as in the level I model.

Table 3.29 Results of Level II Model

Persistence	Value
Reaction (air)	17.7 %
Advection (air)	82.0 %
Reaction residence time	464 h = 19.3 d
Advection residence time	101 h = 4.2 d
Overall residence time	83 h = 3.4 d

The persistence is dominated by advection (82%) over the OH radical degradation (18 %), which is an important statement on the fate of benzene in air. The main removal mechanisms are export by air masses and photodegradation leading to a calculated overall residence time in the atmospheric mixing layer of 3.4 days.

Level III Model: steady state, non-equilibrium with degradation, advection and intermedia transfer

The level III model is the same as the level II model and allows for intermedia mass transfer. It also allows to input the chemical into each compartment separately or into two or three compartments simultaneously (air, water, soil) and to observe intermedia mass transfer, degradation and advection processes.

Table 3.30 Level III Model

Intermedia transfer	Half-lives
air to water	25 900 h = 2.95 a
air to soil	37 486 h = 4.28 a
water to air	293 h = 12.2 d
water to sediment	131000 h = 14.95 a
soil to air	51.6 h = 2.15 d
soil to water	3656 h = 152.3 d
sediment to water	546 h = 23 d

Level III calculations show that benzene has the tendency to stay airborne, when released to air and to volatilise with a half-life of 12.2 d from water to air, when released into surface waters.

Benzene will have enough time to be bioavailable to aquatic organisms, when released into surface waters by industry activity. The major removal processes are photodegradation, biodegradation in water, as well as air and water advection. Soil and sediment are no burial sinks for benzene. Gas deposition from air to soil and water is a negligible process.

Figure 3.1 shows the result of the EQC-Model calculation Level III. It illustrates the environmental partitioning of benzene after emissions into air, water and soil (based on the summary of exposure data for benzene; see chapter 3.1.6.1. Emission data are taken from table 3.47). The pathways show the relative magnitudes of the intermedia transfer processes.

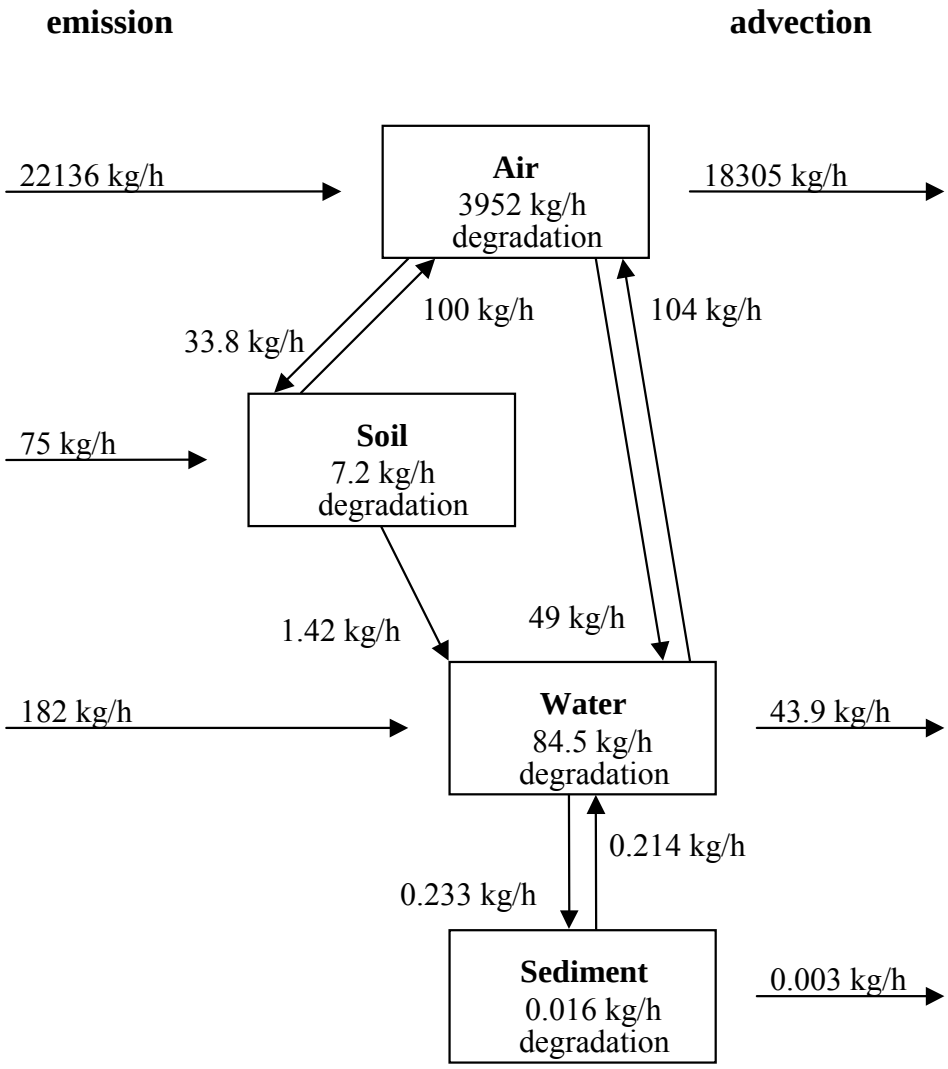


Figure 3.1: Intermedia transfer process of benzene

3.1.1.5 Bioacculumation

Freitag et al. (1985) examined the bioaccumulation of benzene in fish, algae and activated sludge. Experimental protocols were described in detail in Korte et al. (1978). For the fish test the golden orfe *Leuciscus idus melanotus* was chosen as test organism. Five fish weighing 2-5 g each were exposed to 50 µg/l of ^{14}C-labelled benzene for three days in a closed system. The fish were not fed during this time. After three days the radioactivity in the whole fish was determined and referred to the average constant concentration of benzene in the water. A BCF of < 10 (related to wet weight) was calculated.
For the algae test the green algae *Chlorella fusca* was used. Algae (20 mg d.w.) were exposed to 50 µg/l ^{14}C-labelled benzene for 24 hours. After this time algal cells were separated by centrifugation and the radioactivity was measured in the algae and in the supernatant. A BCF of 30 (related to wet weight) could be determined.
In the third test activated sludge from a municipal sewage treatment plant (1 g d.w./l) was exposed to 50 µg/l ^{14}C-labelled benzene in a nutrient solution for five days. Then an aliquot was taken and filtered through filter wadding. From measurement of the radioactivity in the filtrate and in the residue the distribution of benzene between activated sludge and water was obtained. A BCF of 1700 (related to dry weight) could be calculated.

Trucco et al. (1983) investigated the bioaccumulation of ^{14}C-labelled benzene in *Daphnia pulex* using a closed system. 20 daphnids per set were employed. The uptake of benzene was tested under three conditions: from water alone, from algae (*Ankistrodesmus falcatus*) preloaded with benzene and from a medium in which both water and algae were contaminated.
The concentration of benzene in water was 0.04 µg/l. *Ankistrodesmus falcatus* was preloaded with benzene by exposing the algae for 48 hours to a benzene concentration of 50 µg/l. After repeated washing the algae were dosed to the daphnids at a density of 10^4 algal cells per milliliter. The accumulated benzene concentration was 1.5 pg per algal cell. The daphnids were exposed to the different systems for 24 hours. After this time they were placed into a clean medium solution for 72 hours to examine the clearance. Bioconcentration factors of 225 (uptake from water alone), 203 (uptake from preloaded algae) and 153 (uptake both from water and algae) were found. It is unknown, wether the bioaccumulation factors were related to wet or dry weight. After 72 hours 88 % of the accumulated benzene was lost by the daphnids exposed solely via the water phase and 83 % by the daphnids exposed to both water and algae.

Korn et al. (1976) examined the bioaccumulation of ^{14}C-labelled benzene in striped bass (*Morone saxatilis*) and northern anchovies (*Engraulis mordax*). Fish were exposed in seawater to benzene concentrations of 0.6 µg/l to 3.2 mg/l (northern anchovies) and 0.06 mg/l (striped bass) for 48 h under static conditions. After exposure fish were held under flow-through conditions in filtered seawater to study depuration. The benzene concentrations in seawater employed in the experiments dropped to 30 - 43 % of their initial values within 48 hours of the start of the exposure experiments.
For northern anchovies the highest accumulation was found at initial benzene concentrations of 8.4 µg/l. The highest BCF was found in the gallbladder (8450), followed by the intestine (505) and the liver (309). In striped bass also the gallbladder accumulated most benzene (BCF = 53.4) but accumulation was generally lower than in northern anchovies.

All BCF were related to the initial benzene concentration. As the ^{14}C-radioacitivity was measured both benzene and possible metabolites were detected. Two days after termination of exposure the remaining ^{14}C-radioactivity in the gallbladder of northern anchovies was 63 and 69 %.

The bioaccumulation of ^{14}C-labelled benzene in different tissues of pacific herring *Clupea harengus* was examined by Korn et al. (1977). A static exposure of the fish to 100 nl/l benzene for 48 h was preceded and followed by a continuous water flow of 2 l/min. Radiometric analysis of water samples was conducted at 0, 6, 24 and 48 h. Benzene concentration in the seawater after 48 h was 69 % of the initial concentration. 6 hours after start of exposure and then daily for 7 days gallbladder, intestine, pyloric caeca, gill, brain, liver, muscle, kidney and immature male and female gonad tissues were sampled and analyzed for ^{14}C. The following BCFs were determined: 31 (gallbladder), 7 (gills), 6 (intestine, pyloric caeca, brain), 5 (liver), 4 (muscle, kidney) and 2 (gonad). After 5 days of depuration only in the gallbladder ^{14}C was found. In all other tissues a fast depuration was observed.
A second experiment was conducted to find out whether benzene or metabolites was accumulated in the gallbladder. 6 fish were exposed to 100 nl/l benzene. After 48 h the gallbladder was extracted and the extract was analyzed for benzene by GC. No detectable benzene (detection limit: 0.1 nl/g) was found. This indicated that most or all of the ^{14}C measured in the gallbladder was not due to benzene but to one or more metabolites.

Eldridge and Echeverria (1978) exposed eggs and larvae of pacific herring *(Clupea harengus pallasi*) to ^{14}C-labelled benzene. Eggs and yolk-sac larvae were exposed through the water phase whereas postyolk-sac larvae were both exposed via benzene-treated water and benzene-treated live food. As food source the marine rotifer *Brachionus plicatilis* was used. To contaminate the food rotifers were allowed to accumulate benzene for 48 h. The benzene concentration in the exposed rotifers was not measured. However, previous experiments conducted by the authors found BCF values related to ^{14}C of 10^3 to 10^4 for periods up to 8 days for the rotifers. This high accumulation may be due to the fact that the rotifers are not able to discharge or metabolize benzene. Eggs and larvae of pacific herring were exposed for 48 respectively 72 h. After 24 h the benzene concentration in the water decreased to about 50 to 23 % of the initial concentration. After 48 h no benzene was detectable. Eggs and yolk-sac larvae accumulated benzene quickly within 6 to 12 h reaching maximal BCF values of about 11. Also non-feeding postyolk-sac larvae absorbed benzene quickly within 6 to 12 h. The highest BCF of 2.6 was found at an initial benzene concentration of 1.2 µl/l. Postyolk-sac larvae feeding on contaminated rotifers or rotifers in contaminated water demonstrated a bimodal uptake. Maximum tissue concentrations of 8.16 µl/l were found after 72 h in fed larvae exposed to an initial benzene concentration of 2.1 µl/l. This means a BCF of about 4. Larvae that were exposed only via rotifers previously contaminated with 1.2 µl/l benzene experienced no initial rapid accumulation. Rather a steady rise in contamination to 0.31 µl/l was exhibited.

Manila clams (*Tapes semidecussata*) were exposed for 8 days to the water-soluble fraction of crude oil containing a mixture of 6 monoaromatics (Nunes and Benville 1979). The amount of aromatics in water was measured three times a day.
The mean benzene concentration was 1.6 mg/l. Every 48 h a subsample of 10 test organisms was pooled and analyzed for aromatic content by GC. No benzene could be detected in the tissue of the clams during the whole exposure period (detection limit: 0.6 mg/l).

Summary of bioaccumulation

The different experiments show that benzene has a low to moderate bioaccumulation potential. In all but one available tests conducted with fish BCF were clearly below 100. The uptake of benzene was followed by a fast depuration when the test organisms were placed into clean medium. In one test conducted with northern anchovies a BCF of 8450 was measured in the gallbladder. As only ^{14}C-analysis was conducted not only accumulated benzene but also possible metabolites were detected. Moreover, bioaccumulation in certain organs of fish is difficult to interprete as it is not possible to calculate the BCF for the whole fish. Therefore, for the assessment of the bioaccumulation potential only BCFs that are related to the whole fish are used. The highest available BCFs related to whole fish were measured by Freitag et al. (1985) and by Eldridge and Echeverria (1978). A BCF of < 10 was obtained using *Leuciscus idus*. For *Clupea harrengus* the highest measured BCF was about 11. These values are supported by the BCF of 13 that can be estimated from the log Kow of 2.13 using the linear relationship developed by Veith et al. (1979). In the further assessment a BCF of 13 is used. It has to be kept in mind that aquatic invertebrates serving as food source for fish may accumulate benzene to a high degree if they are not able to discharge or metabolize it.

3.1.1.6 Summary of Degradation and Distribution

The following table summarises the partition coefficients, bioconcentration factors and rate constants that have been calculated for benzene. These values reflect the characteristic environmental fate profile of benzene.

Table 3.31 Environmental data profile

Parameter/Unit	Input value	Cal. Value	Source
Physical Properties			
Molecular weight [g/mol]	78.114		IUCLID
Octanol-water part. coeff.[log10]	2.13		experimental
Water solubility [mg/l]	1800		experimental
Vapour pressure [Pa]	9970		experimental
Boiling point [^{o}C]	80.1		experimental
Melting point [^{o}C]	5.5		experimental
Henry's law constant [Pa m^3/mol]		432.6	cal. according to TGD(1)
Partition Coefficients			
Organic carbon-water part. coeff.[l/kg]		134.1	cal. from Pow according to TGD: a=0.52; b=1.02
Solid-water part. coeff.in soil [l/kg]		2.68	cal. according to TGD(1)
Solid-water part. coeff.in sediment [l/kg]		13.4	cal. according to TGD(1)
Solid-water part. coeff. Suspended matter [l/kg]		13.4	cal. according to TGD(1)
Suspended matter-water part. coeff.[m^3/m^3]		4.25	cal. according to TGD(1)
Soil-water part. Coeff.[m^3/m^3]		4.26	cal. according to TGD(1)
Sediment-water part. coeff.[m^3/m^3]		7.51	cal. according to TGD(1)
Air-water part. coeff.[m^3/m^3]		0.178	cal. according to TGD(1)
Fraction associated with aerosol particles [-]		1E-8	cal. according to TGD(1)
Exposure Bioconcentration Factor			
Bioconcentration factor for aquatic biota		13	cal. according to TGD
Rate constants [d^{-1}]			
Degradation rate constant with OH radicals [cm^3/molec · s]	1.2E-12		exp., see table 3.19
Degradation in air [d^{-1}]	0.0517		see chapter 3.1.1.3.1
Hydrolysis in surface water [d^{-1}]	6.93E-7		default value (EUSES)
Photolysis in surface water [d^{-1}]	6.93E-7		default value (EUSES)
Biodegradation in surface water [d^{-1}]	4.7E-2		according TGD
Degradation in bulk surface water [d^{-1}]	4.7E-2		according TGD
Biodegradation in soil [d^{-1}]	2.31E-2		according TGD
Degradation in bulk soil [d^{-1}]	2.31E-2		according TGD
Biodegradation in aerated sediment [d^{-1}]	2.31E-2		according TGD
Degradation in bulk sediment [d^{-1}]	2.31E-3		according TGD

(1) for the calculations see appendix A I

The data and findings on the fate of benzene are interpreted as follows. Benzene is highly volatile and relatively persistent in air, water and soil. Benzene is an airborne chemical. It does not geo- and bioaccumulate. The main sink is the degradation with OH radicals in the troposphere. A half-life of 13.4 days is calculated from the first order rate constant k_{OH} representing northern hemisphere conditions. The half-life depends on the OH radical concentration which according to solar radiation varies by day-time, season and latitude.

Benzene released to air will stay airborne. Fugacity model calculations demonstrate that 82 % is exported by air flow out of Europe and 18 % is photochemically degraded. Air mixing within the northern hemisphere takes about one month [Ballschmiter 1991]. In winter the benzene half-life of more than one month may be sufficient for complete mixing of benzene in the northern hemisphere producing a steady state concentration of about 500 to 1500 ng/m^3. In summer the higher OH radical concentration in the tropical areas may scavenge benzene rather efficiently. Interhemisphere mixing of air masses between the northern and southern hemisphere takes one year. The benzene half-life is too short for this process to be of relevance.

Nothing is known about the vertical distribution of benzene in the northern hemisphere. Behrendt and Brüggemann (1994) used the EXATM- model to calculate the global distribution and fate of benzene in the tropos- and stratosphere. These authors found that the steady state concentration in the troposphere is reached within 115 days, and assuming no degradation in the stratosphere, a steady state concentration in the stratosphere is reached in 5.6 years. The escape of benzene into the stratosphere, however, seems unlikely, because of the efficiency of OH radical and photolysis degradation in the higher troposphere and the stratosphere.

Benzene will not deposit on aerosols because of its high vapour pressure. Dry and wet deposition can occur. Matthies (1998) calculated a substance specific infiltration depth of 1.6 m of benzene in soil according to the Damköhler concept that is based on diffusion in soil (other substances: benz(a)pyren 0.00083 m, HCB 0.13 m, trichloro- ethene, 1.9 m). Benzene emission with rain water to soil will either volatilise or enter into pore water of soil. From the pore water of soil benzene will leach to ground water depending on the low elimination in soil by biodegradation. Benzene is found in ground water all over Europe and may increase in concentration over time (appendix A II table 3).

The high volume input into air and the quick intermedia partitioning results in the fact that benzene is found in virtually every environmental compartment as shown by the monitoring data (appendix A II). Benzene released to water will volatilise, with a calculated half-life of 0.05 – 68 days in winter and 0.03 – 42 days in summer (see table 3.22).

Considering all available test results it seems appropriate to classify benzene as readily biodegradable. Several authors have examined the biodegradation of benzene under anaerobic conditions. They either found negligible biodegradation or the biodegradation took place only after long adaptation phases of several months. The only available test on biodegradation in soil does not allow a half-life for benzene in soil to be derived. Therefore the biodegradation in soil has to be estimated based on the tests conducted in the aqueous phase.

3.1.2 Aquatic compartment

3.1.2.1 Release during production and processing of pure benzene

Releases to waste water occur during production and further processing. For those companies who did not submit traceable exposure data the default releases into the waste water of 0.3 % of the production quantity and of 0.7 % of the processing quantity as provided for in the TGD were assumed. In so far as traceable exposure data were available from the exposure questionnaire by the companies [APA 1995, 1999 and additional communications] site specific data were used in the determination of the $Clocal_{water}$.

3.1.2.2 Determination of the $Clocal_{water}$ for production and processing Generic approach

Site specific calculations of the $Clocal_{water}$ could be performed for all benzene production sites. Site specific data was absent only for the processed quantity of approximately 1 868.8kt/a. For these sites a generic exposure scenario was used. A typical company, involved only in the processing of pure benzene, with a processing quantity of 100 kt/a (mean value of processing sites, table 3.2 Pc1 to Pc12) was used for the calculation.

The generic exposure scenario for the release of intermediates into waste water during further processing is described in the TGD. This corresponds to a realistic "worst-case" scenario. A $Clocal_{water}$ of 27.46 µg/l is obtained based on a relevant processing quantity of 100 000 t/a benzene for an individual site.

Emission factor: release to waste water	0.007 (0.7 %)
Emission after WWTP	0.061 (6.1%)
No. of days	300 d/a
Dilution: default river flow	60 m^3/s
Factor $(1+K_p \cdot SUSP_{water})$	1

$$Clocal_{water} = \frac{100000\ t/a \cdot 0.007 \cdot 0.061}{300\ d/a \cdot 60\ m^3/s \cdot 86400\ s/d} = 27.46\ \mu g/l$$

3.1.2.3 Determination of the $Clocal_{water}$ for production and processing

The $Clocal_{water}$ can be calculated for individual sites using the currently available data of the individual producer and/or processing companies from the APA questionnaire [APA 1995 and 1999 and additional communications] and site specific information available to the rapporteur.

Exposure information, e.g. release into the waste water or the receiving stream, WWTP discharge concentration, was provided in few cases. For some companies no site-specific data were available, e.g. volumetric flow rate for the WWTP, volumetric flow rate for the receiving water, and in cases where exposure data was absent or not traceable, the "default values" from the TGD were applied (see table 3.2 and 3.32).

Table 3.32 Data Used to Calculate the Clocalwater

Input data	**Value/unit**	**Source**
Emission Scenario	IC3/UC33	TGD: ESD Intermediates
Production volume	site specific, otherwise IUCLID maximum value [t/a]	provided by producer or by IUCLID
Emission factor: f_{water}	site specific, otherwise default: f = 0.003 (production) f = 0.007 (processing)	provided by producer or TGD default
Fraction of emission directed to water by STP: $F_{STPwater}$	0.061 (6.1 %)	calculated using SimpleTreat
Emission duration : $T_{emission}$	300 d	TGD
Receiving water flow rate	site specific, otherwise default: 60 m^3/s	TGD
Dillution for the emission to the sea	site specific otherwise default: 10	TGD
Factor (1+Kp · SUSPwater)	1	TGD
WWTP flow	site specific, otherwise default: 2000 m^3/d	TGD
Output data		
Emission per day to WWTP	kg/d	
Emission per year to receiving water	t/a	
$Clocal_{water}$	µg/l	

The following table shows the results of the calculation.

Table 3.33 Site specific calculation of $clocal_{water}$

Site	Production (kt/a)	Processed (kt/a)	Release fraction to WWTP	Release to WWTP (kg/d)	Release to receiving water (t/a)	Clocal $_{effl.}$ (µg/l)	$Clocal_{water}$ (µg/l)	$PEClocal_{water}$ [µg/l](2)	Release to air from WWTP(1) (kg/d)
Production									
P1	63	0	2.41E-06	0.51	0.01	128.9	0.02	0.3	0.22
P2	172.05	0	2.86E-05	16.42	0.153	100	0.1	0.38	7
P3	77	0	0.000995	255.38	4.67	1220	42.65	42.93	108.79
P4	135	0	0.003	1350.00	24.71	41180	15.88	16.16	575.10
P5	170	0	2.65E-12	(0.0000015)	(4.5E-07)	10.0	1.00	1.28	0.00
P6	63.59	0	1.79E-06	0.38	0.01	5.0	0.50	0.78	0.16
P7	142.1	0	1.08E-06	0.51	0.01	5.0	0.00	0.28	0.22
P8	506	0	1.92E-07	0.32	0.01	5.0	0.00	0.28	0.14
P9	250	0	0.003	2500.00	45.75	76250	1.70	1.98	1065.00
P10	61	0	0.003	610.00	11.16	18610	7.18	7.46	259.86
P11	64	0	0.0007	149.33	0.02	9.3	0.93	1.21	63.60
P12 closed 1999									
P13	160	0	0.000013	7.00	2.10	no wwtp	50.00	50.28	no wwtp
P14	127	0	0.003	1270.00	23.24	38740	14.94	15.22	541.02
Sum:	**1990.74**	**0**	/	**6159.85**	**111.84**	/	/		**2621.11**
Prod. And Proc.									
PP1	140	70	0.003/0.007	3033.33	55.51	92520	35.69	35.97	1292.20
PP2	170	170	0.01	5666.67	103.70	12000	39.87	40.15	2414.00
PP3	110	110	0.000021	7.68	0.14	420	42.00	42.28	3.27
PP4	497.4	377.5	2.5E-6/6.0E-4	764.13	13.98	23310	8.99	9.27	325.52
PP5	296	355	/	84.84	3.10	20.0	0.13	0.41	36.14
PP6	120	120	3.28 E-6	1.31	0.02	40.0	0.03	0.31	0.56
PP7	400	400	0.0000505	55.34	0.13	1.0	0.06	0.34	23.58
PP8	53.7	53.7	0.01	1790.00	32.76	54600	21.05	21.33	762.54
PP9	72	72	0.01	2400.00	43.92	29280	29.24	29.52	1022.40

Site	Production (kt/a)	Processed (kt/a)	Release fraction to WWTP	Release to WWTP (kg/d)	Release to receiving water (t/a)	Clocal $_{effl.}$ (µg/l)	Clocal$_{water}$ (µg/l)	PEClocal$_{water}$ [µg/l)[(2)]	Release to air from WWTP[(1)] (kg/d)
PP10	580	640	/	1093.00	20.00	33330	12.86	13.14	465.62
PP11	100	100	0.01	3333,33	61.00	101700	39.21	39.49	1420.00
PP12	990	990	7.63 E-6	25.18	0.56	64.0	0.20	0.48	10.73
PP13	200	400		183.33	3.36	5592	2.16	2.44	78.10
PP14	450	180		30.84	0.69	115.9	0.02	0.3	13.14
PP15	57	57	0.01	1900.00	34.77	57950	22.35	22.63	809.40
PP16	128	128	0.01	4266.67	78.08	47320	4732.00	4732.28	1817.60
PP17	107	107	0.01	3566.67	65.27	22900	2290.00	2290.28	1519.40
PP18	50	50	0.01	1666.67	30.50	50830	19.60	19.88	710.00
PP19	10	10	0.01	333.33	6.10	10170	3.92	4.2	142.00
PP20	450	162	/	14.16	0.26	280	4.40	4.68	6.00
PP21 closed									
PP22	275.00	129.00	/	56.40	16.92	no wwtp	9.82	10.1	no wwtp
sum:	**5256.1**	**4681.2**	**/**	**30272.88**	**570.76**	**/**	**/**		**12872.20**
Processing									
Pc1	0	10	0.007	233.33	4.27	7117	2.74	3.02	99.40
Pc2	0	128	0.0000244	8.56	0.19	40.4	0.06	0.34	3.65
Pc3	0	48	0.007	1120.00	20.50	455.5	1.14	1.42	477.12
Pc4	0	108	0.007	2520.00	46.12	6149	2.58	2.86	1073.52
Pc5	0	5	0.007	116.67	2.14	3558	1.37	1.65	49.70
Pc6	0	214.404	0.0000018	1.21	0.02	40	0.01	0.29	0.52
Pc7 import only									
Pc8	0	6.40	0.0000043	0.08	0.03	2	0.54	0.82	0.03
Pc9	0	70	0.007	1633.33	29.89	49820	19.21	19.49	695.80
Pc10	0	7	0.007	163.33	2.99	4982	1.92	2.2	69.58
Pc11	0	10	0.007	233.33	4.27	7117	2.74	3.02	99.40
Pc12	0	550	7.3 E-7	1.34	0.02	40.8	0.02	0.3	0.57
sum:	**0**	**1156.804**	**/**	**6031.18**	**110.44**	**/**	**/**		**2569.29**
Total	**7246.84**	**5838**		**42464**	**793.04**				**18062.6**

(1) Indirect releases come from stripping processes in waste water treatment plants. According to the SimpleTreat calculations (see table 3.26; 42.6% of the releases are to the air and 6.1% to the water pathway). (2) PEClocal = $Clocal_{water}$ + $PECregional_{water}$ (see section 3.1.6.2)

Based on the calculations presented in the above table, a release of 12 739.2 t/a of benzene into WWTPs and 793.04 t/a into the hydrosphere results from production and further processing at 48 sites.

For the processing of 1 868.8kt/a benzene at unknown sites the default values from the TGD were used to estimate the emission of benzene to water. The emission to waste water amounts to 13 081.6 t/a and the emission to the hydrosphere to 798 t/a.

3.1.2.4 Release for the use of benzene

Benzene is used as a laboratory reagent (see table 3.3). Benzene occurs in small quantities in various solvents on a hydrocarbon basis (Danish Product Register, 1995). 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.

3.1.2.5 Release from other areas

Petrol is a highly volatile substance and is generally produced, transported, and stored in closed systems. Emissions to water during its normal distribution and its use in vehicles are negligible. Only occasional accidental spills would result in an escape to surface water. This possible exposure to benzene is not taken into account.

The remaining source of emissions to water is the refining process, which produces relatively large amounts of waste water. Refinery waste water is usually treated on-site. At the current time, the majority of refineries treat waste water by gravity separation, air flotation and biological treatment (CONCAWE, 1994b).

In order to obtain specific data on the composition of waste water streams in three petroleum and two lube oil refineries in Germany analytical examinations were performed over 18 months (1989-1990). The following benzene concentrations in the influent and effluent of the biological treatment plant were determined. Using a dilution factor of 10 for the release to surface water the $Clocal_{water}$ was calculated. The elimination rate lies between 88.15 (for A) and 99.84 % (for E).

The absolute emission of benzene from refineries is predicted in chapter 3.1.1.1.3 (table 3.15).

Table 3.34 Infuent and effluent concentrations in the WWTP's of petroleum and lube oil refineries (DGMK, 1991)

Refinery	Benzene concentration in µg/l		
	Influent of WWTP	Effluent of WWTP	$Clocal_{water}$
petroleum refinerie A	7.6	0.9	0.09
petroleum refinerie B	1200	1.9	0.19
petroleum refinerie C	50	0.3	0.03
lube oil refinerie D	0.12	0.14	0.014
lube oil refinerie E	0.93	< 0.2	< 0.02

Waste water discharges of 8 service stations and 1 fuel depot in the city of Munich and 1 fuel depot in Bremen were analysed for their main components in 1983 and 1984. Waste water from service stations mainly originates from car wash facilities while, in the case of fuel depots, it consists mainly of contaminated rain water from paved surfaces. The waste water is pretreated in mandatory gravity separators before discharge to the public sewer systems. Table 3.35 shows the concentration of benzene in waste water. Using a dilution factor of 100 (for release to the public sewer system and surface water) the $Clocal_{water}$ can be calculated.

Table 3.35 Concentration of benzene in waste water from service stations and fuel depots (DGMK, 1985)

Locality	Number of samples	Benzene concentration in µg/l		
		range	average	$Clocal_{water}$
2 service stations with car wash incl. washing of underbody	12	0.1 - 15	4.44	0.044
1 service station with wash bay without washing of underbody	5	0.89 - 16	4.92	0.049
3 service stations with wash bay incl. underbody washing with fresh water	18	0.89 - 34	5.51	0.055
1 service station with wash bay and underbody washing with recirculated water	6	0.26 - 2.8	1.43	0.014
1 service station with workshop and no car wash	6	6.4 - 334	70.65	0.71
2 fuel depots	11	0.02 – 4200	787.90	7.88

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

3.1.2.6 Sediment

The concentration of benzene in sediments was calculated from formula (35) of the TGD with $K_{susp/water}$ being 4.254 m^3/m^3 (table 3.24) and three benzene concentrations in local surface waters.

Table 3.36 $PEClocal_{sediment}$

$PEClocal_{water}$ [µg/l]	**$PEClocal_{sed}$ [µg/kg]**
lowest monitored value: 0.1	0.37
polluted surface fresh water: 31.7	117.3
highest default calculation: 4 732	17 504.3

There exist very few monitoring data of benzene in sediments (see appendix A II table 14). Nowak et al. (1996) reported that a methanogenic mixed culture from the German Saale river sediment was able to transform chlorobenzenes by reductive dechlorination via monochlorobenzene to unsubstituted benzene after a short lag phase of only 1 week.

3.1.2.7 Summary of aquatic monitoring data (incl. sediment)

Monitoring data are reported in the literature, particulary from government and public institutions. Several national and international organisations maintain water monitoring programmes that continuously measure benzene in major rivers (e.g. Rhine, Elbe). Tables 1 to 6 in appendix A II present summaries of published data for the aquatic environmental compartments according to the following scheme:

- location
- concentration
- measuring period
- remarks
- references.

Surface Water

Benzene concentrations found in water compartments are summarised in the following table. This table presents typical concentrations or concentrations ranges of benzene in water.

Table 3.37 Benzene concentration in water compartments

Category	Concentration Range [µg/l]	Typical Value $PEC_{monitored}$ [µg/l]	Appendix A II see table No	Typical value $PEClocal_{water}$ (1) [µg/l]
Surface fresh water	<0.1 – 31.7	not det. <0.1 polluted: <5	1	low: 0.02-5 medium:>5-50 high: >50-4 732
Sea water	<0.005 – 0.02	0.005	2	---
Estuaries	<1 – 89.4	1 – 3	1 and 2	---
Groundwater	0.005 – 5.1 contaminated: 1250	0.03	3	---
Drinking water	0.005 – 1	<0.1	4	---
Rainwater	0.03 – 0.46	0.1	5	---
Industrial Waste Water Treatment Plants	influent : 0.1 – 15 600 effluent < 0.2 – 78 000	influent 10000 effluent 100	6	effluent low: < 5 - 40 med.: 40- 455 high: 1 220-152 600

(1) calculated in chapter 3.1.2.3

The comparison of monitored and predicted water concentrations in fresh water rivers shows that benzene is released in very low concentrations from industrial waste water treatment plants. The default TGD calculations show benzene concentrations that cannot be confirmed by monitoring data (only some highly polluted rivers and estuaries (Elbe ≤ 5 µg/l, UK rivers and estuaries ≤ 89.4 µg/l). Monitoring data show regional differences in pollution levels.The river Rhine is practically free of benzene, while the river Elbe is still polluted. The monitoring data for the river Elbe show that between the sampling stations Boizenburg (river km 559.0), Zollenspieker (river km 598.7), where the city of Hamburg is situated, and Grauerort (river km 660.5; situated in the North Sea estuary) the benzene concentration increased from 1 to 5 and then decreased to 0.5 µg/l. [ARGE Elbe 1996].This phenomenon could serve as proof of the fact that benzene released to surface waters volatilises reasonably quickly to air, as predicted by the EQC model.

Sediment monitoring data are scarcely found in the literature (see appendix A II table 14) because benzene is an airborne chemical. The low water/soil and water/sediment partition coefficient of about 7 m^3/m^3 (table 3.24) confirms these experimental findings.

3.1.3 Atmosphere

The major releases of benzene to the atmosphere are automotive exhaust emissions, evaporative losses and combustion of fossil materials. The total emission from these sources is summarised in chapter 3.1.1.1.4, table 3.16. These disperse releases must be taken into account in the evaluation of the monitoring data and in the calculation of the regional PEC.

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 (see table 3.26) 42.6 % of the releases from WWTP to the air and 6.1 % to the water pathway. The $PEClocal_{air}$ can be calculated for the individual sites by using the currently available emission data of individual producer and/or processing companies [APA 1995, 1999 and additional communications]. Where no site-specific data were available, the $PEClocal_{air}$ calculation was performed using the "default values" of the TGD in the Gaussian Plume Model (OPS Model) as described by van Jaarsveld (see table 3.38).

In calculating the $PEClocal_{air}$ both the emission from a direct point source of the companies as well as the indirect emissions from WWTPs were taken into account. The regional concentration is used as background concentration and, therefore, is added to the local concentration. Based on the TGD only the maximum emission from the two sources (direct emission and indirect emission from WWTP) was used for the calculation of $PEClocal_{air}$.In calculating the deposition flux and the regional exposure the emissions from the two sources (direct emission and indirect emission from WWTP) were summed up.

Generic approach

Site specific calculations of the $PEClocal_{air\text{-}annual}$ could be performed for all benzene production sites. Site specific data was absent only for the processing quantity of approximately 1 868.8 kt/a. For these sites a generic exposure scenario was used. A typical company, involved only in the processing of pure benzene, with a processing quantity of 100 kt/a (mean value of processing sites, table 3.2 Pc1 to Pc12) was used for the calculation.

The generic exposure scenario for the release of intermediates into air during further processing is described in the TGD. This corresponds to a realistic "worst-case" scenario. Assuming a relevant processing volume of 100 000 t benzene/a for an individual site, a $PEClocal_{air\text{-}annual}$ of 1 906 $\mu g/m^3$ and a $DEPtotal_{annual}$ of 2 128 $\mu g/m^2$ d are obtained.

Table 3.38 Data used in OPS model for $PEClocal_{air}$ calculation

Input data	Value/unit	Source
Local direct emission rate to air during emission episode: $Elocal_{air}$	kg/d	provided by producer (APA 1995, 1999 and additional communications) or calculated with default values of TGD (see table 3.2)
Local direct emisison rate to STP during emisison episode: $Elocal_{water}$	kg/d	taken from chapter 3.1.2
Fraction of emission to air from STP: $Fstp_{air}$	42.6 %	calcuated by SimpleTreat Model
Emission duration : Temission	300 d	TGD
Main category (prod./proc.)	1b or 1c / 1b or 3	TGD (see table 3.2)
Fraction main source	1	TGD
Regional concentration (rural and pristine area) $PECreg._{air}$	1.54 µg/m^3	table 3.49
Fraction of chemical bound to aerosol: $Fass_{aer}$	10^{-8}	Junge equation, TGD
Aerosol-bound deposition flux: $DEPstd_{aer}$	0.01 mg/m^2 d	TGD
Gaseous deposition flux as a function of Henry's Law coefficient: $DEPstd_{gas}$	$3 \cdot 10^{-4}$ mg/m^2 d	TGD
Output data		
Annual local air concentration 100 m away from point source: PEClocalair-annual	µg/m^3	
Annual total deposition flux to soil within 1000 m^2 around point source: $DEPtotal_{annual}$	µg/m^2 d	

The following table shows the site specific input data for the calculation of $PEClocal_{air}$.

Table 3.39 Site specific emission to air

Site	Production (kt/a)	Processed (kt/a)	Release fraction to air direct	Release to air direct (kg/d)	Release to air direct (t/a)	Release to air from WWTP[(1)] (kg/d)	Used emission for the risk assessment (kg/d
Production							
P1	63	0	6.26E-04	108.05	39.42	0.22	108.05
P2	172.05	0	0.000061	34.98	10.50	7	34.98
P3	77	0	0.00078	200.20	60.00	108.79	200.20
P4	135	0	0.01	4500.00	1350.00	575.10	4500.00
P5	170	0	0.0000277	15.70	4.71	0.00	15.70
P6	63.59	0	0.0000113	2.40	0.72	0.16	2.40
P7	142.1	0	0.0000167	7.91	2.37	0.22	7.91
P8	506	0	0.0000143	24.12	7.20	0.14	24.12
P9	250	0	0.0000084	7.00	2.10	1065.00	1065.00
P10	61	0	0.000059	12.00	3.60	259.86	259.86
P11	64	0	0.00017	36.72	11.00	63.60	63.60
P12 closed 1999							
P13	160	0	0.0011	580.00	174.00	-no wwtp	580.00
P14	127	0	0.000638	270.09	81.00	541.02	541.02
sum:	**1990.74**	**0**	**/**	**5798.7**	**1746.62**	**2621.11**	**7402.84**
Prod. And Proc.							
PP1	140	70	/	833.33	250	1292.20	1292.20
PP2	170	170	6.8E-06	3.87	1.16	2414.00	2414.00
PP3	110	110	0.0011	403.33	121.00	3.27	403.33
PP4	497.4	377.5	2.6E-4/1.35E-4	599.43	179.83	325.52	599.70
PP5	296	355	/	33.33	10.00	36.14	36.14
PP6	120	120	0.0011	440.00	132.00	0.56	440.00
PP7	400	400	0.00007	93.33	28.00	23.58	93.33
PP8	53.7	53.7	0.0011	196.90	59.07	762.54	762.54
PP9	72	72	0.0001042	25.01	7.50	1022.40	1022.40
PP10	580	640	/	510.00	153.00	465.62	510.00
PP11	100	100	0.0011	366.67	110.00	1420.00	1420.00

Site	Production (kt/a)	Processed (kt/a)	Release fraction to air direct	Release to air direct (kg/d)	Release to air direct (t/a)	Release to air from WWTP[1] (kg/d)	Used emission for the risk assessment (kg/d
PP12	990	990	1.50E-05	49.50	15.00	10.73	49.50
PP13	200	400	/	266.67	80.00	78.10	266.67
PP14	450	180	/	55.00	16.50	13.14	55.00
PP15	57	57	0.0011	209.00	62.70	809.40	809.40
PP16	128	128	0.0011	469.33	140.80	1817.60	1817.60
PP17	107	107	0.0011	392.33	117.70	1519.40	1519.40
PP18	50	50	0.0011	183.33	55.00	710.00	710.00
PP19	10	10	0.0011	36.67	11.00	142.00	142.00
PP20	450	162	/	800.00	240.00	6	800.00
PP21 closed							
PP22	275	129	-	79.00	23,70	no wwtp	79.00
sum:	**5256.1**	**4681.2**	**/**	**6046.04**	**1813.96**	**12872.20**	**15242.21**
Processing							
Pc1	0	10	0.025	833.33	250.00	99.40	833.33
Pc2	0	128	5.63E-07	0.24	0.07	3.65	3.65
Pc3	0	48	0.025	4000.00	1200.00	477.12	4000.00
Pc4	0	108	0.025	9000.00	2700.00	1073.52	9000.00
Pc5	0	5	0.025	416.67	125.00	49.70	416.67
Pc6	0	214.404	0.025	17867.00	5360.10	0.52	17867.00
Pc7 import only							
Pc8	0	6.4	0.000064	1.14	409.00	0.03	1.14
Pc9	0	70	0.0004715	110.02	33.00	695.80	695.80
Pc10	0	7	0.025	583.33	175.00	69.58	583.33
Pc11	0	10	0.025	833.33	250.00	99.40	833.33
Pc12	0	550	7.3 E-06	13.38	4.00	0.57	13.38
sum:	**0**	**1156.804**	**/**	**33658.4**	**10506.1**	**2569.29**	**34247.63**
Total	**7246.84**	**5838**		**45503.1**	**14066.75**	**18062.6**	**56892.68**

[1] Indirect releases come from stripping processes in waste water treatment plants. According to the SimpleTreat calculations (see table 3.26; 42.6 % of the releases are to the air and 6.1 % to the water pathway).

Based on the calculations presented in the table 3.39, direct air releases of 14 067 t/a and indirect air releases of 5 418.66 t/a via waste water treatment plants results from production and further processing at 48 sites.

For the processing of 1 868.8 kt/a benzene at unknown sites the default values from the TGD were used to estimate the emission of benzene to air. The direct emission to air amounts to 46 720t/a and the indirect emission to air via waste water treatment plants amounts to 5 572 t/a.

In the following table representative sites with their local air concentration and deposition rates are summarised:

Table 3.40 Calculation of local air concentrations and deposition rates

Representative sites from table 3.39	Emission to air [kg/d]	$PEClocal_{air\text{-}annual}$ [µg/m³]	$DEP\ total_{annual}$ [µg/m² d]
Generic scenario	8 333.3	1 906	2 128
Pc6 (Maximum emission)	17 867.0 (direct emission)	4 084	5 361
Pc8 (Minimum emission)	1.14 (direct emission)	1.48	0.347
PP1 (Mean emission)	1 292.2 (via WWTP)	297	524
PP2 (90 percentil emission)	2 414.0 (via WWTP)	553	596

3.1.3.2 Summary of atmospheric monitoring data

Benzene is a widely occurring air pollutant. It belongs to the class of VOCs (Volatile Organic Compounds) (UN ECE Convention on Long-Range Transboundary Air Pollution and Protocol on VOCs) that are extensively monitored in ambient and indoor air [UN ECE 1996a]. Several Governments maintain monitoring programmes that operate continuously (United Kingdom, Germany, Austria, Sweden; see tables 7 to 12 in appendix A II) or measure benzene on a regular basis. In air quality studies, the hourly annual mean and 98 percentile values are commonly used to reflect the long term average and maxima. The database of benzene immission concentrations in air is rather extensive and well documented [CEFIC 1996, Nielsen et al. 1991, GDCh 1992, Boehnke et al. 1997]. Where available annual mean values, ranges and 98 percentile values are given. For the air compartment the following eight scenarios were investigated. The background benzene concentration in European continental pristine air is 0.6 to 1.9 µg/m³, while the background concentration in oceanic Atlantic air masses is 0.03 to 0.5 µg/m³ [Boudries et al., 1994].

Table 3.41 Benzene in air compartments

Category	Concentration Range [µg/m^3]	Typical Value $PEC_{air\text{-}monit.}$ [µg/m^3]	Appendix A II see table No	Typical value $PEClocal_{air}$ (1) [µg/m^3]
Ambient city air	1 - 275	10 – 20	7	---
Urban industrial areas	6 - 63	5	7	2 – 4 084
Rural and pristine areas	0.5 - 4.4	1.5	8	---
Oceanic air masses	0.03 - 0.5	0.3	8	---
Fuel service stations	2 – 27000	120	9	---
Inside vehicles in cities	3 - 139	40	9	---
City indoor air	1 - 90	15	10, 11	---
Smoker exposure indoor air	0.7 - 90	11	11, 12	

(1) calculated in chapter 3.1.3.1

Further data from recent ambient air measurements in European cities are presented below.

Table: 3.42 Ambient air concentrations in streets of European cities

City	Mean concentrations [µg/m^3]	Period	Reference
Austria • Vienna: streets	annual mean: 8.8 – 17.1	1992/93	Hanus-Illnar and Hrabcik 1995
Denmark • Copenhagen: street	weekly mean: 12.3 – 31.4	1994/95	Hansen and Palmgren 1996
France • Paris : street	min./max. : 2 – 64	1993	Coursimault et al. 1995
Germany • Berlin: street	annual mean: 7.47	1993/94	BIFAU 1994
Germany • Frankfurt: street	annual mean: 5	1995 and 1996	HLFU 1997
Germany • Düsseldorf: street • Essen: street	annual mean 13.5 11.6	1993	Pfeffer et al. 1995
Greece • Athens: street	annual mean: 16.2	1993/94	Moschonas and Glavas, 1996
Italy • Rome: street	annual mean: 18.6	1992/93	Fuselli et al. 1995

City	Mean concentrations [µg/m3]	Period	Reference
Italy Rome: street	annual mean: 47	1992/93	Brocco et al. 1997
Italy Rome: street	mean of hourly averages measured at 4 urban monitoring stations for 60 d during 7 a.m. to 2 p.m.: 13.1 range: 6.2 – 24.8	1998/1999	Crebelli et al. 2001
Sweden 30 Swedish cities	annual mean: 2.4 – 6.2	1994/95	Mowrer et al. 1996
Switzerland Zürich: street Geneva: street	June – Dez. Mean 6.0 +/- 1.4 3.9 +/-1.2	1993	Monn and Hangartner 1996
United Kingdom London: street	annual mean: 13	1991/92	UK Department of the Environment 1994
United Kingdom Edinburg: street Belfast South Cardiff East London Bloomsbury	annual mean 4.5 6.2 9.4 7.1	1993	National Environmental Technology Centre for the Department of the Environment 1997

As shown in table 7 of appendix A II benzene has been monitored in many European cities and regions for the last 15 years. Table 3.43 below presents annual mean values in Frankfurt/Main and a neighbouring town. The factor between annual mean values and the corresponding maximum values varies at least between 2 and 10, but can reach even more extreme values. The differences among the cities may be due to differences in petrol composition and in the proportion of cars equipped with catalytic converter in the respective country. These data may be adequate in describing the geographical pattern and be representative for the years 1992 to 1995. Typical monitoring values were taken as $PEC_{air-monit.}$ (table 3.41).

In addition, measured benzene concentrations in the air at the boundaries of three European refineries are available (CONCAWE, 1999). Continuous samples were collected for 26 two-week periods. Sampling locations were fixed at 12 or 16 points around the refineries. Annual average values were in the range of < 1 – 31 µg/m³.

In a further report (CONCAWE, 2000) exposure of workers at refineries to benzene was measured. For the job group “off-site operators” that – among others - is described as carrying out tasks at water effluent treatment plants the exposure to benzene was in the range of 0.008 – 23.3 mg/m³ with a mean value of 0.32 mg/m³. Assuming, that waste water treatment plant operators are exposed at the actual emission source (the wwtp) this concentration range gives an indication on the actual air concentration of benzene at wwtp of refineries.

By the TGD definition the $PEClocal_{air}$ represents a situation at a distance of 100 m from the emission point. No monitoring data are available that represent such a situation for benzene production and processing sites. Ambient monitoring data represent regional air concentrations in industrial areas of 200 · 200 km, such as the Rhine/Ruhr area.

The benzene concentration in ambient city air originates from road traffic and its diurnal pattern correlates well with that of carbon monoxide and NO_x concentrations. Of interest are the trend data measured by the pilot station of the Umweltbundesamt in suburban residential areas in Frankfurt/Main (till 1986) and Offenbach (from 1987). They show a steady downward trend from 1982 to 1994 (table 3.43). This downward trend was confirmed for 30 municipalities in Sweden (URBAN project) during the sampling periods 1992/93 to 1994/95, with reductions of up to 50%. 1994/95 annual mean values range between 2.4 and 6.2 µg/m^3 The Swedish authors contribute this decrease to the increasing percentage of cars equipped with catalytic converters in Sweden [Mowrer et al. 1996]. Field et al. (1996) reported that the benzene concentration in central London city air (Exhibition Road) fell by 65% from 1979 to 1992, from 32.4 to 12.3 µg/m^3 (summer mean), despite national increases in motor fuel consumption and the volume of traffic. A recent Dutch air quality report also reported the downward trend of urban benzene concentrations [RIVM 1996].

The monitoring programme (1991-96) in Austria showed in 1995/96 annual means of 4.7 – 12.8 µg/m^3 in Austrian cities (Hanus-Illnar and Hrabcik 1995; 1996).

The monitoring data show that in most European cities the projected limit value of 10 µg/m^3 (annual mean) is still exceeded (see table 3.42).

More recent monitoring data are needed for European cities to show the situation at the end of the century.

Table 3.43 Trend Measurements for Ambient Air Concentrations in Residential Areas of Frankfurt am Main and Offenbach (Annual Average) [UBA 1997]

Year	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Air conc. [µg/m^3]	37	17	10	11	11	10	11	12	10.5	10	7.5	5.5	5.3

Indoor Air

The major benzene sources in homes are tobacco smoke (appendix A II, tables 11 and 12), furnishing materials, heating systems, and motor vehicle traffic. Müller (1991) showed that the indoor concentration/time profile follows the motor vehicle traffic frequency and sharply falls off on weekends with low traffic. The indoor/outdoor ratio of 0.8 indicates that benzene readily diffuses into homes. These findings are confirmed by Rothweiler et al. (1992). The concentration in indoor air in flats in the neighbourhood of petrol filling stations is by a factor of two higher than that in ambient air. Mean values of 10.2 in indoor air and 5.6 µg/m^3 in

control reference flats were measured in Frankfurt/Main. The corresponding outdoor concentrations were: 9.3 and 4.8 µg/m^3 , respectively. These concentrations were independent of distance to the filling station (10 to 40 m), location of flat in building, and the traffic situation in the street nearby [Heudorf and Henschel, 1995].

Fromme (1995) estimated the proportions of uptake by human beings via the diffent pathways as follows: 9 % ambient air, 53 % indoor air, 8 % food, and 30 % inside cars. Concentrations of volatile organic carbons, including benzene, inside cars are significantly higher than those measured on the sidewalk [Rudolf, 1994; Dor et al., 1995; German Enquete Commission, 1994; Mücke et al. 1984].

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

In Table 3.44a is shown the mean road site concentrations of individual NMVOCs (non-methan volatile organic compounds) at a site in Copenhagen during 5 d in December 1997. Using the POCP equivalence factors it is possible to estimate the relative contribution of non-isolated benzene to the potential overall tropospheric ozone creation for such a NMVOC composition. It has to be emphasised that NMVOC composition from this site in Copenhagen is only used as an example, and that it is unlikely in this specific case that considerable ozone concentrations will build up within the region of Copenhagen as a consequence of these benzene concentrations due to low solar radiation and the prevailing wind conditions.

Table 3.44a Monitoring results of different NMVOCs at Jagtvej, Copenhagen December 1-5 1997 (Christensen (1999), and the relative contribution to potential ozone creation. Table from the EU Toluene RAR, Final Report March 2001

Substance	Mean ppbv	Range ppbv	S.D. ppbv	Median ppbv	POCP g C2H4/g gas[1] low NOx	POCP g C2H4/g gas[1] High NOx	Relative O3 creation[2] low NOx	Relative O3 creation[2] high NOx
Pentane	2.4	0.4-5.7	1.2	2.5	0.3	0.4	2.12E-03	2.83E-03
trans-2-Pentene	0.2	0.01-0.5	0.1	0.2	0.4	0.9	2.29E-04	5.16E-04
2-Methyl-2-butene	0.4	0.02-0.9	0.2	0.3	0.5	0.8	5.73E-04	9.17E-04
cis-2-Pentene	0.1	0.01-0.3	0.1	0.1	0.4[3]	0.9	1.15E-04	2.58E-04
2,2-Dimethylbutane	0.9	0.04-2.3	0.5	0.9	0.3	0.3	9.51E-04	9.51E-04
Cyclohexane	0.5	0.04-1.1	0.3	0.5	0.25	0.25	4.30E-04	4.30E-04
2,3-Dimethylbutane	0.4	0.03-1.0	0.2	0.4	0.4	0.4	5.64E-04	5.64E-04
2-Methylpentane	2	0.2-5.2	1.1	2.1	0.5	0.5	3.52E-03	3.52E-03
3-Methylpentane	1.1	0.1-2.7	0.6	1	0.4	0.4	1.55E-03	1.55E-03
n-Hexane	0.8	0.1-2.3	0.5	0.8	0.5	0.4	1.41E-03	1.13E-03
Isoprene	0.2	0.01-0.6	0.1	0.2	0.6	0.8	3.34E-04	4.46E-04
2-Methyl-1-Pentene	0.04	0.01-0.1	0.02	0.02	0.5[4]	0.9	6.88E-05	1.24E-04
cis-2-Hexene	0.03	0.01-0.1	0.01	0.02	0.5	0.9	5.16E-05	9.29E-05
2,4-Dimethylpentane	0.2	0.01-0.7	0.1	0.2	0.4[5]	0.4	3.28E-04	3.28E-04
Methyl-cyclohexane	0.3	0.02-0.6	0.1	0.3	0.5	0.6	6.02E-04	7.22E-04
2- and 3-Methylhexane	1.4	0.1-3.7	0.8	1.3	0.5	0.5	2.87E-03	2.87E-03
n-heptane	0.7	0.1-1.9	0.4	0.6	0.5	0.5	1.43E-03	1.43E-03
Benzene	3.4	0.2-8.0	1.7	3.3	0.4	0.2	4.34E-03	2.17E-03
2- and 3-Methylheptane	0.4	0.01-1.0	0.2	0.3	0.5	0.5	9.34E-04	9.34E-04
Toluene	10.2	0.8-21.5	5.6	8.9	0.47	0.6	1.81E-02	2.31E-02
Ethylbenzene	2	0.1-4.9	1.1	1.9	0.5	0.6	4.34E-03	5.21E-03
o-Xylene	2.7	0.1-6.2	1.4	2.6	0.2	0.7	2.34E-03	8.20E-03
m- and p-Xylene	5.5	0.3-12.7	2.9	5.5	0.5	0.95	1.19E-02	2.27E-02
Relative contribution of non-isolated benzene: %							7.34	2.67

The result of this calculation shows that if the VOC composition is as measured in the Copenhagen study non-isolated benzene potentially would exhibit approx. between 2.5 and 7.5 % of the total VOC contribution to ozone creation.

3.1.3.4 Creation of ozone due to isolated benzene

As described the creation of troposheric ozone is dependent on the occurrence of VOC, NO_x, solar radiation and thus OH-radicals in a complicated relationship. The VOC composition will be highly variable and depend on the industrial sources, traffic emissions and natural sources. The contribution from isolated commercial benzene will depend on the composition of local and regional industry. Therefore, average calculations are likely to underestimate the magnitude of the problem within certain regions with high exposure potential.

[1] POCP equivalence factors from Hauschild & Wensel (1998) except for cyclohexane from EU RAR
[2] Calculated at STP
[3] Data for *trans*-2-Pentene used
[4] Average data for alkanes with double bonds used
[5] Average data for alkanes without double bonds used

The total NMVOC emitted in EU15 is shown in the table below.

Table 3.44b Emission of ozone precursors in EU15 (EEA 2000)

NMVOC in EU15 (Kilotonne)									
1980	1985	1990	1991	1992	1993	1994	1995	1996	1997
14434	14315	14852	14388	14037	13494	13683	13257	12904	12687

Total continental emission to air of isolated benzene (direct and from wwtp) is calculated to be about 72 000 t/a based on the production volume from 1994 - 2001. The mean total emission of NMVOC in 1994 to 1997 is approx. 13 000 kt/a. The proportion of isolated benzene relative to total NMVOC is approx. 0.5 %.

The POCP equivalence factor for the total NMVOC is not known because the composition of individual NMVOC species is not available. Benzene may have a slightly higher photochemical ozone creation potential than the average NMVOC and thus contribute slightly more to the ozone creation than indicated by the proportion of isolated benzene relative to total NMVOC.

It has to be emphasised that the local and regional NMVOC composition may have a higher concentration of benzene than indicated by the average calculations due to differences in local NMVOC sources.

To conclude isolated benzene contributes in the order of 0.5 % to the total NMVOC emission. Thus isolated benzene in general only contribute to a small extent to the total SMOG problem, however, for a single substance among hundreds of different VOCs the contribution is significant.

3.1.4 Terrestrial compartment

The topsoil terrestrial compartment receives input through the application of sludge and continuous airborne dry and wet deposition. The elimination from soil occurs via leaching, volatilisation and biodegradation. The main part that reaches soil would be expected to evaporate. These removal processes are considered in the model calculation of the PECsoil.

3.1.4.1 Release during production and processing of pure benzene

One company reported industrial soil emissions during production and processing of 132 t/a. [APA 1995]. The continental industrial soil emissions were calculated from the total European production quantity of 7 247 kt/a with the TGD default emission factors for production (0.00001) and the total European processing quantity of 5838 kt/a with the TGD default emission factors for processing (0.0001). The result of this calculation is an emission of 656 t/a.

Wet deposition

Monitoring data show that rain water contains benzene in concentrations of 0.1 to 0.46 µg/l in city areas of Berlin [Lahmann et al. 1977]. RIVM (1988) reports that the average measured concentration in rain water in the Netherlands is about 0.030 µg/l. (see appendix A II, table 5). RIVM (1988) argues that benzene in the atmosphere distributes between air and rain water according to the Henry's law constant $K_{air\text{-}water}$. At an ambient air concentration of 2 µg/m^3 and the dimensionless Henry coefficient $K_{air\text{-}water}$ of 0.178 the concentration in rain is calculated to be 11.2 ng/l. At an annual rainfall of 700 mm/a and a rainwater concentration of 10 ng/l about 24.9, 2.5 and 0.3 t/a, respectively, are rained out in the EU (area 3 560 000 km^2), Germany (356 978 km^2) and the Netherlands (41 000 km^2). Warmenhoven et al. (1989) calculated the total benzene deposition of European countries to the North Sea to be 420 t/a resulting in iso-deposition lines ranging from 32 g/km^2 a (= 88 ng/m^2 d) to 3.2 g/km^2 a (= 8.8 ng/m$_2$ d). These deposition rates are more than a factor of 1 000 lower than the deposition rates near the emitter.

Dry deposition

Experimental data on the dry deposition of benzene are lacking. With a vapour pressure of 9970 Pa at 25 °C the air/aerosol partitioning was calculated to be $Fass_{aer} = 10^{-8}$ according to the Junge equation; i.e. there is no adsorption of benzene to the aerosol solid phase. Judeikis (1982; quoted in RIVM 1988, p. 34) showed that saturation of benzene vapours in soil occurs rapidly. Chiou (1985) found that water vapour sharply reduced the sorption capacity of organic compounds to dry soil; in water-saturated soil the sorption capacity was about two orders of magniture lower.

Total deposition

The deposition was calculated as annual total deposition fluxes to soil near the emitter (see chapter 3.1.3.1). These deposition fluxes range from 0.347 to 5 361 µg/m^2 d with a mean value of 524 µg/m^2 d. Local soil deposition was calculated for three deposition fluxes: 50, 500 and the maximal value of 5 400 µg/m^2 d using the TGD algorithm. The following two tables summarise the input values and results.

Table 3.44c Input values for soil exposure

Parameter	**Value/Unit**
Input data	
Annual average total deposition flux: $DEPtotal_{ann}$	low: 50 µg m^{-2} d^{-1} mean: 500 µg m^{-2} d^{-1} maximum: 5 400 µg m^{-2} d^{-1}
Soil-water partition coefficient: $K_{soil\text{-}water}$	4.26 m^3 m^{-3}
Air-water partition coefficient: $K_{air\text{-}water}$	0.178 at 20 °C
Rate constant for removal from top soil: $kbio_{soil}$	0.023 d^{-1}
Concentration in dry sewage sludge: C_{sludge}	0 mg/kg (see chapter 3.1.4.2)
$PECregional_{soil}$: $PECregional_{natural\text{-}soil}$	20 ng/kg
Output data	
$PEClocal_{soil}$	table 3.45: three values: µg/kg

Table 3.45 Results : Local soil exposure

Endpoint	**Deposition Flux [µg/m² · d]**			**$PEClocal_{soil}$ [µg/kg]**		
Three values	low	mean	max.	low	mean	max.
natural soil	50	500	5 400	1.21	11.9	129
agricultural soil	50	500	5 400	1.21	11.9	129
grass land soil	50	500	5 400	1.33	13.2	142

Leaching

The soil sorption Koc of values between 18 to 1 023 l/kg (table 3.24) does not predict adsorption to soil particles. Benzene released to soil can move to the atmosphere through volatilisation, to surface water run-off, and to ground water if released well below the surface water. With Koc values of >18 l/kg, benzene is considered fairly mobile in soil [Kenaga 1980; Karickhoff 1981; IPCS 1993]. Leaching to ground water from soil is influenced by several parameters including soil type (sand versus clay), amount of rainfall, depth of ground water, soil pores and extent of benzene degradation.

The soil deposition fluxes of about 50 to 5 400 µg/m^2 d as a result of the emission during the production and processing of pure benzene may lead to rain wash-outs into the pore water of soil. Once „trapped“ in pore water benzene is no longer able to volatilise or biodegrade and is then transported to deeper soil levels with the effect that the ground water can be contaminated. This hypothesis may explain the fact that benzene is found in ground water at several sites in Europe. The monitored ground water concentrations at different European locations are in the range of 0.05 µg/l (see appendix A II table 3).

3.1.4.2 Release from other sources

Benzene in sewage sludge

Measurements of the benzene content in sludge from communal waste water treatment plants in the German federal state of Brandenburg indicate that benzene is generally not present in sewage sludge in winter and summer (detection limit 5.2 µg/kg dry weight) [Schnaak et al. 1995]. This result is confirmed by another source [ATV 1991; Wild and Jones 1992]. This result is also predicted by the SimpleTreat calculation that provides a 1.2 % adsorption to sewage sludge. During drying and transportation of the sewage sludge the benzene would be volatilised. The regional soil contamination through sludge is neglected.

As the sewage sludge arising from the production and/or processing of benzene in the chemical industry is for the most part disposed of by incineration, release into the soil as a result of the spreading of sewage sludge on farmland is not assumed.

Leaching from Landfills

Landfill sites are a potential, however small, source of benzene releases into the local environment. Föst et al (1989) reported the presence of benzene in 5 leachate samples from German hazardous waste landfill sites at levels of 20 to 1180 µg/l and in the leachate from sanitary landfills at lower levels of 1.1 to 572 µg/l.

Young and Parker (1983) analysed the gaseous emissions from 6 UK landfill sites for a variety of organic compounds. Benzene was found to be present at a concentration of 4.2 mg/m^3 within a landfill containing 7 month old domestic waste, and at a concentration of 23 mg/m^3 within a landfill containing 5 year old industrial waste. A high level of 114 mg/m^3 benzene was found at one point within a landfill containing domestic and industrial wastes.

3.1.4.3 Summary of soil monitoring data

Very few monitoring data exist on benzene concentrations in soil and sediments. They are not representative and do not allow a comparison with $PEClocal_{agriculture\text{-}soil}$.

Table 3.46 Benzene Concentrations in Soil Compartments

Category	Concentration Range [µg/kg]	Typical Value $PEC_{monitored}$ [µg/kg]	Appendix A II see table No
Sediments in estuaries	1-4	2	14
Gasworks site	1 000 – 2 000	contaminated: 2 000	14
Sewage sludge of municipal WWTP	0.02 – 20 mg/kg dry weight in 60-80% of samples	---	Drescher-Kaden et al. 1989
Sewage sludge of municipal WWTP	generally not detected	---	Schnaack et al. 1995

3.1.5 Non compartment specific exposure 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.

3.1.6 Continental and regional emission

3.1.6.1 Summary of exposure data

Table 3.47 below summarises the exposure data and figure 3.2 illustrates the mass flow of benzene in the environment.

Table 3.47 Summary of exposure data for benzene

Source	Total release [t/a]	Remarks
Water		
Production and/or processing [1] • to WWTP • to hydrosphere	 25 821 1591	Emission is calculated with site specific data (if available) or TGD default parameters • before treating in WWTP • after treating in WWTP
Refineries [2] • to WWTP • to hydrosphere	 26 1.6	Calculation based on DGMK, 1991 • before treating in WWTP • after treating in WWTP
Air		
production and/or processing [3] • direct • via WWTP	 60 787 11 000	Emission is calculated with site specific data (if available) or TGD default parameters
oil refineries [2] • direct • via WWTP	 985 11	 • predicted from German emission factor • calculation based on DGMK, 1991
coking plants [2]	615	Based on the emission factor for Germany in 1988
road traffic [2]	114 817	Calculation via petrol consuption and emission factor for Germany
petrol distribution [2]	2 984	Predicted from German emission factor
combustion of fossil fuels: commercial, and residential heating [2]	1 500	Predicted from the consuption of hard and brown coal in the EU
solvent use [2]	1 100	Predicted from German emission factor
waste treatment and disposal: landfill sites[2]	110	Predicted from Dutch emission inventory
Soil		
production and/or processing [4]	656	Emission is calculated with the TGD default parameters

[1] Calculation of chapter 3.1.2
[2] Calculation of chapter 3.1.1.1.3
[3] Calculation of chapter 3.1.3
[4] Calculation of chapter 3.1.4

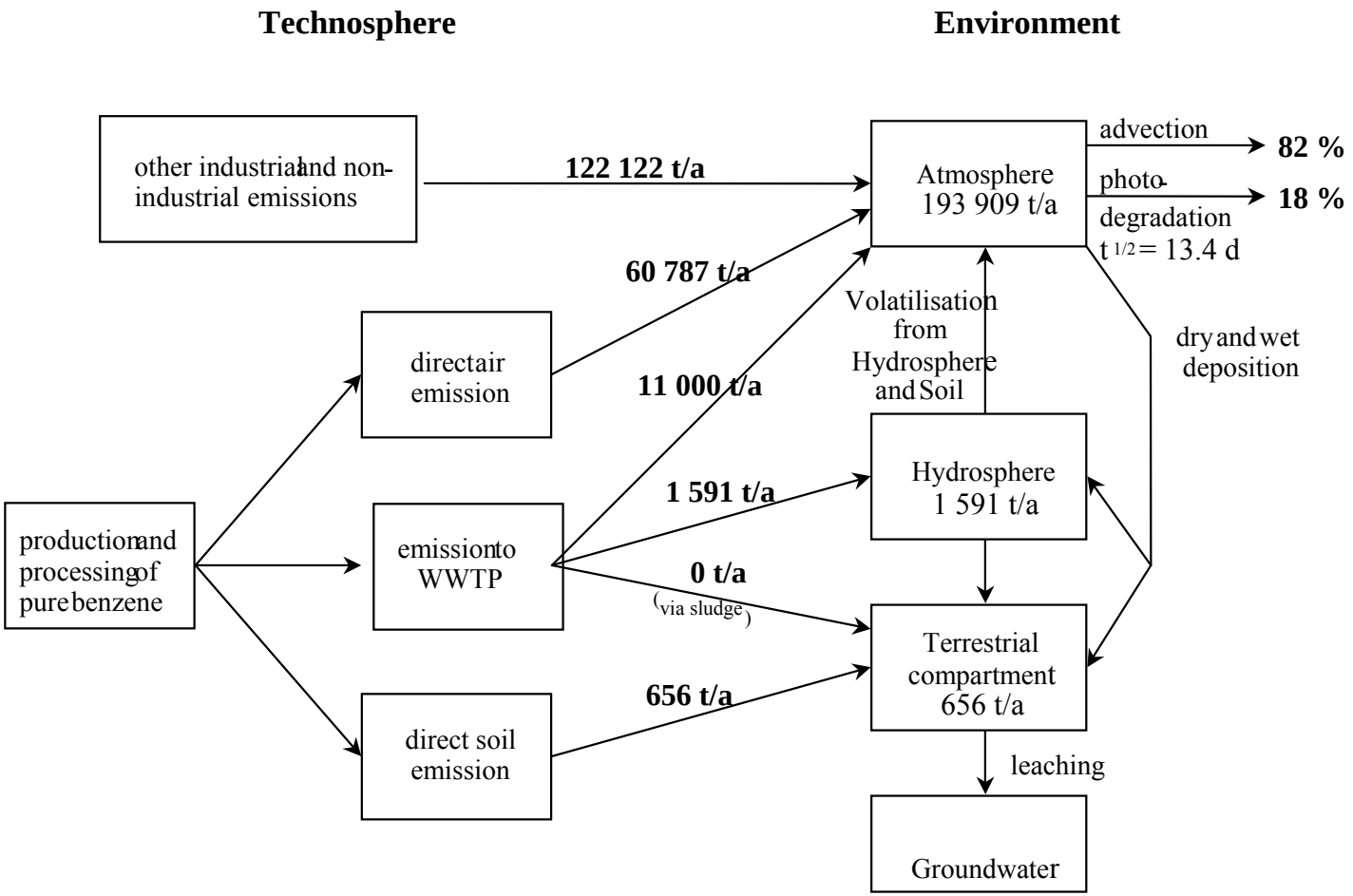


Figure 3.2: Mass flow of benzene into the environment from different sources

3.1.6.2 SimpleBox calculation

The SimpleBox calculations provide an insight in the budget of benzene moved and degraded in the boxes „Europe (continental)“ and „regional“ (200 km · 200 km). The physico chemical properties, the partition and degradation rate constants are listed in tables 1.1, 3.21 and 3.24. All releases, from point sources and diffuse sources, were considered in the determination of a regional background concentration. The calculations for the regional PECs were performed with SimpleBox 2.0. The local emissions for the production and processing of benzene were summarised and distributed between the regional and continental area at a ratio of 10% to 90%. 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 total releases were considered for the purpose of calculating the regional environmental concentrations.

Table 3.48 SimpleBox input values

release to	continental model in t/a	regional model in t/a
air (direct)	164 618	18291
industial soil	590	65.6
waste water	23 262	2 585

The figures given in the table were included exactly as they were estimated in the previous chapters in order to ensure comprehensibility. The exactitude of the figures is not, however, intended as an indication of the absolute correctness.

The input data for the model calculations are presented in detail in the appendix A III. The following regional environmental concentrations result from the calculations:

$PECregional_{aquatic}$ = 0.275 µg/l

$PECregional_{air}$ = 1.54 µg/m^3

$PECregional_{agr.soil}$ = 0.017 µg/kg

$PECregional_{natural\ soil}$ = 0.02 µg/kg

The result from this fugacity model calculation is that 99.2 % of the continental benzene is present in air. This result is in agreement with the EQC Model (chapter 3.1.1.4). and the worldwide monitoring data [Boudries, 1994 (see table 3.20)]. The conditions for the regional model are even more severe: only 6 % is degraded. This means, that all European states receive airborne benzene from their neighbours and export benzene to them.

Minor amounts are degraded in water and soil and leach into groundwater. The concentrations of the SimpleBox model agree fairly well with the monitoring data which roughly confirms the order of magnitude of the estimated emission rates.

Table 3.49 Comparison of SimpleBox and monitoring concentrations

Compartment	**SimpleBox**		**Monitoring**
	regional	**continental**	**see appendix A II**
air	1.54 µg/m^3	0.73 µg/m^3	1.5 - 4.4 µg/m^3 : pristine air 6 - 63 µg/m^3: industrial areas
water			
dissolved	0.275 µg/l	0.03 µg/l	<100-300 ng/l (Rhine) <5 µg/l Elbe, Hamburg
sediment	1.35 µg/kg	0.158 µg/kg	2.0 µg/kg
soil			
natural soil	0.02 µg/kg	0.009 µg/kg	not available
agricultural soil	0.017 µg/kg	0.008 µg/kg	not available
groundwater			
	7 ng/l	3 ng/l	5 – 30 ng/l

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

3.2.1 Aquatic compartment

A lot of toxicity tests with aquatic organisms were conducted using benzene as test substance. The results are presented in the following tables.

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.

3.2.1.1 Toxicity to fish

3.2.1.1.1 Short-term toxicity to fish

Table 3.50 shows the available valid test results for benzene obtained in short-term tests with fish.

Table 3.50 Short-term fish toxicity data

Species	Duration	Effect value [mg/l]	Test system	Reference
Oncorhynchus mykiss	96 h	LC_{50} = 5.3 (effective conc.)	flow-through	DeGraeve et al. 1982
Oncorhynchus mykiss	96 h	LC_{50} = 5.9 (effective conc.)	semistatic	Galassi et al. 1988
Oncorhynchus mykiss	96 h	LC_{50} = 21.6 (effective conc.)	flow-through	Hodson et al. 1984
Oncorhynchus kisutsch (marine/ freshwater)	96 h	LC_{50} = 12.4 (nominal conc.)	static	Moles et al. 1979
Oncorhynchus nerca	96 h	LC_{50} = 9.5 (fresh water), LC_{50} = 4.9 (sea water) (nominal conc.)	static	Moles et al. 1979
Oncorhynchus tschawytscha	96 h	LC_{50} = 10.3 (nominal conc.)	static	Moles et al. 1979
Oncorhynchus gorbuscha	96 h	LC_{50} = 15 (fresh water), LC_{50} = 7.4 (sea water) (nominal conc.)	static	Moles et al. 1979

Species	Duration	Effect value [mg/l]	Test system	Reference
Salvelinus malma (marine)	96 h	LC_{50} = 10.5 (fresh water) LC_{50} = 5.5 (sea water) (nominal conc.)	static	Moles et al. 1979
Cottus cognatus	96 h	LC_{50} = 13.5 (nominal conc.)	static	Moles et al. 1979
Thymallus arcticus	96 h	LC_{50} = 12.9 (nominal conc.)	static	Moles et al. 1979
Gasterosteus aculeatus	96 h	LC_{50} = 21.8 (nominal conc.)	static	Moles et al. 1979
Pimephales promelas	96 h 7 d	LC_{50} = 15.6 (effective conc.) LC_{50} = 14.02 (effective conc.) NOEC = 10.02 (effective conc.)	flow-through larval test effect: growth/ survival	Marchini et al. 1992
Pimephales promelas	96 h	LC_{30} = 15.1 (effective conc.)	flow-through	DeGraeve 1982
Morone saxatilis (marine)	96 h	LC_{50} = 9.58 (effective conc.)	flow-through	Meyerhoff 1975
Poecilia reticulata	96 h	LC_{50} = 28.6 (effective conc.)	semistatic	Galassi et al. 1988
Pimephales promelas	24 h 48 h 96 h	LC_{50} = 34.4 - 35.6* LC_{50} = 32 - 35.1* LC_{50} = 32 - 33.5* (nominal conc.)	static	Pickering / Henderson 1966
Lepomis macrochirus	96 h	LC_{50} = 22.49 (nominal conc.)	static	Pickering / Henderson 1966
Carassius auratus	96 h	LC_{50} = 34.42 (nominal conc.)	static	Pickering / Henderson 1966
Poecilia reticulata	96 h	LC_{50} = 36.6 (nominal conc.)	static	Pickering / Henderson 1966
Lepomis macrochirus	24 h 48 h	LC_{50} = 20 LC_{50} = 20 (nominal conc.)	static	Turnbull et al. 1954
Poecilia reticulata	14 d	LC_{50} = 63.5 (nominal conc.)	semistatic	Koenemann 1981

* test results for hard resp. soft water

Other test results are available in addition that could not be checked on validity due to missing information on test conditions.

Short-term effect values between 4.9 mg/l and 63.5 mg/l were reported. The most sensitive species seem to be the salmonids. In seawater a LC_{50} of 4.9 mg/l was derived with *Oncorhynchus necra* in a static system. The effect value was determined from the initial benzene concentration. However, the authors found a decrease of benzene concentration to 75 % after 24 hours and to 10 % after 96 hours. Therefore, the real effect value may be significantly lower than the nominal value reported by Moles et al. In freshwater, the lowest LC_{50} of 5.3 mg/l was obtained with *Oncorhynchus mykiss* in a flow-through system with analytical monitoring of the benzene concentration.

The experimental values are in general agreement with QSAR estimation according to the TGD (1996) which results in a fish (96h) LC_{50} of 49 mg/l for non polar narcotic acting substances. However, it should be noted that benzene may not only cause adverse effects due to non-polar narcotic action as the substance is a human carcinogene. Therefore, it cannot be excluded that the substance may cause ecological relevant adverse effects based on specific modes of action.

3.2.1.1.2 Long-term toxicity to fish

Results from early-life-stage tests with two fish species are available.

Black et al. (1982) tested benzene in an embryo-larval test with *Oncorhynchus mykiss* as test organism.

In a flow-through system (temperature: 13 °C; dissolved oxygen: 9.8 mg/l; water hardness: 104.3 mg/l $CaCO_3$; pH: 8.0) eggs were exposed to the test substance within 30 minutes after fertilization. Four benzene concentrations between 0.013 mg/l and 5.02 mg/l were tested. Exposure was maintained through 4 days after hatching. Average hatching time for *Oncorhynchus mykiss* was 23 days. Benzene concentration was measured daily by GLC or HPLC.

One test parameter was the egg hatchability, including all embryos (normal or aberrant). Another test parameter was the survival of normal organisms, determined at hatching and 4 days posthatching. Normal organisms were defined as those animals that were free of gross teratic defects.

In the following table the test results are presented:

Table 3.51 Embryo-larval test with *Oncorhynchus mykiss*

Benzene conc. [mg/l]	Percent hatchability	Percent survival normal organisms	Percent survival normal organisms
		at hatching	4 days posthatching
0.013	90	90	90
0.021	82	80	80
0.62	67	63	63
5.02	60	56	55

Log probit analysis was used by the authors to determine the LC_{50} at hatching and 4 days after hatching. Values of 8.64 resp. 8.25 mg/l were obtained.

No NOEC or EC_{10} was determined by the authors. Therefore an EC_{10}-value was derived by probit analysis on the basis of the available test results. An EC_{10}-value of 3.5 µg/l could be determined that can be regarded as NOEC for 23-27 day exposure.

The long-term toxicity of benzene to larvae of *Pimephales promelas* was studied by Russom and Broderius (1991) in an early life stage test (ELS). Larvae ≤ 24 h old were exposed to 5 benzene concentrations in the range of 1.5 to 25 mg/l (nominal) and a control in a flow-through system for 32 days (temperature: 25.5 °C, dissolved oxygen: 6 mg/l, water hardness: 46 mg/l $CaCO_3$, pH: 7.7). Hatching of the larvae was finished after 120 hours. The test concentration was measured at least twice a week during the exposure period. The major test endpoints were percentage of normal larvae at hatch, percent survival and growth effects such as wet weight, length and dry weight. For benzene a LOEC of 1.6 mg/l was found for the endpoints wet weight and total length. From this value a NOEC of 0.8 mg/l can be dervied according to the TGD, as the LOEC was in the range of 10-20 % effect.

This value is reasonably in agreement with QSAR estimations of values for chronic toxicity on fish and by the TGD for non-polar acting substances of 4.73 mg/l (30 days, FELST). However, it should be noted that benzene may not only cause adverse effects due to non-polar narcotic action as the substance is a human carcinogene. Therefore, it cannot be excluded that the substance may cause ecological relevant adverse effects based on specific modes of action.

3.2.1.2 Toxicity to aquatic invertebrates

3.2.1.2.1 Short-term toxicity to invertebrates

Table 3.52 shows the available valid test results for benzene obtained in short-term tests with invertebrates.

Table 3.52 Short-term invertebrate toxicity data

Species	Duration	Effect value [mg/l]	Effect	Test system	Reference
Daphnia magna	24 h	EC_{50} = 18 (effective conc.)	immobilization	closed system	Galassi et al. 1988
Daphnia magna	24 h 48 h	EC_{50} = 10 EC_{50} = 10 (nominal conc.)	immobilization		Janssen/Persoone 1993
Daphnia pulex	96 h	LC_{50} = 15 mg/l (effective conc.)	mortality	closed system	Trucco et al. 1983
Ceriodaphnia dubia	48 h	LC50 = 17.2 (effective conc.)	mortality	closed system	Niederlehner et al. 1998
Ischnura elegans	48 h	LC_{50} = 10 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Gammarus pulex	48 h	LC_{50} = 42 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Cloëon dipterum	48 h	LC_{50} = 34 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Corixa punctata	48 h	LC_{50} = 48 (nominal conc.)	mortality	closed system	Sloof et al. 1983

Species	Duration	Effect value [mg/l]	Effect	Test system	Reference
Chironomus gr. thummi	48 h	LC_{50} = 100 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Asellus aquaticus	48 h	LC_{50} = 120 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Erpobdella octoculata	48 h	LC_{50} > 320 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Lymnaea stagnalis	48 h	LC_{50} = 230 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Hydra oligactis	48 h	LC_{50} = 34 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Dugesia cf. lugubris	48 h	LC_{50} = 74 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Tubificidae (*Limnodrilus sp.* and *Tubifex sp.*)	48 h	LC_{50} > 320 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Nemoura cinerea	48 h	LC_{50} = 130 (nominal conc.)	mortality	closed system	Sloof et al. 1983
Artemia salina (hypersaline waters)	24 h 48 h	LC_{50} = 66 LC_{50} = 21 (nominal conc.)	mortality		Price et al. 1974
Nitocra spinipes (marine)	24 h	LC_{50} = 82 (salinity: 1.5 %) LC_{50} = 111.5 (salinity: 2.5 %) (nominal conc.)	mortality		Potera 1975
Palaemonetes pugio (marine)	24 h	LC_{50} = 38 (salinity: 1.5 %) LC_{50} = 33.5 (salinity: 2.5 %) (nominal conc.)	mortality		Potera 1975
Aedes aegypti (4th instar larvae)	24 h	LC_0 = 12.9 LC_{50} = 59	mortality		Berry/Brammer 1977
Cancer magister (marine)	96 h	LC_{50} = 108 (nominal conc.)	mortality		Caldwell et al. 1977
Palaemonetes pugio (marine)	24 h 48 h 96 h	LC_{50} = 43.5 LC_{50} = 35 LC_{50} = 27 (nominal conc.)	mortality	open	Tatem et al. 1978

Other test results are available in addition that could not be checked on validity due to missing information on test conditions.

Effect values in the range from 10 to > 320 mg/l were found for different invertebrate species. Among them daphnia seems to be most sensitive to benzene. EC_{50}-values between 10 and 18 mg/l were found for it. The lowest EC_{50} of 10 mg/l after 48 h was obtained by Janssen and Persoone (1993). Although this value is based on nominal concentrations and therefore the effective concentration could be significantly lower it is used as effect value for short-term toxicity with invertebrates in the assessment.

The experimental EC_{50} (48h) for *Daphnia* is in general agreement with QSAR estimations according to the TGD (1996) which results in a Daphnia (48h) EC_{50} of 35.4 mg/l for non-polar narcotic acting substances. However, it should be noted that benzene may not only cause adverse effects due to non-polar narcotic action as the substance is a human carcinogene. Therefore, it cannot be excluded that the substance may cause ecological relevant adverse effects based on specific modes of action.

3.2.1.2.2 Long-term toxicity to invertebrates

The reproductive toxicity of benzene on *Ceriodaphnia dubia* in a 7-day semi-static closed glass vial system was studied by Niederlehner et al. (1998). A NOEC of 3 mg/l, a LOEC of 8.9 mg/l and an EC_{50} of 11.6 mg/l was found. All effect values are related to measured concentrations.

Caldwell et al. (1977) tested the long-term toxicity of benzene to the marine dungeness crab (*Cancer magister*). In two assays the larvae (progenies of 1 female crab collected in the wild) were exposed within few hours of hatching to three different benzene concentrations in seawater (0.17/0.18 mg/l, 1.1/1.2 mg/l and 6.5/7 mg/l in the 1st and 2nd assay) in a flow-through system for up to 60 days. Benzene concentration was measured routinely by UV absorption methods. The mortality, the duration of the larval stages and the size of larvae have been examined. Control mortality increased steadily during the two tests. At the end of the experiments control survival was only10 % in the fist assay and about 35 % in the second. At the lowest benzene concentration no significant effect was found compared to the control. At 1.1 resp. 1.2 mg/l and 6.5 resp. 7 mg/l all larvae died between day 10 and day 20. The mortality rate at the lower concentrations was less than that at the concentration of 6.5-7 mg/l. No influence of benzene on the duration of the larval stages and the size of the larvae was found. From the poor control survival it can be concluded, that the test animals were in poor health and/or stressed by test factors other than the benzene exposure. Therefore, the result of this study cannot be used for risk assessment purposes.

Cantelmo et al. (1981) determined the effect of benzene on molting of juvenile *Callinectes sapidus* (blue crab, marine). Crabs collected from the wild were induced to automize the third appendage. One group was exposed to a nominal benzene concentration of 1 mg/l, the other group served as control. The test solution was changed every 24 hours, while the water of the control animals was changed only twice per week. To assess the concentration of benzene in the test solution the actual concentrations were monitored in a control experiment by GC analysis. Over a 9 hour period the benzene concentration fell linearly until it stabilizes at 0.26 - 0.3 mg/l 6 hour after the introduction. The authors concluded that the animals were exposed to 260 - 300 µg/l for 18 hour each day. It was found that the animals were significantly influenced by the benzene exposure. 35 % of the exposed animals molted during the study

compared to 69 % of the control animals. 56 % of the exposed crabs died before molting, of the controls 23 % died. The percentage of crabs that died during ecdysis was nearly the same for both conditions (8.2 % and 9.4%). The time required to molt was significantly increased for animals exposed to benzene. The control animals took an average of 33 days while the benzene treated animals required an average of 50 days.

The study shows several validity restrictions: as the solutions of the test and control animals was not changed at the same intervalls, the test animals were exposed to a different regime of carrier solvent than the control animals. In addition, it is not clear from the paper, whether the controls were run in parallel with the treatments or independently. Therefore, no direct comparison is possible. The molting of only 69 % of the animals in the control group and the dead of 23 % of the control animals before molting is not acceptable. Therefore, the result of this study cannot be used for risk assessment purposes.

Therefore, the NOEC of 3 mg/l found for *Ceriodaphnia dubia* is used as long-term effect value for invertebrates in the further assessment.

This value in general agreement with QSAR estimations of values for chronic toxicity on *Daphnia* by the TGD for non-polar acting substances of 6.4 mg/l (16 days, reproduction). However, it should be noted that benzene may not only cause adverse effects due to non-polar narcotic action as the substance is a human carcinogene. Therefore, it cannot be excluded that the substance may cause ecological relevant adverse effects based on specific modes of action.

3.2.1.3 Toxicity to aquatic plants

The following table shows the results from available valid tests on aquatic plants with benzene as test substance.

Table 3.53 Algae toxicity data

Species	Duration	Effect value [mg/l]	Effect	Test system	Reference
Selenastrum capricornutum	72 h	E_bC_{50} = 28 E_rC_{50} = 100 E_bC_{10} = 8.3 E_rC_{10} = 34 (effective conc.)	growth inhibition	closed system	TNO 2000
Selenastrum capricornutum	72 h	EC_{50} = 29 (effective conc.)	growth inhibition	closed system	Galassi et al. 1988
Selenastrum capricornutum	8 d	EC_{50} = 41 (nominal conc.)	growth inhibition (biomass)	closed system	Herman et al. 1990

Selenastrum capricornutum	4 h	EC_5 = 10 EC_{16} = 100 EC_{95} = 1000 (nominal conc.)	inhibition of photosynthesis		Giddings 1979
Ankistrodesmus falcatus	4 h	EC_{50} = 310 (nominal conc.)	inhibition of ^{14}C-carbonate uptake	closed system	Wong et al. 1984
Chlamydomonas angulosa.	3 h	EC_{50} = 461 (nominal conc.)	inhibition of $^{14}CO_2$ uptake	closed system	Hutchinson et al. 1980
Chlorella vulgaris	3 h	EC_{50} = 312.5 (nominal conc.)	inhibition of $^{14}CO_2$ uptake	closed system	Hutchinson et al. 1980
Phaeodactylum tricornutum (marine)	2 h 24 h	LOEC = 100 LOEC = 50 (nominal conc.)	inhibition of photosynthesis	closed system	Kusk 1981
Phaeodactylum tricornutum (marine)	96 h	LOEC = 50 (nominal conc.)	growth inhibition	closed system	Kusk 1981
Akrosiphonia sonderi (marine)	2 h	$175<EC_{50}<350$ (nominal conc.)	inhibition of photosynthesis	closed system	Kusk 1980

Among the available algae toxicity tests only 2 studies with a standardised exposure period of 72 hours are available. In both studies closed systems were employed and the effect values are based on measured concentrations. As in the study of Galassi et al. only an EC_{50} value was derived and no information is available on the no effect level, the results found by. TNO will be used for the further effects assessment.

These experimental values are in general agreement with QSAR estimations according to the TGD (1996) which results in an algae (72-96h) EC_{50} of 34 mg/l. However, it should be noted that benzene may not only cause adverse effects due to non-polar narcotic action as the substance is a human carcinogene. Therefore, it cannot be excluded that the substance may cause ecological relevant adverse effects based on specific modes of action.

3.2.1.4 Toxicity to amphibians

In an embryo-larval test with the amphibian species *Rana pipiens* (Leopard frog) and *Ambystoma gracile* (Northwestern Salamander) different benzene concentrations were tested by Black et al. (1982).

In a flow-through system (temperature: 20.2 ± 0.5 °C; dissolved oxygen: 7.5 mg/l; water hardness: 96.6 ± 1 mg/l $CaCO_3$; pH: 7.7 ± 0.02) eggs were exposed to 5 resp. 6 different benzene concentrations within 30 minutes of fertilization for *Rana pipiens* and within 2-8 hours postspawning for *Ambystoma gracile*. Exposure was maintained through 4 days after hatching. Average hatching time was 5 days for *Rana pipiens* and 5.5 days for *Ambystoma gracile*. Benzene concentration was measured daily by GLC or HPLC.

Test parameters were egg hatchability, including all embryos (normal or aberrant) and survival of normal organisms determined at hatching and 4 days posthatching. Normal organisms were determined as those organisms that were free of gross teratic defects.

The following test results were obtained:

Table 3.54 Embryo-larval test with *Rana pipiens*

Benzene conc. [mg/l]	Percent hatchability	Percent survival of normal organisms	Percent survival of normal organisms
		at hatching	4 days posthatching
0.016	95	95	95
0.048	90	90	90
0.61	81	81	79
2.99	64	64	62
5.07	39	32	32

Table 3.55 Embryo-larval test with *Ambystoma gracile*

Benzene conc. [mg/l]	Percent hatchability	Percent survival of normal organisms	Percent survival of normal organisms
		at hatching	4 days posthatching
0.016	99	99	99
0.044	97	97	97
0.61	89	89	87
2.69	75	75	70
5.43	49	44	44
36.7	31	23	15

Log probit analysis was used by the authors to determine the LC_{50} at hatching and 4 days after hatching. For *Rana pipiens* values of 4.03 resp. 3.66 mg/l and for *Ambystoma gracile* of 6.68 and 5.21 mg/l were calculated.

Additionally, the authors determined with the same statistical method LC_1- and LC_{10}-values at 4 days posthatching. For *Rana pipiens* a LC_1-value of 3.2 µg/l and a LC_{10}-value of 75.6 µg/l was determined, while for *Ambystoma gracile* values of 68.2 resp. 478.1 µg/l were obtained.

3.2.1.5 Toxicity to microorganisms

Table 3.56a shows the available results from tests with miocroorganisms.

Table 3.56a Microorganism toxicity data

Species	Duration	Effect value [mg/l]	Effect	Reference
Pseudomonas putida	16 h	TGK* = 92 (nominal conc.)	cell multiplication inhibition	Bringmann/Kühn 1980
Nitrosomonas spec.	24 h	IC_{50} = 13 (nominal conc.)	inhibition of ammonia consumption	Blum/Speece 1991
activated sludge	15 h	IC_{50} = 520 (nominal conc.)	inhibition of oxygen uptake	Blum/Speece 1991
methanogens	48 h	IC_{50} = 1200 (nominal conc.)	inhibition of gas production	Blum/Speece 1991
Tetrahymena pyriformis	24 h	EC_0 = 391 (nominal conc.)	cessation of ciliary movement	Rogerson et al. 1983

*TGK = EC_3

Blum/Speece (1991) and Rogerson et al. (1983) conducted their toxicity tests in closed systems. For the test with *Pseudomonas putida* (Bringmann/Kühn 1980) it is unclear whether it was conducted in sealed vessels.

The most sensitive microorgamism species was *Nitrosomonas* spec. Therefore, the effect value from this test will be used for the risk assessment of sewage treatment plants.

3.2.1.6 Determination of PNEC for water

A lot of ecotoxicity tests with a variety of different species are available for benzene. However, most tests are short-term studies.

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), comparing to a somewhat lower overall sensitivity of algae.

The lowest effect value was obtained in an embryo-larval-test conducted with *Oncorhynchus mykiss*. In this test Black et al. (1982) found a 23-27 d EC_{10} for hatching and survival of 3.5 µg/l. The effect values found by Black et al. for several substances (e.g. toluene) are usually very low compared to effect values found by other authors. No explanation for these large discrepancies could be found. A careful examination of the entire information provided

by Black et al. gave no plausible reason for the inconsistency of the data.. However, as it was not possible to reproduce the effect values found by Black and his co-workers, it was decided by the EU member states not to use these data for a derivation of a PNECaqua if other valid fish early life stage tests are available. Therefore, the effect values found by Black et al. for *Oncorhynchus mykiss* are not employed in the further effects assessment. Also the effect values found by Black et al. for the amphibian species *Rana pipiens* and *Ambystoma gracile* are not used for the effects assessment for the same reason. As there are no other tests with amphibians from other authors available, it cannot be exluded that amphibian species may be more sensitive to benzene than other aquatic species.

Instead, the NOEC of 0.8 mg/l found by Russom and Boderius in the ELS test with *Pimephales promelas* is used as basic value for the PNECaqua derivation.

Long-term tests with species from three trophic levels are available. Therefore, the application of an assessment factor of 10 on the lowest NOEC is justified.

Therefore: **$PNEC_{aqua}$ = 0.8 mg/l / 10 = 0.08 mg/l**

3.2.1.7 Determination of PNEC for microorganisms in WWTP

The lowest result (24 h-EC_{50} = 13 mg/l) was obtained with a test conducted with nitrifying bacteria. According to the TGD an assessment factor of 10 has to be applied to this value.

Therefore: **$PNEC_{microorganism}$ = 13 mg/l / 10 = 1.3 mg/l**

3.2.1.8 Determination of PNEC for sediment

Not enough data are available on the occurrence of benzene in sediment. Neither are there any results from sediment tests with benthic organisms. 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 on plants

Only a few results were available to support an effects assessment in the atmosphere.

Currier (1951) exposed young plants (barley, tomatoes, carrots) to benzene vapour at different test concentrations (172, 250 and 500 g/m^3). Kind and percent injury (reference: leaf area) were monitored in addition to death rate after short-term exposure lasting 0.25 - 2 (4) h. The determination of death and effect rates was carried out 24 h and 1, 2 and 4 weeks after the treatment. A 2 h exposure to 250 g/m^3 resulted in 100 % injury and death in tomatoes; the injury rates in barley and carrots were 98 % and 95 % respectively. Exposure to 172 g/m^3 and

lasting up to 4 h lead to 100 % recovery in barley within 4 weeks. In addition, growth stimulation in the exposed plants was observed at concentration levels which produced no or very slight injuries. (With regard to the original concentration figures presented by the author, it should be kept in mind that they were „erroneously reported too low by a factor of 10“ (Currier and Peoples 1954, p. 156)). In essence, Currier and Peoples (1954) confirmed the information given by Currier (1951) on the low susceptibility of higher plants to benzene as vapour or in aqueous solution. They found e.g. that 4 h exposure of barley to 94 g/m^3 benzene resulted in no injury 1 day, 2 and 4 weeks after exposure. 8 h exposure to the same concentration resulted in “trace” injury.

Pinckard et al. (1939) exposed tobacco seedlings to benzene in air in fumigation chambers under varying conditions. In one experimental series, comparative tests in closed systems without gas flow were conducted. Young seedlings were either exposed potted in bell jars or were appended in suction flasks, protecting their roots against direct benzene exposure by wrapping. The seedlings were treated for 12 - 19 h with benzene concentrations ranging from 32 to 160 g/m^3 at temperatures of 23.5 - 26.1 °C. Further investigations were carried out in chambers with continuous renewal of the air-benzene mixture. In these tests, 10 h exposure to concentrations in the range of ca. 3.2 to 130 g/m^3 at different temperatures (9°C and 25.5 °C) was chosen. In all tests the degree of injury (flaccid appearance, necrosis), potential for recovery and death rate were monitored. In the investigations employing flow-through exposure conditions, the susceptibility of dry and wet seedlings was compared, too.

In addition, the comparative impact of pure and commercial benzene (purity 90 %, toluene content 4 %) was explored. In the test chambers without continuous renewal first signs of injury were observed at 32.4 g/m^3 (commercial benzene) in one of two test sets. This value may be regarded as a potential toxicological threshold concentration for the commercial product. In the tests with flow-through conditions somewhat lower, though very similar results were obtained, indicating the position of the no-effect level. An EC_0 of 17.2 g/m^3 could be established for pure benzene at 26 °C referring to dry seedlings. For wet seedlings and the commercial product an EC_0 of 32.4 g/m^3 was obtained (9 °C). While these results are influenced by the different spacing of test concentrations, the respective concentration levels for 100 % mortality pointed to an overall higher impact on exposed wet seedlings: at about 100 g/m^3 dry seedlings suffer only moderate injuries when exposed to pure benzene (LC_{100} about 130 g/m^3) while all wet plants were killed even when exposed to the less potent commercial product. With regard to the reliability of the discussed effect values it is mentioned that they represent average values originating from several tests per concentration. Exposure concentrations < 32 g/m^3 were calculated, the higher ones measured. It should be taken into account that the injury rates recorded include a short recovery time (up to 2 h).

Summary:

Benzene seems not to be of concern for plants with regard to exposure via the atmosphere except at very high concentrations. No formal PNEC will be 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.

Regarding effects of ozone (which benzene may contribute to the formation of) the CSTEE in their “Opinion on Risk assessment underpinning new standards and thresholds in the proposal for a daughter directive for tropospheric ozone", adopted at the CSTEE by written procedure on May 21, 1999”, comments:

“The effects of ozone on vegetation are also documented. Similarly to humans, oxidative stress/damage due to reaction with unsaturated organic compounds, sulphydryl compounds, formation of aldehydes, hydrogen peroxide, as well as cellular changes including altered membrane permeability are described. More specifically, reduced photosynthesis, impaired CO2 fixation and altered cell growth leading to reduction in root/shoot ratios and in flower formation are observed. This may result in ecological balance shifts as less ozone-sensitive species are favoured.

Presumably a tolerance phenomenon occurs in plants with continual exposure, though it appears to be poorly documented.”

Further: “For neither man, animals nor for plants has a threshold been established for either acute or chronic effects. This raises the issue of what type and degree of change is of health significance

From an environmental management viewpoint there is a major additional problem as indicated above that in many areas, ozone levels are above those levels where some biological effects are known to occur. “

and

“However, the CSTEE noted that there are several factors that can affect the toxicity of ozone for plants and large differences in the actual threshold must be expected for different environmental and ecological conditions.”

Effects on animals and humans are expected within the same range of exposure.

The current threshold values in use in the EU according to Directive 92/72/EEC are shown in the table below.

Table 3.56b Threshold values for ozone concentrations set in Directive 92/72/EEC (EC, 1992)

Threshold for:	Concentration (in µg/m3)	Averaging period (h)
Health protection	110	8
Vegetation protection	200 65	1 24
Population information	180	1
Population warning	360	1

These threshold values are currently being revised in order to prepare a new EU Directive on troposheric ozone. The new proposal of thresholds are set at observable effects of 5% reduction in yield for crops and a decrease of 10% in biomass for forests. Changes below these levels were considered to be statistically not significant and of low relevance in ecological terms (CSTEE 1999). It is noted that the threshold values for ozone are approximately at the same level for protection of both the human health and the health of vegetation.

3.2.3 Terrestrial compartment

Information about benzene impact on terrestrial organisms is extremely scanty. The only available tests that were conducted with soil were two 14 d growth tests with higher plants (*Avena sativa* and *Brassica rapa*) and a 28 d mortality test with earthworms (*Eisenia fetida*). All three tests were performed within the frame of a research project (Kördel et al. 1984/ Korte and Freitag 1984) and conducted according to the respective OECD guidelines. In none of the tests growth inhibition respectively mortality was observed as effect of exposure to benzene concentrations ranging from 0.1 - 1000 mg/kg. In plants even growth stimulation was found at all concentrations tested. Taking into account both the high volatility of benzene and the lack of measured benzene concentrations in soil it can be concluded that the results of the studies suffer serious validity restrictions. Nevertheless, considering the data reported on half-life and biodegradation of benzene in soil (chapter 3.1.4.1; Tab. 3.45) a decrease in benzene content of more than 50 % during the first 5 to 6 days of exposure appears to be unlikely. Therefore, the results obtained for that exposure period can be used to derive a concentration level of about 700 - 800 mg/kg below which no growth inhibition respectivley mortality in the test organisms should be expected.

In addition to the above cited tests the toxicity of benzene to earthworms (*Eisenia fetida*) was examined in filter paper contact tests by Roberts and Dorough (1984) and by Neuhauser et al.

(1986). In both studies earthworms were individually exposed to benzene in capped paper-lined glass vials for 48 hours in the dark. Roberts and Dorough found an 48 h-LC_{50} value of 0.1 - 1 mg/cm^2. In the paper from Neuhauser et al. a 48 h-LC_{50} of 98 µg/cm^2 is given.

As Heimbach (1984, 1988) demonstrated the poor correlation between results from filter tests and those from artificial soil tests conducted with the same substance, these two values were not used in the risk assessment.

A $PNEC_{soil}$ is not determined from the discussed data as it is not possible to derive an exact effect value from the given soil tests. Therefore, the PNECsoil is derived from the PNECaqua of 0.08 mg/l using the equilibrium parttioning method:

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

Using a $Ksoil_{-water}$ of 4.26 m^3/m^3 and a RHO_{SOil} of 1700 kg/m^{-3} results in a $PNEC_{soil}$ of:

Therefore: **$PNEC_{soil}$ = 0.2 mg/kg**

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

3.3.1.1 Summary of PEC's and comparison with the PNEC's

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, for the site specific ratios see table 3.57).

Surface water

The reported monitoring data of benzene in surface fresh water are between < 0.1 µg/l and 31.7 µg/l, in sea water and estuaries < 0.005 – 89.4 µg/l and in groundwater 0.005 - 1250 µg/l.

A regional background concentration of 0.28 µg/l for benzene in the hydrosphere is calculated from all of the releases of benzene into the environment (see chapter 3.1.6). This background concentration is added to the $Clocal_{water}$ calculated in chapter 3.1.2. thus obtaining the PEClocal concentrations for the individual point sources.

The data for the calculation of the $Clocal_{water}$ are summarized for each individual company in table 3.33. In the calculations it was assumed that the companies are connected to an in-house biological waste-water treatment plant. This means that considerably higher concentrations in surface water can be expected if individual companies release their waste water directly into the receiving stream as direct dischargers.

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 only 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 (for the site specific ratios see table 3.57) involved in the production and/or processing of benzene. The currently available data indicate a risk to the aquatic biocenosis for these sites.

Table 3.57 Site specific PEC/PNEC ratios for the aquatic compartment

Site	Site specific exposure data[1)]	Elimination in WWTP	Volume flow of WWPT[2)]	Dilution or river flow[3)]	$Clocal_{effl}$ / $PNEC_{microorg.}$	$PEClocal_{water}$ /$PNEC_{aqua}$	Remarks
Production							
P1	available	SimpleTreat	site specific	site specific	0.1	0.004	
P2	available	site-specific	site-specific	default	< 0.1	0.005	
P3	available	SimpleTreat	site specific	site specific	0.9	0.53	
P4	not available	SimpleTreat	Default	default	31.7	0.20	
P5	available	/	/	default	< 0.1	0.016	no WWPT on site
P6	available	SimpleTreat	site specific	default	< 0.1	0.010	
P7	available	SimpleTreat	site specific	site specific	< 0.1	0.004	
P8	available	SimpleTreat	site specific	site specific	< 0.1	0.004	
P9	not available	SimpleTreat	Default	site specific	58.7	0.025	
P10	not available	SimpleTreat	Default	Default	14.3	0.093	
P11	available	site-specific	site specific	Default	< 0.1	0.015	
P12							closed in 1999
P13	available	/	/	Default	/	0.63	no wwtp
P14	not available	SimpleTreat	Default	Default	29.8	0.19	
Prod. And Proc.							
PP1	not available	SimpleTreat	Default	Default	71.2	0.45	
PP2	not available	SimpleTreat	site specific	site specific	9.2	0.50	
PP3	available	SimpleTreat	site specific	Default	0.32	0.53	
PP4	available	SimpleTreat	Default	Default	17.9	0.12	
PP5	available	site specific	site specific	site specific	< 0.1	0.005	
PP6	available	SimpleTreat	Default	site specific	< 0.1	0.004	
PP7	available	site specific	site specific	Default	< 0.1	0.004	
PP8	not available	SimpleTreat	Default	Default	42.0	0.27	
PP9	not available	SimpleTreat	site specific	site specific	22.5	0.37	
PP10	available	SimpleTreat	Default	Default	25.6	0.16	
PP11	not available	SimpleTreat	Default	Default	78.2	0.49	
PP12	available	SimpleTreat	site specific	site specific	< 0.1	0.006	

Site	Site specific exposure data[1)]	Elimination in WWTP	Volume flow of WWPT[2)]	Dilution or river flow[3)]	$Clocal_{effl}$ / $PNEC_{microorg.}$	$PEClocal_{water}$ /$PNEC_{aqua}$	Remarks
PP13	available	SimpleTreat	default	Default	4.3	0.030	
PP14	available	SimpleTreat	site specific	site specific	< 0.1	0.004	
PP15	not available	SimpleTreat	default	Default	44.6	0.28	
PP16	not available	SimpleTreat	site specific	Default	36.4	59.15	
PP17	not available	SimpleTreat	site specific	Default	17.6	28.63	
PP18	not available	SimpleTreat	default	Default	39.1	0.25	
PP19	not available	SimpleTreat	default	Default	7.8	0.05	
PP20	available	SimpleTreat	site specific	site specific	0.2	0.058	
PP21							
PP22	available	/	/	Default	/	0.126	no wwtp
Processing							
Pc1	not available	SimpleTreat	default	Default	5.5	0.038	
Pc2	available	SimpleTreat	site specific	site specific	< 0.1	0.004	
Pc3	not available	SimpleTreat	site specific	site specific	0.35	0.018	
Pc4	not available	SimpleTreat	site specific	site specific	4.7	0.036	
Pc5	not available	SimpleTreat	default	Default	2.7	0.02	
Pc6	not available	SimpleTreat	default	site specific	< 0.1	0.004	
Pc7							import only
Pc8	available	SimpleTreat	site-specific	site-specific	< 0.1	0.01	
Pc9	not available	SimpleTreat	default	default	38.3	0.24	
Pc10	not available	SimpleTreat	default	default	3.8	0.028	
Pc11	not available	SimpleTreat	default	default	5.5	0.038	
Pc12	available	SimpleTreat	default	default	< 0.1	0.004	
generic scenario	not available	SimpleTreat	default	default	54.7	0.35	

[1)] If no site specific and/or not traceable data on exposure were available, the default values from the TGD were used (see table 3.1)
[2)] The default value is 2000 m^3/d.
[3)] The dafault value is D = 10 for emission to the sea or the river flow is 60 m^3/s.

3.3.1.2 Individual risk characterisation

Waste-water treatment plants

Result for sites with $Clocal_{effl}$ /$PNEC_{microorganism}$ ratio is < 1

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

This conclusion applies also to municipal waste water treatment plants.

Result for sites with $Clocal_{effl}$ /$PNEC_{microorganism}$ ratio is > 1

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.

A further possibility would be to improve the data basis by performing a nitrification inhibition test with industrial sludge, which is assumed to be more realistic for the effect assessment for industrial wwtp. However, it was not possible to identify representative wwtp with a relevant nitrification potential. A reason for this could be that nitrification is not a significant process in industrial wwtp from benzene production and processing sites, but there is not enough information to firmly draw this conclusion. Furthermore, several benzene production / processing sites are known to handle other industrial chemicals including nitro- or amino-compounds and for these sites nitrification may be an important process in the wwtp.

If the nitrification inhibition test would not be considered relevant for the industrial treatment plants, alternatively result of the available activated sludge respiration inhibition test could be used to derive a $PNEC_{microorganism}$ of 5.2 mg/l. But even with this PNEC a risk for 21 of 48 industrial wwtp has to be assumed.

It is not expected that the performance of a test with industrial sludge will 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).

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

Surface water

Result for sites with PEClocal/PNEC ratio is < 1

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

This conclusion applies also to the aquatic compartment at the regional level.

Result for sites with PEClocal/PNEC ratio is > 1

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 tracable exposure data for these sites with reasonable effort.

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

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.

Direct releases into the atmosphere occur during production and processing of pure benzene (about 60 787 t/a). Indirect releases come from stripping processes in waste water treatment plants. According to the SimpleTreat calculations 42.6 % of the releases are accounted to the air (about 11 000 t/a). Thus, WWTP are a not negligible source of benzene.

The calculated $Clocal_{air\text{-}annual}$ ranging 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.

As derived in Chapter 3.2.2, the 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 and for risk reduction measures beyond those which are being applied already.

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.

Changes in VOC emissions lead to changes in ozone formation. The efficiency of VOC emission reductions in reducing ground level ozone concentrations may vary from place to place and is depend on the occurrence of NO_x, the solar radiation and the prevailing wind conditions. Thus the effects on ozone creation of emissions arising from the production and use of the isolated commercial product benzene may differ substantially between different regions in the EU.

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.

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 are documented on plants, animals and humans. Reporting on monitoring results are most frequently done in relation to exceedance of thresholds for information or warning of the human population, but this reporting may also give indication on the magnitude of environmental effects, because effect concentrations seem to be in the same order of magnitude for both vegetation and humans. The threshold values set by the European Union to protect human health and the vegetation are frequently exceeded (cf. e.g. De Leeuw et al, 1996)

In 1995 90% of the EU population (both urban and rural) experienced an exceedance of the current EU threshold for health protection (110 240 μg/m3, 8h average) for at least one day during the summer 1995. Over 80% experienced exposure above the threshold for more than 25 days. The highest concentrations (≥240 μg/m3) were recorded in Italy and Greece (WHO 1999, cf. also DeLeeuw et al, 1996)).

In 1999 the threshold for information of the public in EU (180 μg/m3, 1h average) were not exceeded in 4 member states while up to 70% of the monitoring stations in other member states did exceed this threshold (Sluyter & Camu 1999). On average 27% of all monitoring stations in EU did exceed the threshold. The number of days that the threshold were exceeded ranged from 2 days in Luxembourg to 68 days in Italy (out of 153 days in the reporting season).

The severity of exceedance of the EU threshold for health protection (110 µg/m3, 8h average) has been estimated by WHO (1999). The 1995 summer ozone incidence is estimated to have caused 1500-3700 deaths (0.1-0.2% of all deaths) and further 300-1000 extra emergency hospital admissions due to respiratory diseases. "It is likely that the total number of health impacts is higher than the estimated impact of the days with high levels only. This is suggested by epidemiological studies where the effects can be seen also below the 110 µg/m3 level." (WHO 1999).

If these figures are used to estimate the impact of emissions from the production and use of the commercial product benzene through formation of ozone then this emission may have caused around 15 deaths in the summer of 1995 if a linear relationship 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.

Conclusion (iii) There is a need for limiting the risk; risk reduction measures which are already 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

A regional background concentration of 0.02 µg/kg is calculated from all of the releases of benzene into the environment (see chapter 3.1.6). This background concentration relates to natural soil which is not contaminated as a result of direct emission or is not located in the immediate vicinity of a point source (production/processing of pure benzene).

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 (see chapter 3.1.4) for three typical companies which produce and/or processe pure benzene. Based on the deposition fluxes of 50, 500 and 5 400 $\mu g/m^2 \cdot d$ 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 and for risk reduction measures beyond those which are being applied already.

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 and for risk reduction measures beyond those which are being applied already.

Air compartment

The major releases of benzene to the atmosphere are automotive exhaust emissions, evaporative losses and combustion of fossil materials. The total emission from these sources are summarized in chapter 3.1.1.1.4, table 3.16. 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 (see chapter 3.1.6.2).

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 fro 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.

Result

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

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.

Changes in VOC emissions lead to changes in ozone formation. The efficiency of VOC emission reductions in reducing ground level ozone concentrations may vary from place to place and is depend on the occurrence of NO_x, the solar radiation and the prevailing wind conditions. Thus the effects on ozone creation of emissions arising from the production and use of the isolated commercial product benzene may differ substantially between different regions in the EU.

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.

Conclusion (iii) There is a need for limiting the risk; risk reduction measures which are already 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 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

The potential of benzene exposure to workers occurs in a range of industries and occupations, the most significant occupations being petroleum production, refining and distribution, chemical plants, coke oven operations, and transportation of benzene and gasoline.

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. 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. Until 31.12.1999, the maximum content of benzene in gasoline was 5 % (v/v) (see section 4.1.1.2).

For workers the inhalation and dermal exposure route is the most likely.

Major sources of exposure to consumers are active and passive smoking, car exhaust, either by inhalation of surrounding air and from indoor of cars. Oral exposure is possible via contaminated food, and dermal exposure by contact with gasoline.

In the Swedish product register, 26 out of a total of 83 products have been labelled as consumer products. The „German federation of lacquer industry“ has declared, that in accordance with national and EEC-regulations benzene is not used in paints and varnishes (personal communication 1997). It has to be clarified whether this is true only for Germany or for the EC-member states, too.

In the Federal Republic of Germany, benzene is used as a component of gasoline. During tobacco smoking, benzene will be liberated.

4.1.1.2 Occupational exposure

Legal conditions

According to the Council Directive 97/42/EC (27.06.1997, amending Directive 90/394/EEC) the overall occupational exposure level of benzene is laid down to 3.25 mg/m^3 (1 ml/m³) from 27. June 2003 onwards. Until 27. June 2003 a transitional occupational exposure level of 9.75 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 were established, up to 16 mg/m³. In part, the member states have splitted OELs with higher OELs for the area of cooking plants, works at gasoline or benzene conduction parts in the chemical or petroleum industry.

The permitted content of benzene has been reduced from 5 % (v/v) to 1 % (v/v) from 1.1.2000 (European Directive 98/70/EC).

According 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 devises built later that 31.12.1995. Transition periods of three to nine years are established for existing devices depending on the throughput (European Directive 94/63/EC).

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 restricted to 0.1 % (w/w) within the EU.

General

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 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.

The assessment of inhalation exposure is mainly based on measured exposure levels from which – if possible – 95^{th} or 90^{th} percentiles are derived as representing reasonable worst case situations. If for one scenario, more than one collective with different 90^{th} percentiles are available, for conservative reasons, the highest 90 percentile is taken.
Beside inhalation exposure, dermal exposure is assessed for each scenario. Two terms can be used to describe dermal exposure:
Potential dermal exposure is an estimate of the amount of a substance landing on the outside of work wear and on the exposed skin.
Actual dermal exposure is an estimate of the amount of a substance actually reaching the skin.
There is an agreement between the EU-memberstates, within the framework of existing substance, to assess - as a rule - dermal exposure as exposure to hands and parts of the forearms. In this, the main difference between both terms – potential and actual - is the protection of hands and forearms by work wear and – more important – the protection by gloves. Within this exposure assessment, the exposure reducing effect achievable by gloves is only considered if information is provided, that for a certain scenario gloves are a widely accepted protective measure and that the gloves are fundamentally suitable for protection against the substance under consideration. As a measure for the latter, tests according to DIN EN 374 are taken as a criteria. For most down stream uses it is commonly known, that gloves are not generally worn. In these cases, dermal exposure is assessed as actual dermal exposure for the unprotected worker. Since quantitative information on dermal exposure is only seldom available, the EASE model is used for assessing dermal exposure, at the most.

Benzene is used as a chemical intermediate. An EU-pattern is given in the risk assessment report provided by the representative company:

Ethyl benzene	52 %
Cumene	20 %
Cyclohexane	13 %
Nitrobenzene	9 %
Alkylbenzene	3 %
Chlorobenzene	1 %
Maleic Anhydride + others	2 %

During the handling of gasoline within the automobile industry, in the area of mechanic engineering and car recycling as well as in car repair shops exposure to benzene may occur.

4.1.1.2.1 Scenario 1: Production, further processing and refinery

Benzene is manufactured and processed further in closed systems. Possibilities of exposure exist if the systems are breached, e.g. during sampling, filling, drumming, cleaning, transfer, maintenance and repair works. A description of the different production processes is given in section 2.1.

Inhalation exposure

Workplace measurements

Measurement results were obtained from 15 of 35 producers. Data provided by UK (HSE) from the years 1984 - 1985 have become outdated and are not used within the framework of this RAR. The assessment of inhalation exposure during production and further processing is performed on the basis of measurement results given in CEFIC/APA 1995 (cited in the risk assessment report provided by the representative company). In addition, measurement results provided by three companies and data described in TRGS (1998) are considered. Exposure data which are used for exposure assessment were obtained between 1990 and 1995. In this time the Council Directive 97/42/EC (27.06.1997, amending Directive 90/394/EEC) had not come into force and the national exposure level were, in part, higher than the transitional OEL of 9.75 mg/m³.

CONCAWE submitted recently taken measurement results which reflect the current conditions in the area of refinery. In table 4.1, measurement values from two periods are given: 1993 – 1998 and from 1999 – 2000. Measurement values taken before 1993 are not used for exposure assessment. Because of the short time interval (year 2000) in which the new data could be taken, the number of measurements representing the current situation is limited.

Table 4.1 Benzene exposures at workplaces during production, refinery, further processing

Job category / activities (activity code, see text)	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95th percentile [mg/m^3]	Duration and frequency
8-h time weighted average						
BENZENE PRODUCTION AND USE - CHEMICAL INDUSTRY [1)]						
Benzene production	published 1995	> 1033	0.002 - 16	0.9	3.5	
Benzene use (ethyl benzene production)	published 1995	11	0.03 - 5.4	0.6	2.5	
Transportation (including filling)	published 1995	> 46	0.01 - 266	0.9	3.4	
Maintenance	published 1995	> 248	0.06 - 62	0.6	2.5	
Laboratory	published 1995	> 124	0.03 - 7.1	0.8	3.2	
Handling	published 1995	> 41	0.1 - 40	1.5	6.0	
Storage (including product movement)	published 1995	136	0.1 - 5.9	0.9	3.6	
Waste operations	published 1995	22	0.03 - 3.1	0.3	1.4	
Operations (prepare for shut down)	published 1995	56	0.06 - 43	5.8	23.0	1/year

Job category / activities (activity code, see text)	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95th percentile [mg/m^3]	Duration and frequency
REFINERY (11 companies) [3)]						
Operators, on-site (1.1)	1993 - 1998	97	0.008 – 7.88	0.22 (am)		
Off-site workers, tank farm activities, e.g. dipping, valve operations	1999 – 2000 1993 – 1998	6 321	< 0.48 – 3.03 0.008 – 23.3	1.21 (am) 0.32 (am)		
Maintenance	1999 – 2000 1993 - 1998	2 373	< 0.1 0.008 – 18.1	0.94 (am) 0.41 (am)		
Miscellaneous (refinery)						
Laboratories, engine disassembly, gasoline blending, octane rating test	1999 – 2000 1993 - 1998	13 628	< 0.2 – 13.85 0.015 – 5.0	0.2–6.08 (am) 0.3 (am)		
BENZENE USE - CHEMICAL INDUSTRY [2)]						
Intermediate – synthesis	--	46 21 37	2 - 19 0.5 - 1.3 1.9 - 4.5	5.6 0.9 2.7		
Synthesis of fibre intermediates operator maintenance	--	-	--	 2.2 0.6 0.32	 < 11.2 < 2.9 < 6	
Production of ethyl benzene, styrene, cumene:						
Benzene operator	1990-1994	20	< 6. 4	0.96		
Cumene operator	1990-1994	10	< 16	1.92		
Other	1990-1994	20	< 3.2	0.32		
Supervision	1990-1994	10	< 1.6	1.6		
Labworker	1990-1994	30	< 16	0.64		
Mechanic Maintenance	1990-1994	300	< 3.2	0.32		
Maintenance	1990-1994	50	< 6.4	0.96		
Industrial cleaner	1990-1994	180	< 32	0.96		

Job category / activities (activity code, see text)	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95th percentile [mg/m^3]	Duration and frequency
Short-term value						
Refinery						
Reformer operators, on-site (1.1)	1999 - 2000	6	< 0.99 – 1.41[4)]	0.96		
Off-site workers, tank field (1.2)	1999 – 2000 1993 - 1998	7 49	< 0.16 0.08 – 11.8	2.19		
Laboratory technicians (1.4)	1999 – 2000 1993 - 1998	6 5	< 0.51 – 0.74 0.28 – 4.6	0.55 1.93		
Maintenance staff (1.3)	1999 – 2000 1993 - 1998	7 7	0.08 – 0.4 0.28 – 8.6	0.28 2.62		
Miscellaneous						
Production	1994	40 49 40	< 1.6 < 0.3 < 64			 30 min
Industrial cleaner		1000	< 64			30 min
Drum fillers Drum handlers)	1999 - 2000	9 3	0.25 – 2.15 < 0.6 - < 1.3	0.81 < 0.9	1.61	
Laboratories, engine, test houses, used barrel cleaning (1.4)	1993 - 1998	5	0.28 – 4.6	1.93		

[1)] CEFIC/APA 1995, cited in the risk assessment report provided by the representative company
[2)] Measurement results provided by three producers
[3)] CONCAWE 1987, 2000, 2001, am: arithmetic mean
[4)] highest measurement results associated with small spillage
VR: Vapour recovery

In CONCAWE (2000) a brief description of the jobs in the refinery is given (missing number of activity codes (given in table 4.1): no data for the corresponding activity):

Table 4.2 Description of jobs given in table 4.1

Activity Code	Job Group	Description of Tasks
Refinery		
1.1	On-site operators	Carry out tasks, such as valve operation, sample collection, and blowing down gauges, in process areas where gasoline or its components (e.g. catalytic reformate) are produced. In general the tasks are infrequent and of short duration (i.e. < 1 hr). The operators also spend part of the shift in a pressurised control room.
1.2	Off-site operators	Carry out tasks in areas such as tank farms (e.g. dipping / sampling / de-watering gasoline storage tanks) and water effluent treatment plants (e.g. API separators). In general the tasks are infrequent and of short duration (i.e. < 1 hr).
1.3	Maintenance workers	Carry out tasks, such as the draining, cleaning, opening and work on enclosed equipment for which there is potential for exposure to gasoline.
1.4	Laboratory technicians	Carry out gasoline analyses (for quality assurance purposes) plus research and octane rating tests.

Short term exposures up to 64 mg/m^3 (30 min) are possible, e.g. during the production of benzene (result reported by a company, see table 4.1).

Based on the measurement technique and the sampling strategy, the measurement results are regarded to be valid. The data reflect occupational exposure in more than 10 companies located in different EU-member states. Therefore the data are regarded to be representative.

Most of the given 95th percentile are below 3.5 mg/m³ with two exceptions: Handling of benzene with a 95th percentile of 6 mg/m³ and the area of fibres synthesis (for different activities) with 95th percentiles of < 2.9 – < 11.2 mg/m³. The information on these activities are limited (no information to handling, no information on the year and number of measurement results). As the conclusion, 3.5 mg/m³ is regarded to represent the reasonable worst case situation.

CONCAWE states that exposure levels of refinery laboratory technicians involved in gasoline quality control testing are relatively high compared to older data and to other activities. The data set is currently subject to verification.

Conclusions

For the purpose of assessing the risks of daily inhalation exposure during the production of benzene (incl. refinery) and the further processing within the large-scale chemical industry including transport, filling, maintenance, storage, waste operations and laboratory works, 3.5 mg/m^3 should be used (95th percentile of workplace measurements). For the assessment of the health risks caused by higher short term exposure, a value of 64 mg/m^3 (30 min) should be taken.

Once a year, higher exposure levels of 23 mg/m^3 are reached during operations for shut down. This exposure level is confirmed by measurement results (short term) obtained in a research project of the National Institute for Occupational Safety and Health (BAuA, Germany). This exposure scenario is not considered within the frame work of this exposure assessment.

The measurement data used for deriving exposure levels relate to a time period before 1997 with the current transitional OEL of 9.6 mg/m^3 not being valid. In part, the national valid OELs of the EU-member states were higher than 9.6 mg/m^3.

Dermal exposure

When producing and further processing benzene dermal exposure could occur during activities like drumming, sampling, cleaning, maintenance and repair work. For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, intermittent
Level of exposure: 0.1 – 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palms of hands) the model yields an exposure level of 42 - 420 mg/person/day.

For assessing actual dermal exposure levels, it has to be considered that the substance is manufactured and further processed primarily in closed systems and that the use of personal protective equipment (PPE, here gloves and eye protection) during exposure relevant activities is highly accepted in the large-scale chemical industry. The extent of protection by PPE (here gloves) depends inter alia on the suitability of the recommended material with regard to the permeation properties of substance.

The knowledge about the used glove materials during production and further processing of benzene is incomplete since only 7 of 35 producers have submitted appropriate information. Additionally, there is a lack of information with regard to the suitability of the recommended materials. Therefore, it cannot be excluded that, besides suitable protective gloves, also unsuitable gloves providing only limited protection are worn.

In the case of benzene, the predominant effect reducing potential dermal exposure is the very high volatility of the substance (vapour pressure 90.7 hPa) which leads to considerable low retention times of the substance on the skin or on the protective gloves. This exposure reducing effect cannot be considered if workers have continuous direct contact with the substance, e.g. dipping hands into the substance. For the area of production and further processing of benzene this situation is regarded to be rather non-probable. Furthermore, it is assumed, that non-occlusive exposure is the predominant exposure situation.

In appendix A V the calculation of the evaporation time of the pure substance is described. For benzene with the EASE estimate of 1 mg/cm², an evaporation time of 8 seconds (T = 30°C) is calculated. For benzene on the gloves, an assumed temperature of 20°C leads to a evaporation time of 13 seconds. An evaporation time of 10 seconds should be taken as an order of magnitude, since it is not known in how far the interaction of the skin with the substance influences the evaporation time.

In conclusion, for the use of suitable gloves, dermal exposure is assessed as low.

Supposing that unsuitable gloves are worn, the exposure level amounts to 42 – 420 mg/person/day. The highest value is regarded to represent the reasonable worst case situation. On account of the high vapour pressure of benzene (99.7 hPa), the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure and leading to much lower dermal exposures than predicted by the EASE model which considers dermal exposure during the whole shift.

4.1.1.2.2 Scenario 2: Recovering of benzene in coking plants

Benzene is recovered from coal-derived chemicals, primarily from coke oven by-products which are released during the coking process. Exposure to benzene is to be expected at the coking ovens but mainly in the area of by-product plants, where benzene is extracted from process gases and upgraded.

The by-product plants can be regarded as closed systems. Exposure may occur if the systems are breached e. g. during filling, transport, cleaning, maintenance, repair works and sampling.

Workplace measurements

Inhalation exposure

Table 4.3 comprises data of different origins, which have been used to assess exposure to benzene in coking plants. In a comprehensive publication Thomas (1991) reports on exposure scenarios and exposure levels in coking plants. The given exposure levels are not used in this RAR, because mainly mean values are given and the duration of exposure are missing.

Table 4.3 Benzene exposures at workplaces belonging to coking plants

Job category / activities	Year of measure-ment	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	90th percentile [mg/m³]	Source
8-h time weighted average						
By-product recovery	1990 - 1991	7 5	< 3.2 > 3.2 - < 15.5[1)]	--	--	TRK 901 (1998)
Coking plant	< 1990	180		--	--	BIA (1993)
Coking oven		--	0.03 - 0.8			
by-product recovery		--	0.1 - 8			
Coking plant						BIA (1993)
In total	1985	460	0.1 - 36.5	--	---	
Coking oven					1.3	
By-product recovery					14.4	
Coking plant						Drummond et al. (1988)
In total	1986	--	< 12	--	--	
Benzene men			4.2			
Battery men			1			

1) In part mean values from several measurements

In the area of coking ovens, high exposures to benzene exist in the section of by-product recovery. Exposure levels up to 15.5 mg/m³ (1990 - 1991) were obtained. Values given in Thomas (1991) emphasis this situation, since high exposure levels especially for the by-product plants are given (up to 118 mg/m³, duration unknown). In the area of coking ovens exposure levels are lower (see table 4.3).

Conclusions

For the purpose of assessing the risks of daily inhalation exposure in coking plants (by-product recovery) 15.5 mg/m³ should be taken (highest measurement result of 12 measurements). It has to be taken into account, that the measurement results refer to a legal situation with a higher OEL than currently valid.

Dermal exposure

For the area of coking plants no information about the use of personal protective equipment (here gloves) could be obtained. Therefore it is assumed, that lower levels of protection standards than in the large scale chemical industry have to be considered and that it cannot be excluded, that gloves are not worn. The resulting exposure level is estimated applying the EASE model:

Input parameters: Non dispersive use, direct handling, intermittent
Level of exposure: 0.1 – 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palms of hands) the model yields an exposure level of 42 - 420 mg/person/day. The higher value (420 mg/person/day) is regarded to represent the reasonable worst case situation. The resulting immediate skin contact is considered as regular dermal exposure. On account of the high vapour pressure of benzene (99.7 hPa), the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V).

Inappropriate application of gloves may lead to the situation that benzene reaches the skin underneath worn gloves (occlusive conditions). Thus the evaporation of the substance is limited in dependence on the permeability of the applied glove material with regard to the penetration of benzene. Neither the amount of benzene reaching the skin underneath the gloves nor the extent of evaporation and consequently the resulting retention time of benzene underneath the gloves can be quantified. For the risk assessment of this worst-case scenario, it may be assumed, that the daily duration of the described exposure scenario - immediate skin contact to benzene underneath gloves - may last a few minutes.

4.1.1.2.3 Scenario 3: Production of perfumes

In the perfume industry, benzene can be used as a extraction agent for flavor substances. According to further information from France, this regional exposure scenario is declining. Members of the International Fragrance Association (IRFA) have replaced benzene. This process was finished 1995. The Association states that there still are countries in which benzene is used for extraction. Detailed information about the exposure relevant activities is not available.

Inhalation exposure

Workplace measurements

Measurements performed in F (1987 – 1995) reveal, that high exposures to benzene occur in the French perfume industry (extraction of flavour substances, up to 594 mg/m^3 (n = 112), median 2.9 mg/m^3 and 90th percentile 84 mg/m^3) (INRS 1999). After 1995, no inspections were made in this industry. According to further information, this regional exposure scenario is declining. Detailed information about the exposure relevant activities is not available.

EASE estimation

Exposure estimation in application of the EASE model for handling the pure substance results in 32 – 64 mg/m³ (10 – 20 ml/m³, T = 20°C, non dispersive use, with LEV, no aerosol formation, T = 20°C, vapour pressure 91.70 hPa) and 160 – 225 mg/m³ (50 – 70 ml/m³, non dispersive use, segregation, no aerosol formation, T = 20°C, vapour pressure 91.70 hPa), respectively. The model estimates confirm the measured exposure levels.

Conclusions

For assessing the risks of daily inhalation exposure, the 90th percentile of 84 mg/m^3 should be taken. However, it has to be considered, that the data are rather out of date and do possibly not reflect the current working conditions. Furthermore, information from France reveal, that this regional exposure scenario is declining.

Dermal exposure

Since it cannot be excluded, that gloves are not worn in the further processing industry, dermal exposure during the handling of benzene containing preparations has to be assessed. The estimation in application of the EASE model

Input parameters:	Non dispersive use, direct handling, intermittent
Level of exposure:	0.1 – 1 mg/cm^2/day

leads under consideration of an exposed area of 420 cm^2 (palms of two hands) to the exposure level of to 42 - 420 mg/person/day. The higher value (420 mg/person/day) is regarded to represent the reasonable worst case situation. On account of the high vapour pressure of benzene (99.7 hPa), the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V).

4.1.1.2.4 Scenario 4: Production of formulations

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. Benzene residues up to 0.1 % (w/w) may, however, be present in various chemical materials, predominantly in formulations as painter's materials (paints, primers, paint strippers, paint diluents and cleaners), lubricants, abrasives and glues (Rastogi 1993).

Benzene exposure is assumed to occur during the production of preparations (e. g. photo chemicals, paints, adhesives). It is assumed, that no pure benzene is handled but organic solvents based on certain refinery fractions. The concentration of benzene in these preparation is unknown (for model estimations, 1 % benzene is assumed). Exposure relevant are filling, transfer, repair, cleaning and maintenance.

Inhalation exposure

Measurement results relating to the production of paints, printing inks and varnishes provided from F range from 0.1 to 0.15 mg/m^3 (n = 9, duration > 4 hours, 1987 – 1995, INRS 1999). After 1995, no inspections were made in this industry.

EASE estimation

The EASE estimation is performed for the EASE scenario: non dispersive use, no aerosol formed, T = 20°C, vapour pressure 91.7 hPa, LEV present and results in exposure levels of 32 – 64 mg/m³. For a rough estimation, a benzene concentration of 1 % in the liquid and 0.02 % in the vapour (valid for gasoline) is taken leading to exposure levels of 0.128 – 0.265 mg/m³.

Taking into account that the production of formulations is often performed batch wise it is assumed, that exposure relevant activities (e.g. filling) are performed not during the whole shift but for 2 hours per day, leading to a levels of 0.127 – 0.064 mg/m³. Theses values are in accordance with the measurement results (up to 0.15 mg/m³).

Conclusion

For assessing the risks of daily inhalation exposure during the production of formulations, 0.15 mg/m^3 (highest measurement results, ranging is the lower range of the EASE estimate) should be taken. However, it has to be considered, that the data are rather out of date and do possibly not reflect the current working conditions. It has to be taken into account, that the measurement results refer to a legal situation with a higher OEL than currently valid.

Dermal exposure

Since it cannot be excluded, that gloves are not worn in the further processing industry, dermal exposure during the handling of benzene containing preparations has to be assessed. For a rough estimation, a concentration of 1 % benzene is assumed. Exposure estimation in application of the EASE model (non dispersive use, direct handling, intermittent) results in 0.001 - 0.01 mg/cm^2/day. Considering an exposed area of 420 cm^2 (palms of two hands) dermal exposure amounts to 0.5 – 4.2 mg/person/day. The higher value (4.2 mg/person/day) is regarded to represent the reasonable worst case situation. On account of the high vapour pressure of organic solvents and of benzene (99.7 hPa), the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V). For solvents with low concentrations of benzene, the evaporation time is assumed to be in the same range or lower.

4.1.1.2.5 Scenario 5: Distribution of gasoline

In the petroleum industry possibilities for exposure exist mainly during handling of gasoline, which contains up to 1 % (v/v) benzene, e.g. during filling and transfer activities. A detailed description of the work sites and exposure relevant activities is given in reports provided by CONCAWE (1994c, 1987, 1999, 2000).

Inhalation exposure

Workplace measurements

CONCAWE submitted recently taken measurement results which reflect the current conditions in the area of refinery and distribution of gasoline. In table 4.4, measurement values from two periods are given: 1993 – 1998 (content of benzene in gasoline up to 5 %) and from 1999 – 2000 (data taken during handling of gasoline with benzene concentrations < 1 %). Measurement values taken before 1993 are not used for exposure assessment. Because of the short time interval (year 2000) in which the new data could be taken, the number of measurements is limited.

Table 4.4 Benzene exposures at workplaces belonging to the petroleum industry (CONCAWE 1987, 2000, 2001)

Job category / activities (activity code, see text)	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Arithmetic mean [mg/m^3]	90th percentile [mg/m^3]$^{1)}$	Duration and frequency
8-h time weighted average						
Distribution - road (10 companies)						
Tanker drivers (top loading) (2.1.1)	1993 - 1998	69	<0.04- 48.16	2.07	-	-
Tanker drivers (bottom loading) - No VR (2.1.2) - VR (2.1.3) - no VR (2.1.2) - VR (2.1.3)	 1999 – 2000 1999 – 2000 1993 – 1998 1993 - 1998	 30 31 223 137	 < 0.1 – 1.3 0.23 – 3.36 0.008 – 15.0 0.03 – 1.99	 0.52 0.64 0.82 0.37	 1.26	-
Gantry operators (bottom loading), no VR (2.1.5) Supervision (2.1.6)	1999 – 2000 1993 – 1998 1993 - 1998	3 126 151	< 0.4 – 0.7 0.003 – 4.2 0.001 – 3.2	0.44 0.64 0.36	- - --	-
Road tanker terminal, maintenance (2.1.8)	1999 - 2000 1993 – 1998	2 52	< 0.1 0.017 – 7.9	 0.52	-	-
Distribution - rail car loading (6 companies)						
Rail car operators (2.2.1, 2.2.2, 2.2.4), – Top loading no VR – Top loading, VR – Bottom loading, VR – Rail car supervisors (2.2.7) - Top loading, no VR (2.2.1) - off-loading (2.2.5)	 1999 – 2000 1999 – 2000 1999 - 2000 1993 – 1998 1993 – 1998 1993 - 1998	 16 20 3 5 69 43	 0.18 – 7.9 < 0.11 – 0.73 <0.1 – 0.38 < 0.2 0.008 – 14.8 0.03 – 9.3	 0.24 0.23 0.27 1.34 1.29	 6.80 0.43 -	 - -
Distribution - shipping (marine loading, 4 companies)						
Deck crew, closed loading, loading and disconnection (2.3.2)	1999 – 2000 1993 - 1998	4 2	<0.1 – 0.21 0.51 – 0.6	0.12 0.56	-	-
Ship deck crew, open loading (2.3.1.1)	1993 – 1998	41	0.08 – 5.4	0.56	-	-
Ship deck crew, unloading (2.3.1.2)	1993 – 1998	32	0.023 – 3.7	0.51	-	-
Jetty staff (loading, disconnection) (2.3.5)	1999 – 2000 1993 - 1998	2 46	<0.1, 0.1 0.023 – 1.7	 0.37	-	-
Short-term value						
Distribution-road						
Tanker drivers (during top loading) (2.1.1)	1993 - 1998	114	0.03 – 39.2	6.84	-	
Delivery of motor gasoline at service stations, with VR	1999 - 2000	6	< 0.19 – 2.80	0.80	-	-

Job category / activities (activity code, see text)	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Arithmetic mean [mg/m^3]	90th percentile [mg/m^3][1)]	Duration and frequency
(2.1.3)						
Bottom loading, - no VR (2.1.2) - VR (2.1.3)	 1999 – 2000 1993 – 1998 1993 - 1998	 15 39 72	 < 0.15 – 3.90 0.023 – 30.6 0.08 – 17.5	 1.5 2.55 1.4	-	-
Road tanker terminal supervisor (2.1.7)	1993 - 1999	8	0.23 – 11.2	2.20	-	-
Distribution – rail						
Top loading – VR (2.2.2) – No VR (2.2.1)	 1999 – 2000 1993 – 1998	 3 9	 < 0.67 0.67 – 5.5	 2.0	-	-
Off-loading (2.2.5)	1993 - 1998	4	0.38 – 2.4	1.7	-	
Distribution – shipping (marine loading)						
Deck crew, open loading (2.3.1.1)	1993 - 1998	4	0.23 – 0.3	0.23	-	-
Jetty staff (2.3.5)	1993 - 1998	24	0.23 – 5.8	0.79	-	-
Unloading (2.3.1.2)	1993 – 1998	2	0.23, 1.2	0.7	-	-

[1)] 90th percentiles calculated by the representative company
[2)] From CONCAWE 1987, older data, absence of good local exhaust ventilation
[3)] highest measurement results associated with small spillage
VR: Vapour recovery

In CONCAWE (2000) a brief description of the jobs is given (missing number of activity codes (given in table 4.4): no data for the corresponding activity).

Table 4.5 Description of jobs given in table 4.4

Activity code	Job	Description
2.1	**Road Tanker Terminal**	
2.1.1	Drivers: Top loading	Fill own vehicles with gasoline via top submerged loading and deliver to service stations; typically 2-3 loadings / deliveries per day.
2.1.2	Drivers: Bottom loading	Fill own vehicles with gasoline via bottom loading (without vapour recovery) and deliver to service stations; typically 2-3 loadings / deliveries per day.
2.1.3	Drivers: Bottom loading	Fill own vehicles with gasoline via bottom loading (with vapour recovery) and deliver to service stations; typically 2-3 loadings / deliveries per day.
2.1.5	Rack operators	Fill road tanker vehicles for drivers (normally via top submerged loading).
2.1.6	Supervisors / terminal operators	Includes general overseeing of road tanker gasoline filling.
2.1.7	Supervisors / terminal operators	Includes general overseeing of road tanker gasoline filling.
2.1.8	Maintenance	Carry out tasks, such as the draining, cleaning, opening and work on enclosed equipment for which there is potential for exposure to gasoline.
2.2	**Rail Car Location**	
2.2.1	Operators: Top loading	Fill rail cars with gasoline via top submerged loading (without vapour recovery); includes opening and closing of hatches and valves. This task can extend over several hours per day.
2.2.2	Operators: Top loading	Fill rail cars with gasoline via top submerged loading (with vapour recovery); includes opening and closing of hatches and valves. This task can extend over several hours per day.
2.2.4	Operators: Bottom loading	Fill rail cars with gasoline via bottom loading (with vapour recovery); includes opening and closing of hatches and valves. This task can extend over several hours per day.
2.2.5	Operators: Off-loading	Off-load gasoline to storage (includes hose connection / disconnection and sampling).
2.2.7	Miscellaneous	Unspecified or mixture of duties.
2.3	**By ship (product carrier, coastal craft, barge)**	
2.3.1.1	Deck crew: Open loading	Fill ships with gasoline with the cargo hatches or ullage ports open. Displaced vapour is discharged close to deck level. Specific tasks include connection / disconnection of cargo lines, checking tank fill levels and tank dipping.
2.3.1.2	Deck crew: Unloading	Discharge gasoline cargoes. Specific tasks include connection / disconnection of cargo lines. Less opportunity for exposure to gasoline vapour than in 2.3.1.1.
2.3.2	Deck crew: Closed loading	Fill ships with gasoline with the cargo hatches and ullage ports closed. Displaced vapour is discharged remotely. Ullage measurements are read automatically. Specific tasks include connection / disconnection of cargo lines.
2.3.5	Jetty staff	Supervise gasoline cargo loading and unloading operations. Specific tasks include gasoline sampling, tank dipping and the handling of hoses.

The assessment of inhalation exposure is based mainly on the data from the time period 1999 – 2000 although the number of measurement results is limited. The older data refer to exposure situations with gasoline containing higher amounts of benzene (up to 5 %) and cannot be regarded as representative for the current situation. In addition, 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 that 31.12.1995. Transition periods of three to nine years are established for existing devices depending on the throughput (European Directive 94/63/EC). The influence of the changed conditions can be seen in comparing exposure levels at workplaces with VR (vapour recovery) and without VR (see table 4.4).

High exposure levels were obtained during direct handling of gasoline, e. g. filling activities (rail car loading, marine loading), especially at workplaces without vapour recovery. The relative high fluctuations of the exposure levels are caused by the influence of the conditions during works outside (wind, temperature) and by the application of different techniques (e. g. filling with or without gas recovery system; top or bottom loading).

Conclusions

For the purpose of the assessment of the risks resulting from daily exposure by inhalation the following 8 h shift averages should be taken for the distribution of gasoline (road, ship, rail):

Scenario 5 a: 6.8 mg/m^3 (without vapour recovery, 90th percentile, measurement results from 1999 - 2000). This exposure level was obtained at rail car loading. For the other kinds of distributions exposure levels are lower.

Scenario 5 b: 1.26 mg/m³ (with vapour recovery, 90th percentile, measurement results from 1999 - 2000)

It is assumed that these values represent the current exposure situation. It is to be expected, that workplaces without vapour recovery will be replaced or will be equipped with a recovery system in future. This is foreseen according to the European Directive 94/63/EC which defines technical standards which are obligatory for all devises built later that 31.12.1995. Transition periods of three to nine years are established for existing devices depending on the throughput.

The short term value from the period 1999 – 2000 exceeds the shift averages only slightly (highest value: 3.9 mg/m³) and are therefore not taken forward to risk characterisation.

Dermal exposure

For works related to the distribution of gasoline lower levels of protection than in the area of refinery are to be expected. It is assumed, that protective gloves are not always worn and that immediate dermal exposure to gasoline (1 % benzene) may occur. Dermal exposure is assessed in application of the EASE model (non dispersive use, direct handling, intermittent) considering a content of 1 % benzene and an exposed skin area of 420 cm^2 (both hands) to 0.42 – 4.2 mg/person/day.

Conclusion

The higher value of the estimated range (EASE model, 4.2 mg/person/day) is regarded to represent the reasonable worst case situation. On account of the high vapour pressure of gasoline (350 - 900 hPa (CONCAWE 1992)) the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V). For gasoline with low concentrations of benzene, the evaporation time is assumed to be in the same range or lower.

Inappropriate application of gloves may lead to the situation that benzene reaches the skin underneath worn gloves (occlusive conditions). Thus the evaporation of the substance is limited in dependence on the permeability of the applied glove material with regard to the penetration of benzene. Neither the amount of benzene reaching the skin underneath the gloves nor the extent of evaporation and consequently the resulting retention time of benzene underneath the gloves can be quantified. For the risk assessment of this worst-case scenario, it may be assumed, that the daily duration of the described exposure scenario - immediate skin contact to benzene underneath gloves - may last a few minutes.

4.1.1.2.6: Scenario 6: Automobile industry, mechanical engineering, car repair, and car recycling

The exposure situations “automobile industry, mechanical engineering, car repairing, and car recycling” are clustered because of the similarity of the source of exposure (gasoline) and the exposure relevant activities (works at the fuel system). In the automobile industry and in the area of mechanic engineering, exposure to benzene occurs, if engines are tested and gasoline is handled e.g. during works at fuel systems. In car repair shops, exposure may occur during maintenance and repair of gasoline engines specially during work at fuel systems (e.g. fuel injection, carburettor adjustment). During car recycling, exposure to benzene is possible if gasoline is drained off or works at the fuel system are performed. The draining off is performed by means of letting off, pneumatic sucking off or by using compressed air. The tanks are mechanically punctured by special equipment with using rubber seals for withdrawal.

Table 4.6 Benzene exposures at workplaces belonging to the automobile industry and to the area of engineering

Job category / activities	Years of measurement	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	90th percentile [mg/m³]	Source
8-h time weighted average						
Works at fuel systems	before 1992	36	< 6.2	-	-	BIA (1993)
Test driver (taking in fuel)	before 1992	13	< 3.2	-	-	TRGS (1998)
Taking in fuel, new cars		33	< 2			
Investigations of fuels in laboratories		8	< 5.8			
Works after repair		51	< 3.2			
Mechanical engineering [1]	1991 - 1995		-			BGAA (1997)
- in total		335		0.2	2.8	
- Without exhaust ventilation		109		0.7	3.2	
- With exhaust ventilation		187		0.2	1.0	
Short-term level						
Test driver (taking in fuel)	before 1992	-	5.8	-	-	TRGS (1998)
Investigations of fuels in laboratories		-	11.8			
Works after repair		-	6.4			
Motor construction, works at the fuel system[2]	published 1994	- -	19 – 38 8 – 11	-	-	SMBG (1994)

[1] Metal working industry, repair shops; activities: repair, maintenance, work at test stands. High exposure levels were obtained around motor test stands and in the area of repairing gasoline pumps or engines

[2] The lower exposure levels (8 - 11 mg/m³) were obtained after an improvement of the ventilation system

Pooled measurement results provided by the German Worker`s Compensation Funds refer to the metal working industry, the area of mechanical engineering and to car repair shops (see table 4.7, BGAA (1997)). However, all 8 h shift averages given in table 4.6 (highest measurement results and 90th percentiles) are located between < 2 and < 6.2 mg/m³. Limited information is available on short term exposure. The highest short term value (number unknown) amounts to 38 mg/m³. Since the measurements were performed before 2000, the exposure levels might not reflect the current exposure situation.

Table 4.7 Exposure to benzene in car repair shops and garages

Job category / activities	Years of measurement	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	90th percentile [mg/m³]	Source
8-h time weighted average						
Car repair shops, mainly franchised car repair shops, different activities	1996	37	0.05 - 0.67	0.24	-	Auffarth et al. (1997)
Car repair shops, works at fuel systems, testing engines	before 1992	10	< 9.3		-	BIA (1993)
Maintenance, inspection, inter alia works at fuel systems	--	47	0.08 - 0.7	0.19	-	TRGS 901 (1998)
Car repair shop, modern equipment, 17 different activities	1991-1992	--	2 - 3[1)]	-	-	SMBG (1992)
Mechanical engineering [2)] in total without exhaust ventilation with exhaust ventilation	1991 - 1995	 335 109 187	-	 0.2 0.7 0.2	 2.8 3.2 1.0	BGAA (1997)
Short-term level						
Car repair shops, works at fuel systems	1996	7	0.2 - 5.7 (3-60 min)[4)]	2.4		Auffarth et al. (1997)
Processing workplaces without ventilation, including maintenance and repair of gasoline engines	-	45	-	1.5	12.7[3)]	BGAA (1997)
Car repair shops, works at fuel systems	-	23	1 - 8	-	-	TRGS 901 (1998)
Car repair shop, modern equipment, different activities (< 1 h)	1991-1992	29	< 3 - < 20	-	-	SMBG (1992)
Car repair shops, works at fuel systems unleaded gasoline leaded gasoline	1992	5 9	< 4.2 (30 min)[4)] < 11.8 (30 min)[4)]	- -	- -	Laitinen et al. (1994)

[1)] 8 h time weighted average were calculated on the basis of short-term levels
[2)] Metal working industry , repair shops, activities: repair, maintenance, work at test stands, High exposure levels were obtained around motor test stands and in the area of repairing gasoline pumps or engines
[3)] Exposure in the range of the 90th percentile (7.8 mg/m³) were found during maintenance and repair of gasoline engines
[4)]-Duration of exposure relevant activities

Data provided by SMBG (1992) regard to modern, well equipped franchised car repair shops with sufficient ventilation.

Most of the data given in table 4.7 are located between 0.67 - 9.3 mg/m³. As a measure of the reasonable worst case situation for handling gasoline containing 5 % benzene might serve the 90th percentile of the data provided by BGAA (1997) which is 3.2 mg/m³ for workplaces

without local exhaust ventilation. Since the measurements were performed before 2000, the exposure levels might not reflect the current exposure situation.

Table 4.8 Exposure to benzene at workplaces belonging to the area of car recycling (personal sampling)

Job category / activities	Years of measurement	Number of samples	Range of measurement data [mg/m³]	Arithm. mean [mg/m³]	95th percentile [mg/m³]
8-h time weighted average					
Disassembly	before 2000	13	max: 1.11	0.43	0.89
	2000	40	max: 0.49	0.07	0.32
Draining	before 2000	26	max: 2.24	0.67	1.65
	2000	38	max: 1.12	0.22	0.69
Workers performing draining and disassembly	before 2000	29	max: 2.5	0.33	1.16
	2000	17	max: 1.08	0.17	0.54
Short-term level					
Disassembly	2000	18	max: 0.59	0.1	0.57
Draining	before 2000	8	max: 2.62	1.12	2.55
	2000	29	max: 0.44	0.15	0.30
Workers performing draining and disassembly	before 2000	5	max: 1.54	0.85	1.47
	2000	3	max: 0.07	0.04	0.07

Measurement results listed in table 4.8 were gathered within a research project of the Federal Institute for Occupational Safety and Health (BAuA, 1997) and from the Länder (Federal States of Germany).The measurement results indicate that exposure levels obtained in the year 2000 are lower than in the time period before 2000 due to the reduction of the content of benzene in gasoline. The most exposure relevant activity is draining. High exposure levels are observed, if spilling of gasoline occurred. For car recycling works 0.7 mg/m³ (95th percentile of measurement data from 2000, draining) is regarded to represent the reasonable worst case situation. The exposure assessment is based on up-to-date measurement results and, therefore, reflects the current exposure situation.

EASE estimation

In the following, EASE estimates are derived for gasoline containing up to 5 % benzene (past condition) and 1 % benzene (current condition). The vapour phase of a gasoline with 1 % (v/v) benzene contains app. 0.5 % (v/v) benzene. For 5 % (v/v) gasoline in the liquid, the vapour contains 2 % (v/v). This relationship was derived by measurements and model predictions (Runion 1975) and is used for the following exposure estimations.

5 % benzene: The EASE estimates for the scenario "non dispersive use, LEV present, no aerosol formed, 5 % (v/v) benzene in the gasoline and 2 % (v/v) in the vapour phase, T = 20°C, vapour pressure 91.7 hPa)" amounts to 0.64 – 1.28 mg/m³. For workplaces without local exhaust ventilation (the other conditions remain the same), the estimated exposure levels are higher: 6.4 – 9 mg/m³.

1 % benzene: The EASE estimates for the scenario "non dispersive use, LEV present, no aerosol formed, 1 % (v/v) benzene in the gasoline and 0.5 % (v/v) in the vapour phase, T = 20°C, vapour pressure 91.7 hPa) amounts to 0.16 – 0.32 mg/m³. For workplaces without local exhaust ventilation (the other conditions remain the same), the estimated exposure levels are higher: 1.6 – 2.25 mg/m³.

Conclusions

The exposure situation "automobile industry, mechanical engineering, car repairing, and car recycling" are clustered because of the similarity of the source of exposure (gasoline) and the exposure relevant activities (works at the fuel system). For assessing the risk of daily inhalation exposure an attempt is made to assess exposure for the current situation (1 % benzene in gasoline).

It can be seen, that the EASE estimates for 5 % benzene (upper value 9 mg/m³) in gasoline corresponds well with the measured values (highest result 9.3 mg/m³, obtained at the workplaces under consideration see table 4.6 – 4.8). For currently used gasoline with up to 1 % benzene, occupational exposure is expected to be lower. Therefore, the EASE estimate of 2.25 mg/m³ seems to be appropriate as representing the reasonable worst case situation, being 3 – 4 times lower than the measured values.

For the purpose of assessing the risks of daily inhalation exposure a level of 2.25 mg/m^3 should be taken (model estimate, supported by measurement results obtained for gasoline with higher concentrations of benzene). This exposure level is based on measured data (older measurement data, 5 % benzene in gasoline) and modified by means of model estimates and is regarded to represent the current exposure at the workplace.

For works at the fuel system short-term exposures up to 38 mg/m^3 (12 ml/m^3) should be taken into account. It has to be considered, that the measurement results refer to a legal situation with a higher OEL than currently valid.

Dermal exposure

Investigations in different car repair shops and car recycling devices in D performed by BAuA (Federal Institute for Occupational Safety and Health) revealed, that workers wear unsuitable gloves or none at all (BAuA 1997, Auffarth et al. 1997) and that immediate contact to gasoline occurs, especially during draining off, when gasoline comes into contact with the hands. The assessment of daily dermal exposure is performed in application of the EASE model (non dispersive use, direct handling, intermittent) considering 1 % benzene in gasoline and an exposed skin area of 840 cm^2 (corresponding to both hands). The exposure levels amount to 0.84 – 8.4 mg/person/day.

Conclusions

The higher value of the EASE estimates (8.4 mg/person/day) is regarded to represent the reasonable worst case situation. On account of the high vapour pressure of gasoline (350 - 900 hPa (CONCAWE 1992)) the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V). For gasoline with low concentrations of benzene, the evaporation time is assumed to be in the same range or lower.

On the other side, it cannot be excluded, that activities accompanied with dermal exposure are repeatedly performed during one shift, thus prolonging the daily duration of immediate dermal contact up to a few minutes (worst-case).

4.1.1.2.7 Scenario 7: Service stations

At service stations exposure to benzene during taking in fuel may occur. Today, tank filling is often done by the consumers themselves.

Inhalation exposure

Measurement results

Table 4.9 Benzene exposures at workplaces belonging to service stations

Job category / activities (activity code , see text)	Years of measure-ment	Number of samples	Range of measurement data [mg/m³]	Arithm. mean [mg/m³]	95th - percentile [mg/m³]	Source
8-h time weighted average						
Attendants - no VR (3.1.1)	1999 - 2000 1993 – 1998	34 417	< 0.21 – 1.6 0.001 – 1.9	0.37 0.25	0.48	CONCAWE (2001) CONCAWE (2000)
- VR (3.1.2)	1999 – 2000	10	< 0.1	< 0.1	< 0.1	CONCAWE (2001)
supervisor	1999 - 2000	1 5	< 0.1 < 0.18 - < 0.28	< 0.1 < 0.21	- -	CONCAWE (2001)
Others (cleaners, managers; 3.5)	1999 - 2000 1993 – 1998	5 5	< 0.18 - < 0.28 0.01 – 0.10	< 0.21 0.03	- -	CONCAWE (2001) CONCAWE (2000)
Petrol pump (3.4) maintenance workers	1993 - 1998	2	0.16 – 0.93	0.55	-	CONCAWE (2000)
Cashiers (3.2)	1999 - 2000 1993 - 1998	12 268	0.18 – < 0.4 0.001 – 1.92	0.27 0.05	< 0.38	CONCAWE (2001) CONCAWE (2000)
Take in fuel Cashiers	1993 1992 - 1994	9 51	0.01 - 0.6 0.001 - 0.65	-	-	Federal monitoring authorities in D
Cashiers	1995	22	0.005 - 0.06	0.027 (geometric mean)		Niedersachsen (1996)
Short-term level						
Supervisor, VR	1993 – 1998	1	< 0.1			CONCAWE (2000)
Petrol pump (3.4) maintenance worker	1993 - 1998	6	0.19 – 11.8 [1)]	3.8		CONCAWE (2000)

[1)] Highest measurement result associated with small spillage
VR: vapour recovery

In CONCAWE (2000) a brief description of the jobs is given (missing number of activity codes (given in table 4.9): no data for the corresponding activity).

Table 4.10 Description of jobs given in table 4.9

Activity code	Job	Description
Service stations		
3.1.1	Service station attendants (without vapour recovery)	Fill customers vehicles with gasoline; exposed to gasoline vapour as a result of this task and the ambient concentration in and around the service station. Exposure may also arise during the bulk delivery of motor gasoline to the service station.
3.1.2	Service station attendants (with vapour recovery)	Fill customers' vehicles with gasoline. Little direct opportunity for exposure to gasoline vapour, although exposure arises from the ambient concentration in and around the service station and may also occur during the bulk delivery of motor gasoline to the service station.
3.2	Service station cashiers	Receipt of payment for gasoline and goods sold in the service station shop. Exposed to ambient concentrations of gasoline vapour in the service station shop.
3.4	Petrol pump maintenance	Carry out in-situ pump maintenance on the forecourt. Exposure to gasoline vapour may occur from residual gasoline in the pump or interventions on components of pump.
3.5	Miscellaneous	Work on service stations without duties involving direct contact with gasoline, e.g. car wash operator.

From the exposure levels provided by CONCAWE it can be seen that existing vapour recovery systems reduce the exposure levels. For attendants, exposure without vapour recovery is up to 1.6 mg/m³ (95^{th} percentile: 0.48 mg/m³) and at workplaces with vapour recovery system < 0.1 mg/m³ (measurement results from 1999 – 2000). Exposure levels of cashiers are up to 0.4 mg/m³ (95^{th} percentile 0.38 mg/m³). Measurement results from other sources are in good agreement with the measurement results provided by CONCAWE (2000).

Conclusions

For assessing the risks of daily inhalation exposure during regular works of service station (attendants, cashiers) the 90^{th} percentile 0.5 mg/m^3 should be used. For workplaces with VR systems, exposure levels are below 0.1 mg/m³. The exposure assessment is based on up-to-date measurement results and should therefore reflect the current exposure situation.

Dermal exposure

It has to be assumed that filling station attendants do not wear suitable gloves or use them only seldom and that immediate dermal contact with gasoline may occur. In application of the EASE model (non dispersive use, direct handling, intermittent) and in consideration of a maximum benzene content of 1 % a dermal exposure of 0 – 0.001 mg/cm²/day is obtained. The higher level is regarded to represent the reasonable worst case situation. Considering an exposed area of 420 cm^2 (part of the hands) an exposure level of 0.4 mg/person/day is obtained.

Conclusions

For assessing the risks, 0.4 mg/person/day should be used. On account of the high vapour pressure of gasoline (350 - 900 hPa (CONCAWE 1992)) the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V). For gasoline with low concentrations of benzene, the evaporation time is assumed to be in the same range or lower. It is assumed, that dermal exposure occurs not daily.

4.1.1.2.8 Scenario 8: Tank cleaning

During manual cleaning of tanks and at tank cleaning stations exposure to benzene may occur. This is observed for cleaning crude benzene tanks, gasoline tanks and heating oil tanks.

Different methods of tank cleaning can be identified in tanks for heating purposes and at refineries (Lillienberg et al., 1992):

1. Pumping out residues followed by manual cleaning (heating oil tank, gasoline and diesel tanks at service stations)

2. Addition of light fuel oil, pumping out, and manual cleaning as in method 1 (tanks at central heating tanks).

3. Addition of small amounts of hot water and pumping out residues by strong compressor units with two workers inside the tank using shovels and squeegees to transport the oil and clean the tank. Occasionally, the workers would tread in the oil-water solution to make the oil less viscous (very large tanks at refineries, heavy fuel oil).

4. Washing the tank with water under pressure and transporting the water-oil-mud residues with aluminium shovels and squeegees to a manhole for pumping out (refineries, low boiling point petroleum).

5. Mechanically washing with a rotor jet cleaner and water (road tankers and railway tanks)

6. Mechanically washing with a rotor jet cleaner and perchloroethylen instead of water (was used for railway tanks containing heavy fuel oils, lubricants or asphalt).

Often, the tanks are ventilated up to 1 week before cleaning.

For crude benzene, a concentration of benzene of 75 % is reported.

For cleaning heating oil tanks it was reported, that personal protective equipment is not always used. On the other side, for cleaning bulk tanks at refineries and depots, tanks involved in gasoline distribution by road, rail and ship, and storage tanks at retail sites. CONCAWE (2001) provided the information that this work is normally carried out by specialist contractors. Safe entry procedures for confined spaces are well established. Entry is only done using fresh air breathing supply and full dermal protection. In, for example, the UK road tankers cleaning work is carried out by specialised personnel under a permit-to-work system.

Inhalation exposure

Workplace measurements

Table 4.11 Exposure to benzene during tank cleaning

Job category / activities	Years of measure-ment	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	95th-percentile [mg/m³]	Source
8-h time weighted average						
Manual works at tank cleaning stations, cleaning heating fuels and diesel fuel tanks, crude benzene tanks cars	1991 - 1995	19	-	14.4	67.7	BGAA (1997)
Gasoline tank cleaners (incl. sludge cleaning,	1993 - 1998	49	0.008 – 38.7	2.10	-	CONCAWE (2000)
Heating oil tanks	published 1992	4	4 – 8 20 – 130 min) [1]	-	-	Lillienberg et al. (1993)
Low boiling-point-petroleum, refinery:						
-After 1 week ventilation before cleaning		4	4 – 10 (60 – 160 min) [1]	-	-	
- After 2 days ventilation		2	78, 66 (100 min) [1]	-	-	
Gasoline station, diesel tank:			8 (76 min) [1]			
Supervising, outside tank		1		-	-	
Heating oil tanks	1999	4	≤ 0.1 (6.5 h) [1]	-	-	Rheinland Pfalz
personal sampling during		2	0.18, 0.44 (3.5 h) [1]	-	-	
cleaning		3	0.6 – 2.1 (< 1 h) [1]	-	-	
Short term level						
Low boiling-point-petroleum, refinery: -After 1 week ventilation before cleaning	-	2	27, 33 (15 min)	-	-	Lillienberg et al. (1993
Gasoline station, diesel tank	-	1	18 (8 min)	-	-	
Heating oil tanks exposure levels within the tank (fixed point measurements)	1999	20	< 0.1 – 26 (1 min)	-	-	Rheinland Pfalz
Heating oil tanks	2000	17	< 0.1 - 2.1	-	-	Berlin
short term exposure (15 min)		therefrom				
		10	< 0.1	-	-	
		6	0.1 – 1	-	-	
		1	2.9	-	-	
Exposure levels within the tank (fixed point measurements)		12	0.3 - 20.7 (2 min)	-	-	

1) in brackets: duration of measurement

The highest exposure levels are observed if crude benzene tanks are cleaned, lower levels if gasoline tanks are cleaned (see table 4.11). In BGAA (1997) it is stated that exposure levels above the mean value were obtained when crude benzene tank cars were cleaned without or with insufficient ventilation. No information could be obtained whether crude benzene tanks are cleaned daily.

For cleaning gasoline tanks, CONCAWE provided data from the period 1993 – 1998. In this period the permitted concentrations of benzene in gasoline were higher than currently. It is described, that gasoline storage tanks cleaning is a specialist activity usually involving specialist contractors.

Investigations in D revealed that heating oil contains approx. 30 mg/kg benzene. It is observed, that during cleaning volatile components evaporate from the oil-mud-mixture. This was observed even for tanks being ventilated 4 days (information from the Länder Berlin and Rheinland Pfalz (Federal States of Germany)). Stationary measurements within the tank after opening reveal benzene concentrations of 0.3 – 26 mg/m³. During tank cleaning, the use of personal protective equipment is commonly used, although exceptions are reported on. Meanwhile, instruction for safe cleaning work have been developed.

EASE estimation

On account of the high volatility of benzene, the EASE model predicts high exposure levels for tank cleaning. In this model estimation, special precaution procedures for the handling of highly toxic substances are not included. However, an EASE estimate for the scenario non dispersive use, LEV present (no aerosol formed, T = 20 °C, vapour pressure 91.7 hPa) which implies an rather high level of technical protection results in an exposure level of 32 – 64 mg/m³, thus confirming the high exposure level observed for crude benzene tank cleaning. In case of gasoline, using the same EASE scenario, lower levels are obtained if a concentration of 1 % benzene is considered.

Conclusions

For assessing the risk of daily inhalation exposure, a subdivision is made because based on the measurement data it can be seen that for cleaning heating tank exposure levels are considerably lower than at cleaning crude benzene tanks or cleaning gasoline tanks.

Scenario 8 a: This exposure scenario covers bulk tanks at refineries and depots, tanks involved in gasoline distribution by road, rail and ship, and storage tanks at retail sites. According to information provided by CONCAWE, this work is normally carried out by specialist contractors. Safe entry procedures for confined spaces are well established. Entry is only done using fresh air breathing supply and full dermal protection. In, for example, the UK road tankers cleaning work is carried out by specialised personnel under a permit-to-work system. As far as no further information is provided, it is assumed that 67.7 mg/m^3 (21.2 ml/m^3) (95th percentile) represents repeated daily exposure during crude benzene tank and gasoline tanks cleaning. The exposure assessment is based on up-to-date measurement results and should therefore reflect the current exposure situation. This value should therefore be taken for assessing the risks of daily inhalation exposure.

Scenario 8 b: Heating oil tanks: Lower levels were measured for heating oil tanks. For assessing the risks, 0.44 mg/m^3 (shift averages) and 2.9 mg/m^3 (short term (15 min)) should be taken. Meanwhile, instruction for safe cleaning work have been developed.

These exposure levels are regarded to represent the reasonable worst case situation.

Dermal exposure

Scenario 8 a: During tank cleaning of crude benzene tank cars, gasoline tanks dermal contact may occur. Considering a content of 75 % benzene and an exposed area of 420 cm^2 (palms of hands) dermal exposure is predicted in application of the EASE model (wide dispersive use, direct handling, intermittent) to 315 - 1575 mg/person/day. The higher value (1575 mg/person/day) is regarded to represent the reasonable worst case situation. For cleaning gasoline tanks, lower levels of exposure are expected.

Scenario 8 b: In case of heating oil tanks, the benzene concentration is approx. 30 mg/kg oil. Dermal exposure is assessed as low (< 1 mg/person/day).

Conclusions

Scenario 8 a: Based on the model estimates, for cleaning crude benzene tanks and gasoline tanks, 1575 mg/person/day should be taken for assessing the risks of daily dermal exposure. It should be considered, that full dermal protection may be applied as described by CONCAWE. However, information on the suitability of the protective equipment is at present not available.

On account of the high vapour pressure of benzene the resulting retention time of benzene on the contaminated surfaces and on the skin is considerably shortened thus lowering dermal exposure. The evaporation time of pure benzene (1 mg/cm²) is calculated to 10 seconds (appendix A V).

Inappropriate use of protective gloves may lead to the situation that benzene reaches the skin underneath worn gloves (occlusive conditions). Thus the evaporation of the substance is limited in dependence on the permeability of the applied glove material with regard to the penetration of benzene. Neither the amount of benzene reaching the skin underneath the gloves nor the extent of evaporation and consequently the resulting retention time of benzene underneath the gloves can be quantified. For the risk assessment of this worst-case scenario, it may be assumed, that the daily duration of the described exposure scenario - immediate skin contact to benzene underneath gloves - may last a few minutes.

Scenario 8 b: In case of heating oil tanks, the benzene concentration is approx. 30 mg/kg oil. Dermal exposure is assessed as low (< 1 mg/person/day).

4.1.1.2.9 Scenario 9: Use of formulations containing residual benzene

For many solvent uses, benzene has been replaced. 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. However, in the past, significant exposure occurred when benzene was used as a solvent in rubber cements, solvent based paints, paint stripper, carburettor cleaners or degreasing agents and in arts and crafts supplies.

In the rubber and plastics processing industry, exposure to benzene may be caused by thermal decomposition of plastics and in association with the application of formulations containing residual benzene.

Inhalation exposure

Workplace measurements

Table 4.12 Benzene exposure in the rubber and plastics industry

Job category / activities	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Source
8-h time weighted average				
Plastics and rubber industries (without local exhaust ventilation) plastics and rubber production, shoe manufacture, glueing	1991 - 1995	22	90th percentile: 1.0	BGAA (1997)
Thermal treatment of plastics (e.g. pressing, laser cutting)	1991 - 1995		< 0.1 [1)]	BGAA (1997)
Screen printing and spark machining in the metal industry	1991 – 1995		< 0.1[1)]	BGAA (1997)
Spray painting	1991 - 1995		< 0.1 [1)]	BGAA (1997)

1) detection limit

For most uses of formulations, the exposure levels are below the detection limit of 0.1 mg/m³.

EASE estimation

As a worst case, the EASE estimations are made for spray applications.

For modelling spraying formulations e.g. paints and adhesives, the input parameters: T = 20 °C, wide dispersive use, aerosol formation is true, dilution ventilation and direct handling are used. The estimated level of exposure amount to 500 - 1000 ml/m^3 for all volatile substances in the formulation. Based on a molar weigh of 100 g/mol, the exposure level of 2100 - 4200 mg/m³ is calculated. Considering the content of benzene is max. 0.1 % (w/w) in the liquid and assuming a solids content of approx 50 %, 0.2 % benzene in the liquid content of the paints, the exposure level is estimated to 4.2 - 8.4 mg/m³ (1.3 - 2.6 ml/m^3).

Spray painting without any protection measures are very unlikely to be performed during the whole shift. Considering a daily duration of exposure relevant activities of approx. 1 hour would effect a reduction of daily exposure to approx. 1 mg/m³.

Conclusions

For uses of formulations, the measurement results obtained at different workplaces reveal that exposure is below 1 mg/m³. This value is in accordance with the EASE estimate (considering a daily duration of 1 hour) and should be taken for assessing the risks.

Dermal exposure

Dermal exposure during handling of preparations with < 0.1 % (w/w) benzene is assessed in application of the EASE model 1.3 - < 6.5 mg/person/day for wide dispersive use (direct handling, intermittent) assuming a exposed area of 1300 cm² mg/person/day. The higher value is regarded to represent the reasonable worst case situation. Taken into account the high vapour pressure of benzene, dermal exposure is assumed to be reduced due to evaporation of the substance.

4.1.1.2.9 Scenario 10: Tire making and retreading

Tires are a large scale product of the rubber industry. Tire making comprise several working steps: compounding, extrusion, calendering, finishing. During tire making and retreading, exposure may occur during thermal decomposition and during use of adhesives or glues for embedding textile fabrics into caouchtouc layers. Strong adhesives are applied to bond the fibre to the rubber forming a composite. The cords are heat treated to impart desired characteristics. The composition of the adhesive formulations depend on the final tire performance requirements. The adhesives are also used for tire retreading, during which the new tread rubber has to be fixed on the tire by means of glueing**.**

Inhalation exposure

Workplace measurements

Table 4.13 Benzene exposure during tire making and retreading

Job category / activities	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Source
8-h time weighted average				
Tires vulcanisation operators industrial rubber operators	--	-- --	4 1.2	Berg et al. (1982)
Tire making compounding, extrusion, curing preparation	1973 - 1977	--	0.3 - 18.9	van Ert (1980) (USA)
Tire retreading application of adhesives, inter alia spraying	1991	8	0 - 10 mean: 4.2	Federal monitoring authorities in D
Tire building and retreading application of adhesives	2001	67	0.01 – 2.7 mean: 0.07	BLIC 2001

Measurement results provided by the Federal Monitoring Authorities in Germany (table 4.13) relating to tire retreading indicate, that during application of the adhesives exposure to benzene could occur. Although the content of benzene in preparations is limited to 0.1 %, exposure levels up to 10 mg/m^3 (3.1 ml/m^3) were provided (in part manual spray application). The measurement results from the Federal Monitoring Authorities in Germany given in table 4.13 were obtained in one company. It is questionable whether these results are representative for tire retreading or for all uses of formulations containing residual benzene. However, it cannot be excluded, that benzene being released during thermal decomposition contributes to inhalation exposure, too.

More recently obtained measurement results were provided by the European Association of the Rubber Industry (BLIC). The results were obtained in 10 companies making and retreading tyres with the highest level of 2.7 mg/m³. No detailed information on the workplaces and activities are available. The association describes, that in the retread sector a significant shift has occurred in the last 5 years towards the use of water based adhesive which are used for 80 % of all retreading operations.

Furthermore, the value provided by the Federal Monitoring Authorities in Germany is in contradiction to more recent investigations describing the exposure situation in the rubber industry in UK and NL (Dost et al., 2000, Swuste and Kromhout, 1996), in which the individual benzene was not detected in the aromatic volatiles.

In the past, Berg et a. (1982) and van Ert (1980) reported on exposure to benzene within the rubber industry during vulcanisation of tyres (up to 20 mg/m^3) (6.25 ml/m^3). Since no up to date data could be obtained it is to be assumed, that these exposure scenarios have become outdated.

Conclusions

For the purpose of assessing the risks of daily inhalation exposure 2.7 mg/m^3 (highest measurement result provided by BLIC) should be taken for the area of tire retreading and making. It is assumed, that this value represents the current situation for tyre retreading and

making.

Dermal exposure

For the use of strong adhesives it to be assumed, that workers avoid the contamination of large skin areas, because the skin is difficult to clean. Therefore, dermal exposure during use of glues containing < 0.1 % (w/w) benzene in the field of tire making and retreading is assessed in application of the EASE model (non dispersive use, direct handling, intermittent) to 0.04 – 0.4 mg/person/day assuming an exposed area of 420 cm². The higher value is regarded to represent the reasonable worst case situation. Taken into account the high vapour pressure of benzene, dermal exposure is assumed to be reduced due to evaporation of the substance.

Conclusions

In conclusion, the highest estimated exposure level of 0.4 mg/person/day is taken forward for assessing the risks of daily inhalation exposure for tire retreading and for the use of formulations. Taken into account the high vapour pressure of benzene, dermal exposure might reduced due to evaporation of the substance. Because of the complex drying behaviour of paints or adhesives, an evaporation time cannot be calculated. Nevertheless it is assumed, that exposure is shorter than shift length (as calculated with the EASE model: exposure per day).

4.1.1.2.11 Scenario 11: Release of benzene as a decomposition product in foundries

Within foundries, exposure to benzene is to be considered if casting into synthetic resin bound casting moulds is performed. In this, benzene may be released as a decomposition product. Detailed information on exposure relevant activities are not available.

Inhalation exposure

Workplace measurements

Table 4.14 Benzene exposure at workplaces belonging to foundries

Job category / activities	Years of measurement	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95th - percentile [mg/m^3]	Source
8-h time weighted average						
Foundry, casting without local exhaust ventilation with local exhaust ventilation	1991 - 1995	 52 11	 -- --	 0.5 < detection limit	 5.4 1.6	BGAA (1997)
Moulding machine	1991	2	--	6.4	--	Federal monitoring authorities in D

Conclusions

For assessing the risks of daily inhalation exposure, 5.4 mg/m^3 (1.7 ml/m^3) without local exhaust ventilation (LEV) and 1.6 mg/m^3 (0.5 ml/m^3) with LEV should be taken (95th percentiles). The exposure assessment is based on data from 1991 – 1995 and do possibly not reflect the current working conditions.

Since benzene is released as a decomposition product, inhalation exposure cannot be assessed in application of the EASE model and comparisons of predicted and measured exposure levels cannot be made.

Dermal exposure

Because benzene is released during thermal processes, normally no immediate skin contact occurs. Considering the only possibility of dermal exposure by touching benzene contaminated surfaces and the high vapour pressure of benzene (99.7 hPa), the dermal exposure level in foundries is regarded as being low (here: < 1 mg/person/day).

4.1.1.2.12 Summary of exposure data relevant for workplace risk assessment

Based on the information available within the frame work of this exposure assessment it is concluded, that occupational exposure to benzene occurs mainly in the production of benzene and its further processing as a chemical intermediate as well as in the refinery and distribution of gasoline. Furthermore, since benzene is a residual component of solvents, exposure may occur during the manufacture and use of solvent based formulations and products (e.g. paints,

adhesives). In addition, there are indications that benzene may occur as a decomposition product in foundries.

A summary of the exposure assessment is given in table 4.15 and 4.16. All values are seen to represent the reasonable worst case situation (RWC: reasonable worst case).

Some additional remarks:

The assessment of occupational exposure is difficult because the legal conditions have changed recently and will change in the near future. These changes relate to the reduction of the permitted concentration of benzene in gasoline from 5 % (v/v) to 1 % (v/v) from 1. January 2000, the changes of the OEL in the EU to 3.25 mg/m³ from 27. June 2003 onwards with a currently valid transitional OEL of 9.6 mg/m³ (valid since 27. June 2000). 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.

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 (Runion 1975) and is used for the prediction.

Dermal exposure is exclusively assessed according to the EASE model. As an exposure reducing effect, the high volatility of benzene is considered. The evaporation time (up to 10 s) is calculated and given in addition to the EASE estimates.

Table 4.15 Summary of exposure data (RWC) concerning inhalation exposure which are relevant for occupational risk assessment

Inhalation exposure									
No.	**Area of production and use**	**Form of exposure**	**Activity**	**Duration**	**Frequency**	**Shift average [mg/m³]**	**Method (years of measurement)**	**Short-term [mg/m³]**	**Method**
Production and further processing of benzene									
1	Production , further processing, refinery	vapour	transfer, filling, sampling, storage, maintenance, cleaning, repair, waste treatment	shift length	daily	**3.5** [1)]	95th percentile (before 1995)	**64** [1)]	highest measurement result (30 min)
2	Recovery of benzene in coking plants by product recovery	vapour	see production	shift length	daily	**15.5** [1)]	highest result (1990 – 1991)	--	--
Formulation									
3	Production of perfumes, use of benzene	vapour	handling (activities unknown)	shift length (assumed)	daily	**84** [1)]	90th percentile (1987 – 1995)	--	-
4	Production of formulations, use of solvents	vapour	charging, filling	shift length (assumed)	daily	**0.15** [1)]	highest result (1987 - 1999)	--	--
Use of gasoline									
5	Distribution of gasoline (marine road, rail), 1% benzene,a) without VR, b) with VR	vapour	filling, loading, transfer	shift length (assumed)	daily	**a) 6.8** (without VR)[3)] **b) 1.26** (with VR) [3)]	90th percentiles (1999 – 2000)	--	--

Inhalation exposure									
No.	**Area of production and use**	**Form of exposure**	**Activity**	**Duration**	**Frequency**	**Shift average [mg/m^3]**	**Method (years of measurement)**	**Short-term [mg/m^3]**	**Method**
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	vapour	works at fuel system, works at test stands, maintenance, drain off gasoline	4 hours (assumed)	daily	**2.25** [4)]	Results obtained before 1995 modified using EASE estimates	**38** [1)]	highest measurement result, before 1994
7)	Service stations, handling of gasoline (1 % benzene) a) without VR, b) with VR	vapour	take in fuel	4 hours (assumed)	daily	**a) 0.5** (without VR) [3)] **b) 0.1** (with VR) [3)]	90th percentiles (1999 – 2000)	--	--
Other									
8	Cleaning of tanks - crude benzene tanks, gasoline tanks (a) - heating oil tanks (b)	vapour	cleaning	8 hours (assumed)	daily	**a) 67.7** [1)] **b) 0.44** [3)]	95th percentile (before 2000) highest result, (2000)	-- **2.9** [3)]	-- highest result (15 min) 2000
9	Use of formulations with residual benzene, e.g. adhesives paints, containing < 0.1% benzene	vapour	glueing	shift length	daily	**1** [5)]	95^{t}h percentile (1991 – 1995)	--	---
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	vapour	glueing, in part spraying	4 hours (assumed)	daily	**2.7** [1)]	highest result, (before 1991)	--	--

Inhalation exposure									
No.	**Area of production and use**	**Form of exposure**	**Activity**	**Duration**	**Frequency**	**Shift average [mg/m^3]**	**Method (years of measurement)**	**Short-term [mg/m^3]**	**Method**
11	Foundries, a) without LEV, b) with LEV	vapour	casting	shift length	daily	**a) 5.4** [1)] **b) 1.6** [1)]	95thh percentile (without LEV) 95th percentile (with LEV) (1991 – 1995)	-- --	-- --

[1)] Exposure levels are assessed based on data from before 1995. Therefore, the data possibly do not reflect the current workplace situation.
[2)] Limited information with regard to the activities and the time period during which the data were obtained.
[3)] Measurement results are regarded to represent the current exposure situation.
[4)] 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
[5)] limited number of measurement results from one company, supported by EASE estimates
VR: vapour recovery

Table 4.16 Summary (RWC) of exposure data concerning dermal exposure which are relevant for occupational risk assessment

Dermal exposure								
No.	**Area of production and use**	**Form of exposure**	**Activity**	**Frequency, contact level [1)]**	**Level of exposure [mg/cm²/day]**	**Exposed area [cm²]**	**Shift average [mg/p/day]**	**Method**
Production and further processing of benzene								
1	Production, further processing, refinery	liquid	transfer, filling, sampling, storage, maintenance, cleaning, repair, waste treatment	daily, intermittent	low 1	-- 420	**low** **420**	expert judg.[2)] EASE[3)]
2	Coking plants, by-product recovery	liquid	see production	daily, intermittent	1	420	**420**	EASE [4)]
Formulation (use of solvents containing residual benzene)								
3	Production of perfumes, handling of benzene	liquid	handling, activities unknown	daily, intermittent	1	420	**420**	EASE[6)]
4	Production of formulations, use of solvents, benzene content unknown, assumption: 5 %	liquid	see production	daily intermittent	0.01	420	**4.2**	EASE[6)]
USE OF GASOLINE								
5	Distribution of gasoline (marine road, rail), 1% benzene	liquid	filling, loading	daily, intermittent	0.01	420	**4.2**	EASE[5)]

Dermal exposure								
No.	**Area of production and use**	**Form of exposure**	**Activity**	**Frequency, contact level [1)]**	**Level of exposure [mg/cm^2/day]**	**Exposed area [cm^2]**	**Shift average [mg/p/day]**	**Method**
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	liquid	works at fuel system, works at test stands, maintenance, drain off gasoline	daily, intermittent	0.01	840	**8.4**	EASE[8)]
7	Service stations, handling of gasoline (1 % benzene)	liquid	take in fuel	not daily, incidental	0.001	420	**0.4**	EASE[7)]
Other								
8	Cleaning of tanks: crude benzene tanks, gasoline tanks 75 % benzene (a) heating oil tanks (30 ppm benzene) (b)	Contact with contaminated surfaces	cleaning	daily, intermittent	3.75	420	**a) 1575** **b) negligible**	EASE[4)] expert judg. [11)]
9	Use of formulations with residual benzene, e.g. adhesives, paints containing < 0.1% benzene	liquid	glueing, painting	daily, intermittent	0.005	1300	**6.5**	EASE[10)]
10	Tire retreading, here: using adhesives, EASE prediction assuming < 0.1 % benzene	liquid	glueing, in part spraying	daily, intermittent	0.001	420	**0.4**	EASE[10)]

Dermal exposure								
No.	**Area of production and use**	**Form of exposure**	**Activity**	**Frequency, contact level [1)]**	**Level of exposure [mg/cm^2/day]**	**Exposed area [cm^2]**	**Shift average [mg/p/day]**	**Method**
11	Foundries	Contact with conta-minated surfaces	--	--	--	--	**low**	exp. judg.[9)]

[1)] contact level according to EASE model
[2)] expert judgement of dermal exposure for the proper use of suitable gloves, consideration of the high volatility of benzene, evaporation time: 10 s (order of magnitude)
[3)] unsuitable gloves, worst-case estimation for unprotected contacts without gloves, lower exposures are expected because of the considerably shortened retention time of benzene on the skin (vapour pressure: 99.7 hPa, evaporation time: 10 s (order of magnitude)), occlusive exposure is regarded as non-probable
[4)] dermal exposure is predicted assuming that gloves are not worn; lower exposures are expected because of the short retention time of benzene on the skin (vapour pressure: 99.7 hPa, evaporation time: 10 s (order of magnitude)); in case of occlusive conditions the retention time may be prolonged to a few minutes
[5)] dermal exposure is predicted assuming that gloves are not worn; lower exposures are expected because of the short retention time of gasoline on the skin (vapour pressure: 50 - 900 hPa, evaporation time: 10 s (order of magnitude)); in case of occlusive conditions the retention time may be prolonged to a few minutes
[6)] dermal exposure is predicted assuming that gloves are not worn (worst case), lower exposures are expected because of the short retention time of benzene or of solvents on the skin evaporation time of pure benzene: 10 s (order of magnitude)
[7)] dermal exposure is predicted assuming that gloves are not worn, lower exposures are expected because of the short retention time of gasoline on the skin (vapour pressure: 50 - 900 hPa, evaporation time: 10 s (order of magnitude)
[8)] dermal exposure is predicted assuming that gloves are not worn; lower exposures are expected because of the short retention time of gasoline on the skin (vapour pressure: 50 - 900 hPa, evaporation time: 10 s (order of magnitude)); repeated immediate contact to gasoline may prolong the retention time to a few minutes per day
[9)] rough estimation; benzene is released as a decomposition product, secondary contact with contaminated surfaces (< 1 mg/p/d)
[10)] dermal exposure is assessed assuming that gloves are not worn, dermal exposure is reduced because of the high volatility of benzene
[11)] expert judgement based on the low concentration of benzene in heating oil (< 1 mg/person/day)
VR: vapour recovery

4.1.1.3 Consumer exposure

Consumer exposure to benzene (active use of a product) results from tobacco smoking and filling gasoline at a filling station.

Additionally, there are data that benzene may be present as a contaminant in consumer products (Rastogi, 1993). According to these data 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 probable content of benzene in consumer products of 2.5 mg/l may be derived.

Inhalation exposure

Exposure from smoking (scenario 1) Cigarette smoke contains high amounts of benzene. The amounts of benzene are between 10 and 100 µg per cigarette respective 150 to 240 µg/m³ in the mainstream. It has to be assumed that smokers will be exposed to a large amount of benzene during smoking since they inhale the mainstream and sidestream directly. The uptake on benzene per cigarette is estimated to account up to 30 µg (Eikmann et al., 2000). From this estimate, a smoker who smokes 20 cigarettes per day will inhale up to 600 µg of benzene. This is in agreement with estimations by Hoffmann et al. (1990/1991) who stated that a smoker absorbs about 400 µg benzene when smoking 20 cigarettes/day.

Wallace & Pellizari (1986) have measured benzene air concentrations in homes of smokers and non-smokers. 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 air 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). The authors do not specify the variation of the data. For passive smokers, it is assumed that exposure duration is 24 hours (worst case) as a non-smoking family member.

The estimate of benzene exposure by passive smoking is in agreement with the uptake of 30 µg per day which has been given by Eikmann et al. (2000). However, taking into consideration, that the air concentrations measured by Wallace & Pellizari (1986) are mean values, these estimates do not characterize extremes of exposures. A comparison with concentrations of benzene in blood of smokers shows high variabiliy with a range from < 60 up to 950 ng/l (95th percentile: 850 ng/ml). It must therefore be assumed, that exposure to benzene may exceed the estimated values considerably.

Exposure from painting (scenario 2)

Exposure to benzene from paints[1] was estimated taking the CONSEXPO Scenario "painting" and the model "painting". For this calculation, 200 g of a paint containing 2.5 mg/l (= mg/kg) as a residual of benzene is painted to an area of 2 m², in a room having a volume of 30 m³,

[1] Solvent based paint, mostly used for painting smaller areas, e.g. wooden material such as doors, and windows

with a personal volume[2] of 5 m³. The duration of actual use is 5 hours, the overall contact time is one day.

Use of the CONSEXPO model reveales an average concentration of benzene during use for the user of 17 µg/m³, for the bystander (non-user) of ~ 3µg/m³.

Exposure during filling gasoline and driving by cars

Inhalation exposure may be characterised by the following scenarios:

Filling the tank of a car at filling stations *(scenario 3)*

It is reported by CONCAWE (2000) that at filling stations the average benzene concentration during a three minutes car refuelling is 0.8-1.0 mg/m³. According to exposure data during gasoline refuelling the overall arithmetic mean concentration 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). For risk characterisation the maximum value of this data set of 1.3 mg/m³ will be selected. Higher concentrations of 4.3 mg/m³ have been given by Vainiotalo et al. (1999) from a previous study during 1984-1985 in which the average benzene content of gasoline was reported to be 4% (w/w).

Extreme concentrations of benzene of 50 mg/m³ at filling stations directly nearby the filling tube have been measured (Eikmann et al., 2000). These values should not be taken for exposure estimations, because this is considered as an extreme situation, and concentrations of benzene will be normally lower.

Exposure from car interior accessories (scenario 4)

As a further scenario, consumers may be exposed to benzene from car interior accessories when driving by car.

Average concentrations of benzene levels inside cars vary between 10 and 120 µg/m³, as shown by different studies from Sweden, USA, and NL (Eikmann et al., 2000). The benzene concentration declines within a period of 10 weeks to less than 10% of this concentration (Brown and Cheng, 2002) 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.

[2] The personal volume in CONSEXPO characterises an hypothetical volume which surrounds the user. The concentration in this volume is assumed to be higher than that in the room. Non users and bystanders inhale lower concentrations.

Oral exposure

For the identified consumer exposure scenarios, exposure to benzene via the oral route would only be associated with accidents. Oral exposure is thus not considered relevant for the risk assessment.

Dermal exposure

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 the risk characterisation.

Conclusion

The following exposure estimates of benzene concentrations 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

4.1.1.4 Humans exposed via the environment

The uptake of benzene by man via ambient air, drinking water, vegetables, milk, and meat is calculated. For benzene it can be assumed that the predominant exposure pathway is via air. According to the TGD both a local and a regional scenario should be considered. No monitoring data are available that could serve as a $PEClocal_{air}$ for industrial production and/or processing sites. The data described in chapter 3.1.3.2 on benzene air concentrations at refineries cannot be regarded as representative for European production and processing sites. Therefore, estimated local air concentrations have to be used. In the exposure assessment (see table 3.39) a range of emissions to air covering three orders of magnitude is estimated depending on the data basis available. Different values representing relevant scenarios for indirect exposure are selected (see table 4.18). All other input values for the estimation are compiled in table 4.17.

Table 4.17 Input of environmental values for indirect exposure of man via the environment

Parameter	Value/Unit	Source
Pow	2.13	table 1.1
Henry partition coefficient	433 Pa m^3/mol	table 3.23
$K_{air-water}$	0.178	table 3.23
fraction of chemical associated with aerosol	10^{-8}	table 3.31
half-life for biodegradation in surface water	15 d	table 3.21
local PEC in surface water (dissolved)	40 µg/l	table 3.33
local PEC in grassland	0.0132 mg/kg	Soil Exposure Model
local PEC in porewater of agricultural soil	4.8 µg/l	Soil Exposure Model
local PEC in porewater of grassland	5.2 µg/l	Soil Exposure Model
local PEC in groundwater under agricultural soil	4.8 µg/l	Soil Exposure Model
regional PEC in surface water (dissolved)	0.28 µg/l	Simplebox
regional PEC in air	1.54 µg/m^3	Simplebox
regional PEC in agriculture soil	0.017 µg/kg	Simplebox
regional PEC in porewater of agricultural soils	0.007 µg/l	Simplebox

Tab. 4.18 Local scenarios considered for indirect exposure

Scenario	Estimated range of emission	Selected value	$PEClocal_{air-annual}$	Resulting DOSEtot
Default emission to air direct (10 sites)	403.33– 9000 kg/d	Mean : 3888 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

For the regional scenario the estimated PECregional (see chapter 3.1.6.2) is used for the estimation. The resultant daily dose is:

DOSEtot = 0.34 µg/kg body weight day

In addition to the scenarios described above, for benzene unintentional releases from road traffic are considered relevant for indirect exposure. Several monitoring data are available representing this situation. 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 (see Appendix A II, table No. 7 and table 3.4.1). Further factors influencing the benzene concentration are climate, season, local geographic conditions and the condition of the local vehicle fleet. 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

DOSEtot = 4.3 µg/kg body weight day

The input data for the model calculation is presented in detail in the appendix A IV.

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.

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

4.1.2.1 Toxico-kinetics, metabolism and distribution

Absorption

Animal data

Benzene appears to be efficiently absorbed following oral dosing in animals. After oral administration of 14C-labeled benzene to rabbits (340-500 mg/kg bw), approximately 80% of the administered radioactivity was eliminated within 2 to 3 days after dosing in exhaled air in urine, indicating that at least this amount was absorbed (Parke and Williams 1953). In more recent studies, gastrointestinal absorption of benzene in rats and in mice was >97% when doses between 0.5 and 150 mg benzene/kg bw were administered by gavage (Sabourin et al. 1987).

Inhalation studies in rodents suggested that the uptake of benzene by the lungs was related to the concentration in a non-linear manner (Sabourin et al. 1987). For inhalation exposures, the mean percentage of inhaled 14C-benzene absorbed and retained in the tissues and blood during a 6-hr exposure decreased from 33% to 15% in rats, and from 50% to 10% in mice, as the exposure concentration was increased from approximately 26 to 2600 mg/m³ (8 to 812 ppm). Greater absorption of benzene at lower concentrations by mice than rats is partially explained by physiological differences in respiratory rate and tidal volume. At similar vapour concentration exposures, mice take up 1.5 - to 2.0-fold the dose per kilogram body weight compared to rats.

Benzene is absorbed through the skin. In studies conducted in rhesus monkeys, miniature pigs, and hairless mice, dermal absorption was <1% following a single direct application of liquid benzene (Franz 1984; Maibach and Anjo 1981; Susten et al. 1985). The rate of absorption could not be determined exactly, however the highest levels of urinary C14-excretion were observed in the first 8 hours following exposure (Franz 1984). Multiple applications to intact skin resulted in greater amount absorbed (Maibach and Anjo 1981).

Benzene in air was rapidly absorbed through the skin of hairless mice that were attached to respirators to avoid pulmonary uptake of benzene vapours (Tsuruta 1989). The rate of absorption of benzene vapour through the skin increased linearly with dose and with exposure time. The skin absorption rates were 0.00032 mg/cm²/hour (4.11 nmol/cm²/hour) at 640 mg/m³ (200 ppm); 0.00189 mg/cm²/hour (24.2 nmol/cm²/hour) at 3200 mg/m³ (1000 ppm); and 0.0059 mg/cm²/hour (75.5 nmol/cm²/hour) at 9600 mg/m³ (3000 ppm). The skin absorption coefficient calculated by dividing the skin absorption rate by the exposure concentration was 0.619 cm/hour (Tsuruta 1989). In rats with closely clipped fur exposed to benzene vapours, the skin absorption coefficient was calculated to be 0.152 cm/hour (McDougal et al. 1990). Thus, there appears to be species differences in the skin absorption coefficient for benzene.

Human data

The inhalation pathway represents the major route of human exposure to benzene. Inhaled benzene taken up by diffusion through the alveoli (Nomiyama and Nomiyama 1974; Snyder et al. 1981b), with the highest extraction occurring at the onset of inhalation exposure with an declining extraction coefficient with time due to the declining concentration gradient between the concentration in the alveoli and concentration in blood. For example, an inhalation study of 23 subjects exposed to 150-350 mg/m³ (47-110 ppm) of benzene for 2-3 hours showed that during the first five minutes of exposure 78-80% was extracted from the inhaled air, but after one hour, the extraction was reduced to approximately 50% (range, 20-60%) (Srbova et al. 1950). Results from men (n=4) and women (n=2), exposed to benzene concentrations of 166-198 mg/m³ (52-62 ppm) for 4 hours, showed no gender differences with extraction (about 50%) reaching a constant level after 2 hours of exposure (Nomiyama and Nomiyama 1974). In a similar study design, three healthy nonsmokers were exposed to benzene at levels of 1.6 ppm or 9.4 ppm for 4 hours (Pekari et al. 1992). The amount of benzene absorbed was estimated from the difference between the concentration inhaled and concentration exhaled. Estimates were 48% for the high dose and 52 % for the low dose, supporting the evidence of Nomiyama and Nomiyama (1974). Additional evidence of benzene absorption following inhalation exposure comes from data on cigarette smokers. Benzene levels were significantly higher in the venous blood of 14 smokers (median level of 547 ng/l) than in a control group of 13 nonsmokers (median level of 190 ng/l) (Hajimiragha et al. 1989). Cigarette smoke is known to contain benzene (Brunnemann et al. 1989; Byrd et al. 1990), and the subjects had no known exposure to other sources of benzene (Hajimiragha et al. 1989).

Studies in humans documenting the rate of absorption of benzene following oral ingestion are not available. However, based on cases of accidental or intentional ingestion, it appears that benzene is readily absorbed after oral ingestion.

Results from in vivo experiments indicate that liquid benzene can be absorbed through human skin. The data show that dermal absorption is not as substantial as absorption following inhalation or oral exposure. The movement of a substance through the skin to the blood occurs by passive diffusion and has been described mathematically by Fick's law. However, this is an oversimplification of the process of skin absorption; various factors (e.g. interaction of benzene with molecules within the skin) affect the transport of the solvent through the skin (Loden 1986).

In vivo experiments by Franz (1984) on four human volunteers, in which 0.0026 mg/cm² of 14C-benzene was applied to forearm skin, demonstrated that benzene was absorbed through skin. More than 80% of the total excreted amount were eliminated in the first 8 hours after application. Calculations on the amount absorbed were based on urinary excretion data and no correction was made for the amount of benzene that evaporated from the applied site before absorption occurred. In addition, the percentage of absorbed dose excreted in urine that was used in the calculation was based only on data from rhesus monkeys and may not be accurate for humans. Hence, the statement that approximately 0.05% of the dose was absorbed has to be considered with some caution.

In another study, 35-43 cm² of the forearm were exposed to approximately 0.06 g/cm² of liquid benzene for 1.25-2.0 hours (Hanke et al. 1961). The degree of absorption was estimated from the amount of phenol eliminated in the urine. The absorption rate of liquid benzene by the skin (under the conditions of complete saturation) was calculated to be approximately 0.4

mg/cm²/hour. However, this absorption rate is likely to be overestimated due to methodological deficiencies (Maibach and Anjo 1981).

In vitro experiments utilizing human skin also support the fact that benzene can be absorbed dermally. An experiment on the permeability of excised human skin to benzene (specific activity 99.8 mCi/mmol; concentration of applied benzene not reported) demonstrated the absorption of 0.17 mg/cm² after 0.5 hours and 1.92 mg/cm² after 13.5 hours (Loden 1986). Following application of 5, 120, 270, and 520 µl/cm² (4.4, 106, 237, and 457 mg/cm²) of benzene to human skin, total absorption was found to be 0.01, 0.24, 0.56 and 0.9 µl/cm² (0.009, 0.211, 0.492, and 0.79 mg/cm²), respectively. Thus, the total amount absorbed appears to increase linearly with dose and exposure time (i.e. the time to complete evaporation). The percentage of the applied dose absorbed at each concentration was constant at about 0.2% (Franz 1984).

Distribution

Animal data

Following exposure of male F344 rats to 1600 mg/m³ (500 ppm) benzene via inhalation steady state concentrations of benzene were reached within 4 hours in blood (11.5 mg/ml), 6 hours in fat (164.4 mg/g) and less than 2 hours in bone marrow (37.0 mg/g) (Rickert et al. 1979). Absorbed benzene was found to distribute in tissues rich in lipids and/or with high perfusion rates, i.e., the kidney, lung, liver, brain and spleen. The relative uptake in tissues appears to be dependent on the perfusion rate of tissues.

Similar to the inhalation route, benzene is rapidly absorbed and distributed to various organs and tissues after oral administration. Relatively low dose levels (0.15 and 1.5 mg 14C-labeled benzene/kg bw) in Sprague Dawley rats resulted in the highest radioactivity/kg bw 1 hour after dosing in the liver and kidney (27% and 34%, resp., of total radioactivity found in all analyzed tissues), intermediate levels were found in the blood (12% of total radioactivity), and the lowest levels in the Zymbal gland, nasal cavity and mammary gland (less than 6% in these tissues) (Low et al. 1989). When higher doses of benzene (15 mg/kg bw) were administered, there were larger increases in the levels found in mammary glands (12%), adipose tissue (percentage of radioactivity not given) and bone marrow (18%) than in other tissues, indicating a shift from well perfused tissues to those with high lipid content.

For the more water soluble benzene metabolites, the distribution differs from that of the parent compound. One hour after oral administration of 15 mg/kg bw of benzene to rats, the highest tissue concentrations of hydroquinone were found in the liver, kidney, and blood (Low et al. 1989). The hydroxymetabolite phenol attained its highest concentrations in the oral cavity, nasal cavity, and the kidney. The major target sites of the conjugated benzene metabolites were blood, bone marrow, oral cavity, kidney, and liver for phenyl sulfate, hydroquinone glucuronide, and trans,trans-muconic acid. The Zymbal gland and nasal cavity were depots for phenyl glucuronide, another conjugated metabolite of benzene.

Benzene metabolites (phenol, catechol, and hydroquinone) were detected in blood and bone marrow of rats following 6 hours of inhalation exposure to benzene (Rickert et al. 1979). Levels in bone marrow exceeded the respective levels in blood. After cessation of exposure,

the levels of phenol in blood and bone marrow decreased much more rapidly than those of catechol or hydroquinone.

Benzene can cross the placenta and distribute to developing offspring. Ghantous and Danielsson (1986) exposed pregnant mice to a benzene concentration of 6400 mg/m³ (2000 ppm) for 10 minutes and found benzene and its metabolites in lipid-rich tissues such as the brain and fat, as well as in perfused tissues such as liver and kidney. Benzene also was found in the placenta and fetuses immediately following exposure. Data are not available to estimate the proportion of the dose that reached the fetus.

Differences in bioavailability of benzene occur following dermal exposure to soil-bound versus pure chemical, with the type of soil being an important factor (Skowronski et al. 1988). Male rats were dermally exposed to 0.004 mg/cm² of 14C-benzene neat or adsorbed to 1 gram of clay or sandy soil. The highest peak plasma concentration of radioactivity was produced by pure benzene, followed closely by sandy-soil adsorbed benzene with the clay-soil adsorbed benzene producing the lowest value. The plasma elimination half-lives of radioactivity were 24.5 hours (sandy soil), 23.0 hours (pure benzene) and 19.4 hours (clay). Retention of benzene at the application site was higher for soil-treated groups where tissue concentrations of radioactivity after 48 hours were highest in treated skin [0.011% (pure), 0.059% (sandy) and 0.119% (clay)], followed by kidney and liver. For the pure benzene group, internal tissue concentrations were highest in kidney, followed by liver and skin. These data suggest that bioavailability of benzene following dermal exposure may be affected by soil type, however, detailed quantitative data are not available. It also suggests that clay soil may bind benzene more tightly, and that benzene is less able to be adsorbed from clay soils than from sandy soils or through contact with pure benzene. The conclusion of the authors (Skowronski et al. 1988) concerning distribution differences cannot be accepted as they did not measure benzene but the C-14-label.

Human data

Data on the distribution of benzene in humans are derived primarily from case studies reporting inhalation exposure to benzene. Overall, the data suggest that benzene is distributed throughout the body following absorption into blood. Benzene is lipophilic and lipid-rich tissues have been found to contain the highest levels. In one autopsy report performed on a youth who died while sniffing reagent grade benzene, the following benzene concentrations were reported: 2.0 mg % in blood, 3.9 mg % in brain, 1.6 mg % in liver, 1.9 mg % in kidney, 1 mg % in stomach, 1.1 mg % in bile, 2.23 mg % in abdominal fat, and 0.06 mg % in urine (Winek and Collom 1971). Benzene also has been shown to cross the human placenta and has been found in the cord blood in amounts equal to or greater than those in maternal blood (Dowty et al. 1976).

Metabolism

Metabolic pathways

The metabolism of benzene is an important determinant in the expression of its toxicity (Snyder and Kocsis 1975; Snyder et al. 1989; Irons and Moore 1980; Schlosser et al. 1995; Valentine et al. 1996). Benzene metabolism has been extensively studied and appears to

follow similar pathways in both animals and humans; however remarkable species variability has been demonstrated.

The liver is the major site of benzene metabolism. Benzene is converted to a number of metabolites by the cytochrome P-450 dependent mixed-function oxidase system. The P-450 enzyme CYP 2E1 appears to exhibit the greatest affinity for benzene and is the most active in benzene metabolism. CYP 2B1 is also capable of hydroxylating benzene, but contributes to the metabolism only at higher concentrations. Oxidative metabolism by CYP 2E1 is required for manifestation of the haematotoxic and genotoxic effects of benzene as confirmed recently by studies on the benzene in vivo metabolism in transgenic CYP 2E1 knockout mice (Valentine et al. 1996).

Moreover, metabolism of benzene by CYP 2E1 has also been observed in bone marrow leading to the formation of phenol and hydroquinone in a ratio of about 7:1 (Schnier et al. 1989).

The toxicity of benzene is enhanced by ethanol through its induction of CYP 2E1, increasing the severity of benzene-induced anemia, lymphocytopenia, and reduction in bone marrow cellularity (Baarson et al. 1982; Post and Snyder 1983 a, b). Other inducers of CYP 2E1 such as isoniazid, isopropanol, diabetes, and fasting would be expected to produce similar enhancement. On the other hand, repeated oral exposures to low levels of benzene (<50 mg/kg bw/d over 3 weeks) to CD-1 mice decreased the CYP 2E1 activity by 34% (Daiker et al. 1996).

The pathways for the biotransformation of benzene are shown in appendix A VI. It is though that cytochrome P-450 enzymes catalyze the addition of a single oxygen atom to the benzene ring, forming the initial monoepoxide, i.e. benzene oxide (Jerina et al. 1968). There are four possible pathways of subsequent benzene oxide metabolism. One pathway includes conjugation by glutathione to yield a premercapturic acid, which is further metabolized in the kidney to the detoxified product: phenyl mercapturic acid. The latter is then excreted in the urine (Henderson et al. 1989; Sabourin et al. 1988). Another suggested pathway is via rearrangement of benzene oxide non-enzymatically to yield phenol. Subsequent hydroxylation of phenol may yield hydroquinone, catechol, or 1,2,4-trihydroxybenzene (benzenetriol). A third pathway yields benzene dihydrodiol by addition of water to benzene oxide. The latter may be oxidized via dihydrodiol dehydrogenase to catechol, thereby providing an alternate pathway for catechol formation. The last postulated pathway is thought to be associated with the opening of the benzene ring to yield the urinary metabolite muconic acid through the intermediary formation of muconaldehyde.

In the attempt to explain bone marrow toxicity the hypothesis is brought forward that phenol, catechol, and hydroquinone are transported to the bone marrow and converted by peroxidase-mediated reactions to electrophilic compounds. For example, in the bone marrow, phenol is rapidly oxidized by the marrow peroxidases to reactive, protein-binding species such as biphenols and biphenoquinones (Sawahata et al. 1985). Hydroquinone also is oxidized in the marrow via a peroxidase-catalyzed reaction to an extremely short-lived semiquinone radical intermediate. This forms p-benzoquinone, a reactive metabolite, known to cause DNA damage and cytotoxic effects in benzene-exposed animals (Smith et al. 1989). However, trans-trans-muconaldehyde may also play a role (Snyder et al. 1989).

Species differences in benzene metabolism

The metabolism of benzene appears to be qualitatively similar in humans and laboratory animals; however, no studies are available for direct comparisons (Sabourin et al. 1988; Henderson et al. 1989). There are apparent species differences in toxification (oxidation) and detoxification (conjugation) reactions of benzene, but the interaction of the pathways in vivo has not yet been characterized adequately (Schlosser et al. 1995).

In rodents, there are some significant quantitative differences in benzene metabolism between rats and mice (Sabourin et al. 1988; Medinsky et al. 1989 a, b; Schlosser et al. 1995). Saturation of overall metabolism in mice but not rats at high doses by both oral and inhalation routes of administration indicates quantitative species differences in metabolism of benzene (Sabourin et al. 1987). For oral gavage exposures, total metabolites per unit body weight were equal in F344/N rats and B6C3F1 mice at doses up to 50 mg/kg bw. However, at higher doses saturation in mice occurred, since total metabolites did not increase whereas total metabolites continued to increase in rats (Sabourin et al. 1987). Likewise for inhalation exposures, the mouse data indicated saturation of metabolism, since there was a plateau in the formation of metabolites at higher doses (>680 mg/m³, 260 ppm) while the rats continued to show an increase in the amount of metabolites formed, but at a non-linear rate (Sabourin et al. 1987).

However, with inhalation exposures, total metabolites formed were higher in mice than rats at all vapor concentrations tested (26-2600 mg/m³ [8-812 ppm]). This is due partially to the higher amount inhaled by mice (Sabourin et al. 1987). A subsequent study comparing metabolism in rats and mice exposed by inhalation to 160 mg/m³ (50 ppm) benzene for 6 hours confirmed that total metabolites in mice exceeded those in rats by greater than 2-fold, which is more than can be attributed to differences in the amount of benzene inhaled (Sabourin et al. 1988).

Further, when benzene metabolism is expressed on a body weight basis (moles of metabolite/kg bw), mice metabolized a greater proportion of absorbed benzene than rats to hydroquinone (HQ), benzoquinone (BQ) and muconic acid (MU) - the putative toxic metabolites (Henderson et al. 1989; Medinsky et al. 1989; Sabourin et al. 1988, 1992). Phenyl sulfate, a detoxification metabolite, and an unidentified water soluble metabolite were present in approximately equal concentrations in rats and mice. This suggests that the proportion of benzene metabolized via pathways leading to the formation of potentially toxic metabolites, as opposed to detoxification pathways, was much higher in mice than in rats (Sabourin et al. 1988).

Henderson et al. (1989) also found higher levels of hydroquinone glucuronide, and trans,trans-muconic acid in benzene exposed mice compared to rats. To investigate whether differences in hepatic metabolism might contribute to differences in metabolite levels, Orzechowski et al. (1995) investigated the pattern of benzene metabolites released from isolated hepatocytes of both species. Hepatocytes from NMRI mice were almost three times more effective in metabolizing benzene than those from Wistar rats. The higher formation of hydroquinone, and the formation of trihydroxybenzene sulfate and hydroquinone sulfate mainly contributed to the higher rate of benzene metabolism. Major differences were found in the higher formation of sulfate conjugates of phenolic metabolites in rat hepatocytes as compared to mouse hepatocytes.

The metabolic pathways and kinetics based on in vitro data are reviewed in detail (Schlosser et al. 1995). Differences in metabolism among mice, rats and humans exist, but the range of

rates found for human tissue samples spans that of mice and rats. For instance, a three-fold variation was observed among human samples in the rate of phenyl sulfate formation (range 0.3 to 0.9 nmol/mg/min) but for laboratory animals, phenol sulfatation was much faster in rat cytosol (1.2 nmol/mg/min) than in mouse cytosol (0.5 nmol/mg/min). Hydroquinone glucuronidation varied by almost three-fold among human samples (range 0.1 to 0.3 nmol/mg/min) and was more rapid in mouse liver microsomes (0.22 nmol/mg/min) compared with rat liver microsomes (0.08 nmol/mg/min).

Interindividual variations of the CYP 2E1 activity in humans have also been observed by measuring the p-nitrophenol hydroxylation in liver microsomes ranging from 0.25 to 3.27 nmol/mg/min (Seaton et al. 1994). Activity measured in mouse (1.56 nmol/mg/min) and rat (0.63 nmol/mg/min) fell in the range of human values.

However, it should be taken in mind that the data were from in vitro studies and their interpretation should reflect this limitation.

Data from metabolic studies performed in nonhuman primates and rodents allow for comparison among species in the in vivo situation. Dose and route of exposure in the monkey (intraperitoneal injection) and the route of exposure in chimpanzee (intravenous injection) were different from the oral gavage route in mice and rats. As previous studies comparing oral and inhalation routes of administration indicate that the metabolic profile seems to be dependent on exposure rate of benzene rather than on the route (Sabourin et al. 1989) the differences in the urinary metabolic profiles observed in monkeys, chimpanzees, and rats compared to those in mice were most likely due to species differences in the contribution of the different metabolizing enzymes to the overall metabolism. Based on urinary metabolites, mice appear to metabolize the largest fraction of absorbed benzene via pathways leading to hydroquinone conjugates and muconic acid metabolites (Sabourin et al. 1992). Thus, mice produce more hydroquinone and muconic acid than monkeys, chimpanzees, or rats. In contrast, the predominant metabolites found in nonhuman primates (and rats) are phenolic conjugates. It is difficult to provide an absolute rank of metabolic differences between the non-human primates (monkeys, chimpanzees) and rats from these studies because the routes of administration and/or dose were not identical.

There are interspecies differences in bone marrow metabolism. In the rat, Zhu et al. (1995) have shown that the cellular glutathione content and quinone reductase-specific activity were 2 and 28 times as much as those from mice, respectively. Both glutathione reductase and quinone reductase are thought to have a critical role in decreasing hydroquinone-induced toxicity in animals.

Although metabolites of benzene have been measured in the urine of occupationally exposed individuals, it is difficult to compare the human and animal data because of the study design and because no study is available in which all known metabolites were measured simultaneously. From the studies available, it can be concluded that after benzene exposure the amount of phenol in the urine is correlated with the exposure levels (r=0.881) (Inoue et al. 1986). In another study (Popp et al. 1994), urinary muconic acid levels were increased during benzene work exposure and were correlated with the blood levels and the benzene air levels. Other authors (Lagorio et al. 1994) found a significant correlation between benzene blood levels and benzene urinary levels, for filling attendants in Italy.

Elimination

Following inhalation exposure to benzene, the major route of elimination of unmetabolized benzene in humans and animals is in exhaled air. Most benzene is metabolized and the metabolites are excreted after phase-II-conjugation predominantly in the urine (appendix A VI). Phenolic metabolites are conjugated with sulfate or glucuronic acid (Henderson et al. 1989). Small amounts of the glucuronides may enter the bile and are found in the feces. Studies in a single human subject exposed to 20.5 mg/m³ (6.4 ppm) benzene for 8 hours and 317 mg/m³ (99 ppm) for 1 hour suggested that excretion in breath has possibly 4 phases of elimination (Sherwood 1988). The initial phase is rapid and is followed by 2 or 3 slower phases. In the same study, the urinary excretion of phenol conjugates was biphasic with an initial rapid excretion phase, followed by a slower excretion phase.

There is evidence that the elimination via metabolism is saturable. After low oral benzene doses (<15 mg/kg bw), >90% of the 14C was excreted in the urine of both mice and rats and there was a linear relationship between dose and excretion of urinary metabolites (Sabourin et al. 1987). Higher oral doses of benzene (>50 mg/kg bw for mice and >150 mg/kg bw for rats) resulted in a larger percentage of the administered benzene being exhaled unmetabolized suggesting a saturation of metabolic pathways.

Modeling of kinetic and dynamic data

Utilizing various data on the uptake, metabolism, and excretion of benzene and its metabolites, various authors tried to developed models for the prediction of concentrations of parent compound and of potentially toxic metabolites with the aim to understand the dose-response relationship and to facilitate inter-species comparisons and risk characterizations. Both compartmentally-based (Bailer and Hoel 1989; Beliles and Totman 1989) and physiologically-based (Medinsky et al. 1989; Paxman and Rappaport 1990; Travis et al. 1990; Bois et al. 1991) kinetic models have been developed. Typically, these models are composed of sets of differential and algebraic equations that describe the absorption, distribution, metabolism, and elimination of a chemical and its key toxic metabolites throughout the body and tissue compartments. Some features that are incorporated into these mathematical models include chemical specific physicochemical parameters (such as blood-tissue partition coefficients) and species differences in physiology and metabolism. Such models have been developed to predict internal doses of benzene and metabolites, to compare specific differences, and to evaluate which measure of dose best correlates with effect. The models vary in complexity and extent of validation (assessed by the ability to predict experimental findings of studies independent of those from which they were constructed). In order to validate the model the need for experimental data increases with increasing complexity. However, most of the parameters introduced into the models are not derived from the same experiments or even the same experimental conditions in which the concentration measurements of benzene and its metabolites were obtained but are taken from textbooks. In other modeling procedures, estimates of multiple parameters are calculated from sparse data coming up with rather doubtful estimates.

Bailer and Hoel (1989) provided one of the earlier models to extrapolate the relationship between administered and internal doses from mice to humans using an inter-species dose conversion approach which assumed that mg/kg bw/day was an equivalent administered dose unit across species. Internal dose for mice and rats was derived from the data of Sabourin et

al. (1987) based on the total amount of benzene metabolites. Thus, internal dose was represented as the fraction of administered dose that was metabolized, and this relationship was assumed to be the same in humans as mice (Bailer and Hoel 1989). They applied this model to results from a rodent carcinogenicity study reported by Huff et al. (1989) to look at the correlation between dose and tumor incidence in animals, and to predict the cancer risks for humans occupational exposed to benzene. When attempting to validate the model's prediction of internal dose against the rodent experimental data for tumors, this approach was reasonably predictive for mice (Bailer and Hoel 1989). The model markedly overpredicted the expected incidence of excess cancers observed in humans (Cox and Ricci 1992).

Recent PBPK models have included more compartments and relationships than the previous models, and use blood flow and metabolic capacity of specific tissue compartments in the derivation of the model parameters (Medinsky et al. 1989; Spear et al. 1991). Medinsky et al. (1989), used mean values of mice and rat kinetic data from studies by Sabourin et al. (1987), while Spear et al. (1991) utilized rat data of Rickert et al. (1979) and Sabourin et al. (1987, 1988).

Travis et al. (1990) devised a model for mice, rats and humans and used experimental data from all three species (Rickert et al. 1979; Sabourin et al. 1987; Sato et al. 1975; Sato and Nakajima 1979; Snyder et al. 1981). This model provides a reasonable fit for internal doses for human and animal data associated with the administration of benzene by inhalation, gavage, or injection. Using the Travis et al. (1990) model, Cox and Ricci (1992) calculated that humans seem to produce a less metabolites from a given administered dose of benzene than would be predicted by the inter-species dose conversion approach by Bailer and Hoel (1989).

Bois and Paxman (1992) constructed a model for benzene and for the formation of metabolites using the data in rats from Rickert et al. (1979) and Sabourin et al. (1987). The model includes both liver and bone marrow as sites for benzene metabolism. The outcome of this model is that exposure rate has a significant effect on the rate of formation of several important metabolites of benzene. The authors used the model to simulate metabolite production in human blood and bone marrow after an 8 hour inhalation exposure of 3.2 mg/m³ (1 ppm) and a 15 minute exposure at 102 mg/m³ (32 ppm) [to simulate a possible exposure for a short term exposure level of 16 mg/m³ (5 ppm). The simulation indicated that levels of metabolites (hydroquinone, catechol, muconaldehyde) were 20% higher after the short term exposure at the higher level [102 mg/m³ (32 ppm)] than after the long term exposure at the lower level [3.2 mg/m³ (1 ppm)]. The authors concluded that there was an appropriate margin of safety with a short term exposure level of 16 mg/m³ (5 ppm) (1/6 of the simulated dose.). Because of many pitfalls, i.a. naive pooling of data, questionable accuracy of the modeling procedure even the derived parameters are of questionable scientific value.

Cox (1993) examined in more detail the consequence of different exposure scenarios on specific toxic benzene metabolites in blood and bone marrow. Modeling was conducted using benzene concentrations ranging from 9.6 to 154 mg/m³ (3-48 ppm) for exposure duration from 360 to 22.5 minutes. For some internal dose surrogates, such as total quantity of benzene metabolites produced, cumulative exposure (i.e. the product of concentration and duration of exposure) was a good predictor. However, in their model they predicted that identical cumulative doses administered for various periods led to very different maximum concentrations of metabolites in the blood and in the bone marrow. The authors infer from their data that the maximum rate of bone marrow metabolism reached for a given cumulative exposure is sensitive to the time pattern of administration. This model, while predictive of

dosimetry, lacked incorporation of toxicodynamic information on cell proliferation and maturation within bone marrow.

In an attempt to account for these limitations, Cox (1995) developed a biologically-based model for benzene, utilizing elements of a biologically-based model for cyclophosphamide, a known immunosuppressive and myelotoxic agent. This approach tried to incorporate pharmacokinetics and pharmacodynamic processes, including those identified as critical to haematotoxicity and genotoxicity. The author assumes that the results could be in line with earlier analyses on benzene which seem to suggest that cumulative dose may not provide an adequate basis for predicting haematotoxic, leukaemogenic, and cytogenetic effects of benzene. However, this model is purely speculative as no data is available to test the validity of the model.

The attempts to construct an integrative PKPD model for benzene fails up to now because of the limited experimental data. The models used so far lack precision and validity and are not appropriate to this specific situation. Although in principle the population approach would be an appropriate method and although tools are available to allow inclusion of data of different species in a single model PKPD of benzene presents a specific problem. First, kinetic data on benzene in man are sparse. The available data are predominantly data on conjugated benzene metabolites in the urine which implies that assumptions on their formation have to be made to calculate kinetic parameters for benzene. Because of the experimental conditions it is not possible to estimate correctly the amount of benzene absorbed and hence it is not possible to estimate its volume of distribution. Thus, estimation of human kinetic data for benzene has to rely mainly on animal data which implies that several assumptions have to be made which are not validated until now.

The Bois and Paxman model (Bois and Paxman 1992) used a five compartment model, comprised of liver, bone marrow, poorly perfused tissues, and well perfused tissues. The assumption in the model include Michaelis-Menten- metabolite formation in liver and bone marrow, the latter incorporated into the model for its relevance to human leukemia, with the exception of the transformation of benzene oxide into phenol, which in the model occurs spontaneously, described by first order kinetics. The model was used to predict metabolite formation for rats exposed nose-only to three different vapor concentrations and at different lengths of exposure. The predicted data were compared to the experimental data of Sabourin et al. (1989) in which 51 ppm (165.6mg/m³) for 6 hours, 153 ppm (496.8mg/m³) for 2 hours, and 558 ppm (1811.8 mg/m³) for 0.5 hours were applied. In this experiment the product of dose levels and duration of doses was constant. The comparison between modelled data and measured data showed that the model over- and underestimated the level of metabolites in the urine. In the next step, the model was used to predict human metabolite formation after an 8 hour exposure at 1 ppm (3.25 mg/m³) , and at 32 ppm (103.9 mg/m³) for 15 minutes. The model predicted that the area under the curve for benzene metabolites (hydroquinone, catechol, and muconaldehyde) was 20% higher after 15 minutes at 32 ppm (103.9 mg/m³) as compared to 1 ppm (3.25 mg/m³) for 8 hours.

The Medinski model (Medinski et al. 1989 a, b, c) used four compartments (liver, poorly perfused tissues, richly perfused tissues, fat). It assumes that the liver is the only organ where metabolism takes place which is an obvious disadvantage of the model. By iterative procedures, the mice data as primary input data for human Vmax-values, (5 different Vmax-values for the different metabolites incorporated into the model), were adjusted until the simulated data agreed with the experimental data. High to low dose extrapolation was not specifically addressed. Comparing the Vmax- and Km-values for mouse, rat and man shows

that the Km-values for mouse and man are identical (this is an assumption in the model) whereas Km-values for rat differ from those in man for most of the metabolic steps. Vmax values for both mouse and rat are several fold higher than those in man. Hence, this model is not helpful in deciding on the most appropriate animal in terms of toxicokinetics.

As it is poorly understood what metabolite is relevant for toxic effects such as leukemia or haematotoxic effects, the 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. For the most relevant effect, an integrative PKPD modeling approach using animal and human benzene data is confounded by the fact that the type of leukemia in animals is different from the type of leukemia in man. Hence all the results and conclusions from PKPD modeling using animal data are not applicable to man.

Summary

The toxicokinetics of benzene have been studied in both animals and humans. The data are summarized in a number of recent reviews including IPCS (1993), ATSDR (1993) and ATSDR (1997). 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 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 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 (conjugative) metabolic pathways. However, at present, it is unclear whether the observed species differences in developing haematotoxicity and leukaemia may be explained by species differences in metabolism.

4.1.2.2 Acute toxicity

Animal data:

Oral:

The acute oral toxicity of benzene is difficult to estimate because existing data are inconsistent: The LD50 after oral administration in adult rodents in one study is reported to be as low as 810 mg/kg bw. In this study animals died after an oral dose of 1870 mg/kg bw within 20 minutes (Cornish and Ryan 1963). Smyth et al. (1962) stated an oral LD50 value for male rats as high as 10016 mg/kg bw.

In a poor documented experiment using 150 male rats, doses of 2000, 2990, 4470, 6690, and 10000 mg/kg of undiluted benzene (no data on purity) were administered by gavage to 10 rats

per dose in the first part of the study, resulting in 0/10, 1/10, 3/10, 5/10, and 9/10 dead animals. In the second part of the study doses of 3000, 4250, 6000, 8460, and 11920 mg/kg were administered to 20 rats per dose, resulting in 0/20, 5/20, 12/20, 17/20, and 17/20 dead rats. An oral LD50 of 5960 mg/kg was calculated. No data are given on clinical signs, on time of deaths, or on necropsy (Withey and Hall 1975).

Kimura et al. tested the acute oral toxicity of 16 solvents in new-born rats (6-12 rats of both sexes per dose), in 14-day olds (6-12 rats of both sexes per dose), in young adults (6 males per dose), and in older rats (6 males per dose). The studies were performed with observation periods of 1 week, and the approximate doses inducing the first observable signs of toxicity were documented. Benzene (analytical grade) was significantly more toxic in 14-day old rats than in young adult or older rats. Oral LD50 values were calculated as 3400 mg/kg for 14-day old rats, 3800 mg/kg for young adult rats, and 5600 mg/kg for older rats, new-born rats were exceedingly sensitive to benzene. A maximum permissible limit for single dose oral exposure was calculated for young adult rats as 0.0002 ml/kg, judged on the basis of 1/1000 of first appearance of the clinical signs dyspnea, ataxia, cyanosis and/or coma. Data on necropsy are not stated (Kimura et al. 1971).

An oral LD50 of 5600 mg/kg was detected for benzene (purity 99.98%) in a study with male rats. Benzene was introduced into the stomach by means of a stomach tube, either as the undiluted material or as an olive-oil or corn-oil solution emulsified with a 5-10% aqueous solution of acacia (gum arabic): The total volume administered was never greater than 7cc. All the surviving rats were observed until recovery was assured (usually about two weeks). When the rats were autopsied, slight liver changes and, in some instances, some kidney involvement of questionable significance were observed. No data on doses or animals per dose, no data on clinical signs, and no more data on necropsy are documented (Wolf et al. 1956).

In a study with an unknown number of groups of 5 male rats per dose (doses not stated) an oral LD50 of 11.4 ml/kg (approximately 10 g/kg) was found. No further data are given (Smyth et al., 1962). Cornish and Ryan reported on acute oral toxicity studies with 10 rats/dose: At high dosages of reagent grade benzene (1870 mg/kg) the animals developed tremors and tonic-clonic convulsions, and many of them died within 20 minutes. One single dose of 88 mg/kg produced slight central nervous system depression, but no deaths. No further data on clinical signs or on necropsy are given. The metabolic fate of benzene was found to be markedly altered in rats fasted 24 hours prior to administration of benzene. In the non-fasted rat, the major metabolites are conjugated phenols other than glucuronides. While in the fasted rat the major excretory pathway is glucuronide conjugation (Cornish et al., 1963).

Inhalation:

Acute inhalation toxicity to rats and mice seems to be low as judged by studies with a single 4 hours inhalation exposure (LC50 for female rats: 13700 ppm (44500 mg/m³; Drew and Fouts 1974) and after a 7 hours exposure (LC50 for mice: 9980 ppm (31790 mg/m³; Svirbely et al. 1943). Clinical signs were restlessness, tremor, muscular twitching, changes in respiration, incoordination and narcosis (Svirbely et al. 1943). Congestion of lungs and liver were the main pathological findings (Drew and Fouts 1974; Svirbely et al. 1943).

An inhalation LC50 value of 13 700 ppm (approximately 44500 mg/m³) / 4 hours resulted in a study with female rats: Benzene vapors were generated by passing air through 2 fritted bubblers in series, each containing benzene (reagent grade and thiophene-free). The first bubbler was maintained at about 35° C in a water bath, thus assuring that the air emerging from the second bubbler was saturated with benzene. The saturated air was diluted with filtered compressed air to the concentration desired. Chamber concentration of benzene was monitored at 30-minute intervals by bubbling a known volume of air through methanol at about 0.5 l/min. The efficiency of benzene absorption in methanol at this flow rate was determined to be greater than 95%. The benzene absorbed was then measured. An inhalation LC50 of 13700 ppm (approximately 44500 mg/m³) was detected for an exposure time of 4 hours. Number of doses, number of animals per dose, and dose concentrations are not given. Animals which died as a result of exposure to benzene usually died during the exposure or in the first 24 hours post-exposure. Deaths appeared to be caused by a depression of the central nervous system. Necropsy was performed on all animals dying during the exposure as soon as possible after the exposure. Survivors were held for 2 weeks and then sacrificed and necropsied. These animals all had higher weight for both lung and liver. Lung and liver congestion, defined as an increase in the number of red blood cells, was the principle observation noted histologically. The only other histological result of importance was an increase in the number of vacuoled hepatocytes seen in the livers of those animals which died from inhalation of benzene (Drew and Fouts 1974).

A group of 6 male or female rats was tested with concentrated benzene vapors (16000 ppm = 51800 mg/m³, no data on purity) in order to detect the maximum period for inhalation of saturated benzene vapors that can be tolerated. The vapor/air mixture was generated by passing 2.5 l/min of dried air at room temperature through a fritted glass disc immersed to a depth of at least one inch in approximately 50 ml of benzene contained in a gas-washing bottle. Five minutes were stated as the maximum time of concentrated vapor inhalation without deaths. No more data are given (Smyth et al. 1962).

Within the same experiment, a LC50 value of less than 16000 ppm (51800 mg/m³) was detected: A group of 6 male or female rats was tested with concentrated benzene vapors (16000 ppm = 51.8 mg/l, amount not analytically verified) for an inhalation period of 4 hours. The vapor/air mixture was generated by passing 2.5 l/min of dried air at room temperature through a fritted glass disc immersed to a depth of at least one inch in approximately 50 ml of benzene contained in a gas-washing bottle. Four out of six rats died within 14 days. No more data are given (Smyth et al. 1962).

An inhalation LC50 of 31800 mg/m³ (10400 ppm) for an exposure time of 7 hours was detected in a study using 182 mice: Benzene (purity 99.5%) was dropped at a constant rate on a gauze in an enclosed flask which was immersed in a constant temperature water bath. All air used was first passed through a flow meter into a flask and the vapor-air mixture was then passed through the mixing tube into the exposure chamber. Values for concentrations were calculated in mg/l by dividing the weight of the solvent vaporized at the end of exposure by the amount of air used. These values were in close agreement with the vapor concentrations measured in the exposure chamber by interferometer. Deaths occurred at concentrations above 15900 mg/m³ (4980 ppm) normally within 8 hours from beginning of exposure: 0/18 mice died after inhalation of 15900 mg/m³ (4980 ppm), 11.1% of 18 mice after 23900 mg/m³ (7490 ppm), 16.7% of 18 mice after 26600 mg/m³ (8330 ppm), 35% of 20 mice after 29600 mg/m³ (9280 ppm), 75% of 15 mice after 32200 mg/m³ (10200 ppm), 50% of 16 mice after 33300 mg/m³ (10450 ppm), 45% of 20 mice after 34900 mg/m³ (10950 ppm), 89% of 18 mice after 36800 mg/m³ (11540 ppm), 75% of 20 mice after 39600 mg/m³ (12430 ppm), and 18/18

mice after 46500 mg/m³ (14600 ppm). Narcosis and dyspnea were the usual signs of toxic action. Immediate deaths, suggestive of respiratory failure, characterised the solvent. Paraffin sections were made from the lungs, liver, kidney, spleen, and heart of animals dying during exposure. Necropsy demonstrated changes in lungs, kidney and spleen (Svirbely et al. 1943).

Dermal:

For rabbits and guinea pigs dermal LD50 values of >8260 mg/kg bw are reported. There are no data on clinical signs and autopsy findings (Roudabush et al. 1965).

Benzene (laboratory reagent grade) was applied undiluted under occlusion to the abraded skin of 2 male and 2 female rabbits according to CFR guideline. The resulting dermal LD50 was detected above 9.4 ml/kg (8260 mg/kg). No more data are given. In the same way, benzene was applied undiluted under occlusion to the intact and to the abraded skin of 4 male guinea pigs according to CFR guideline. The resulting dermal LD50 was also detected above 9.4 ml/kg (8260 mg/kg) for both kinds of application. No more data are given (Roudabush et al. 1965).

Human data:

The ingestion of liquid benzene causes local irritation of the mucous membranes of the mouth, throat, esophagus and stomach. The subsequent absorption of ingested benzene into the blood leads to signs and symptoms of systemic intoxication. The ingestion of a tablespoon (about 15 ml, according a dosage of 176 mg/kg bw) of benzene has been known to cause collapse, bronchitis and pneumonia (Gerarde, 1960).

Benzene is absorbed rapidly via the lungs. The direct aspiration of liquid benzene into the lungs causes immediate pulmonary edema and hemorrhage at the site of contact with the pulmonary tissue (Gerarde 1960).

High concentrations of benzene vapors are irritating to the mucous membranes of the eyes, nose, and respiratory tract. The inhalation of a high concentration of benzene vapor may cause acceleration (of the respiratory rate) followed by drowsiness, fatigue, dizziness, headache and nausea. The pulse rate increases, there may be a sensation of tightness in the chest accompanied by breathlessness, and ultimately the victim may lose consciousness. Convulsions and tremors occur frequently, and death may follow in a few minutes or several hours following severe exposure. Recovery from an acute exposure to benzene depends on the severity of the exposure. Breathlessness, nervous irritability and unsteadiness in walking may persist in severe cases for 2-3 weeks. The following relationship between benzene-air concentrations and physiological effects are stated: 65000-61000 mg/m³ (20020-18788 ppm) with duration of exposure of 5-10 minutes are fatal, 25000 mg/m³ (7700ppm) and 30 minutes of exposure are dangerous to life, 9600 mg/m³ (2957 ppm) and 30 minutes of exposure are endurable, 4800 mg/m³ (1478 ppm) and 60 minutes of exposure cause serious symptoms, 1600 mg/m³ (493 ppm) and 60 minutes of exposure causes symptoms of illness,480-160 mg/m³ (148-49 ppm) and 5 hours of exposure headache, lassitude and weariness, while 80 mg/m³ (24,6 ppm) and 6 hours of exposure are stated as maximum allowable concentration (Gerarde 1960).

Three cases of acute benzene poisoning resulting from an industrial accident aboard a chemical cargo ship are reported by Avis and Hutton (1993). The concentration of benzene fumes to which the three victims were exposed is unknown but the time frame was a matter minutes. At autopsy second degree chemical burns to the face, trunk and limbs, haemorrhagic airless lungs with confluent alveolar haemorrhage, and edema were present. The brains appeared grossly normal but showed microscopic evidence of prominent vascular congestion. High concentrations of benzene were found in blood (30-120 mg/l), body fat (68->120 mg/kg bw) and brain (58-63 mg/kg bw) and lower concentrations in the liver (15-38 mg/kg bw) of the three victims. The mechanism by which benzene causes death in acute poisoning may be either its central nervous depressing properties with resultant respiratory arrest and death or through the production of fatal arrhythmia in an adrenaline primed myocardium. Both cases could be operational with this accident. No relationship between chemical burns and death was mentioned.

Conclusion:

Existing data on human accidents demonstrate that ingestion of 15 ml (176 mg/kg bw) benzene can cause death after collapse, bronchitis and pneumonia and thus, classification as "harmful" and labelling with "R 65, May cause lung damage if swallowed" is warranted. Exposure for 5-10 minutes to benzene vapors of 65000-61000 mg/m^3 is fatal and exposure to 25000 mg/ m^3 for 30 minutes is dangerous to life, while a one-hour exposure to 1600 mg/m^3 causes only some symptoms of illness (Gerarde 1960).

In rats acute oral toxicity ranges from 810 mg/kg bw (Cornish and Ryan 1963) to 10016 mg/kg bw (Smyth et al. 1962). But experiments using high numbers of rats suggest that, for rats, the oral LD50 is above 2000 mg/kg (Whithey and Hall 1975; Kimura et al. 1971). Depending on the dose the main clinical signs are sedation and narcosis. Pathological findings include among others hyperemic and haemorrhagic lungs, adrenals and spine. Acute inhalation toxicity is low with a LC50 value of 44500 mg/m³ (13700 ppm) after a 4-hour exposure for rats. Depression of the central nervous system appeared to be related to death. The main pathological findings were congestion of the lungs and liver (Drew and Fouts 1974). A dermal LD50 value of >8260 mg/kg bw for rabbits and guinea pigs was reported by Roudabush et al. (1965). Therefore, data on animal experiments do not support labelling for acute oral, dermal or inhalation toxicity.

4.1.2.3 Irritation /

4.1.2.4 Corrosivity

Animal data:

Benzene is a slight to moderate skin irritant in rabbits and causes superficial necrosis:

Benzene proved to be a skin irritant and a defatting agent in a Draize test according to OECD Guideline 404 of 1981: The skins of six shaved rabbits were exposed to neat undiluted benzene for 4 hours, using an exposure chamber of 6 cm^2. One hour after exposure edema grade 2 and erythema grade 1 were documented. No edema, but mean scores of 2.0/2.2/2.4 for erythema are stated for the observation times 24, 48, and 72 hours after the end of exposure. Erythema enhanced to grade 3 for all animals within 6 days (Jacobs 1991).

In an experiment with repeated applications of undiluted benzene (purity 99.98%) over a time of 2-4 weeks, superficial necrosis and exfoliation of large patches of skin was documented: Undiluted benzene was dropped routinely in 10 to 20 applications to the ear of white rabbits, and a like number of applications was bandaged onto the shaved abdomen over a period of 2-4 weeks. The animals were observed daily and were weighted weekly. Perceptible to definite erythema, edema and superficial necrosis were documented. These effects resulted in a "chapped" appearance and exfoliation of large patches of skin. No more data are documented (Wolf et al. 1956).

Primary skin irritation graded 3 (out of a scale of 10) was recorded as the severest reaction that developed on the clipped skin of each of five albino rabbits within 24 hours of the uncovered application of 0.01 ml of undiluted benzene. No more data are given (Smyth et al. 1962).

Two drops of undiluted benzene (purity 99.98%) were instilled into the right eyeballs of rabbits. Visual observations of irritation and corneal injury (both internal and external) were made upon the treated eye at the following times after treatment: 3 minutes, 1 hour, one, two and seven days. A 5% aqueous solution of fluorescein dye was used to stain and render visible the external injury of the cornea in all observations after the first three minutes. 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. No more data are given (Wolf et al. 1956).

Applying a method developed by Carpenter and Smith (Carpenter and Smyth, 1946), corneal necrosis graded 3 (out of a scale of 10) was reported for benzene. This test method uses 0.005 ml of the undiluted material which is applied to the center of the corneas of usually 5 rabbits while the lids are retracted. About 1 minute later, the lids are released. Eighteen to 24 hours later, the eye is examined and the injury scored according to a specific scoring system for corneal necrosis. The individual numerical scores of each eye treated with a chemical are added together and then divided by the number of eyes to obtain the score of the injury caused by the treatment. A score level of 5.0 is selected as representative of severe injury. This figure corresponds to necrosis, visible only after staining and covering about 3/4 of the surface of the cornea; or a more severe necrosis covering a smaller area. Guided by the result of the scoring after instillation of 0.005 ml of the substance and a table of standardised injury grades, additional applications are made (using higher volumes of the substance or using dilutions of the substance) until the chemical can be assigned to one of the recognised grades

for corneal necrosis. In a large list of test results is stated for benzene (no data on purity), that a test according to this Carpenter and Smyth method revealed corneal necrosis graded 3. Injury grade 3 is defined as follows: 0.1 ml of the undiluted substances gives injury of up to 5.0 points or 0.5 ml gives injury over 5.0 points. No data on healing time are documented (Smyth et al. 1962).

Human data:

High concentrations of benzene vapors are irritating to the mucous membranes of the eyes, nose, and respiratory tract. Liquid benzene on direct contact with the skin may cause erythema and blistering. Skin contact with benzene removes fat from the tissue which may result in the development of a dry, scaly dermatitis if exposure is repeated or prolonged (Gerarde 1960).

In a report on three fatalities of acute benzene vapor poisoning by acute dermal and inhalation exposure second degree chemical burns to face, trunk and limbs, hemorrhagic lungs and pulmonary edema were stated. However, no relationship was mentioned between these burns and death of the victims (Avis and Hutton 1993).

Conclusion:

In humans, high concentrations of benzene vapor are irritant to mucous membranes of the eyes, nose and respiratory tract (Gerarde 1960). Second degree chemical burns of the face, trunk and limbs after acute benzene vapor poisoning are reported (Avis and Hutton 1993).

In animals benzene is irritant to the skin (Jacobs 1986) and may cause serious damage to eyes (Smyth et al. 1962). The report of Wolf et al. (1966) is considered as key study for the assessment of eye irritation potential: 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% indicate a corneal opacity less than 3. Inflammation can not be scored, edema is slight. The observation effects are plausible regarding the results (superficial corneal necrosis graded 3/10) obtained by Smyth et al. (1962).

Thus, the criteria for the assignment of "R 36/38 irritating to eyes and skin" seem to be justified.

4.1.2.5 Sensitisation

Animal data:

There are no data on animal tests.

Human data:

There are no reports on skin sensitisation or inhalation allergy caused by benzene. 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 handling benzene.

Conclusion:

Due to the fact that there are no reports on sensitisation caused by benzene at the workplace, no sensitisation of the skin and/or by inhalation is expected.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1. Repeated dose toxicity/Animal data

4.1.2.6.1 A. Effects on hematopoiesis

The results from animal studies after repeated exposure to benzene were summarized in the Summary Table 4.19. Literature was cited in order to application route (inhalation exposure<oral administration<other routes), the species used (mouse<rat<other species), and the exposure duration (short term < long term).

All inhalation tests available used whole body exposure chamber. Only the publication of Ward and coworkers (1985) fulfill the minimal requirements on subacute toxicity of the base set level according to the Directive 793/93/EEC. The study report was comparable to the methods of the OECD Guideline 413/EU-method B.29 with respect to hematology, clinical chemistry, gross and microscopic pathology. However, standard design of repeated dose toxicity testing was not sufficient to elucidate the specific effects of benzene exposure. Other studies cited were considered to be appropriate for the risk assessment procedure because they included more specific test parameters.

<u>Inhalation exposure/mouse/short-term studies (≤14 days)</u>

Groups of 5 male DBA/2J mice were exposed to 0, 10, 30 or 100 ppm (32, 96, 320 mg/m³) benzene (6 hr/d) for 5 days (Dempster and Snyder 1990). One day and 5 days after the benzene exposures, the numbers of the two most primitive erythroid progenitor cells (BFU-E and CFU-E) and the numbers of the most primitive granulocytic progenitor cells (GM-CFU) were assessed. One day after benzene exposure, marrow erythroid progenitor cell numbers were depressed in all dose groups while marrow granulocytic progenitor cell numbers were unchanged or elevated. Five days after benzene exposure, the numbers of marrow erythroid progenitor cells have recovered from their depressed levels. In contrast, 5 days after exposure the numbers of granulocytic progenitor cells were depressed in the 10 ppm and 100 ppm groups. Normal ratio of granulocytic and erythroid progenitor cells were reported to be 17:1 in the marrow and 0.03:1 in the spleen reflecting the predominant erythroid hematopoiesis of the spleen. No clear treatment-related effects were seen for the splenic progenitor cells on day 1 after exposure, however on day

5 of recovery there is a dose-response type increase in splenic CFU-E numbers which was considered to possibly reflect the attempts by the spleen to repopulate the erythron after benzene exposure.

In a short-term study (Rozen et al. 1984), inhalation exposure to dose levels of 32, 99.2, 320, and 960 mg/m³ (10, 31, 100, and 300 ppm) benzene vapor to male C57B1/6J mice (5-7 males/group) on 6 days, 6 hr/day, produced a depression on lymphocyte counts at all dose levels and lower RBC counts at ≥320mg/m³ (100 ppm). Reduced numbers of B-lymphocytes (sIgM+ cells) in the femural marrow and reduced T-lymphocytes in the spleen (Thyl.2+ cells) were observed at doses of ≥320mg/m³ (100 ppm).

BALB/c male mice (5-6 animals/group) were exposed to 50 or 200 ppm (~162 or 649 mg/m³) benzene vapor, 6 hr/d for 7 or 14 consecutive days (Aoyama 1986). No deaths or body weight suppression were observed. Relative spleen weight decreased in all treatment groups. Also, the relative thymus weight decreased in all groups except for the 50 ppm group treated on 7 days. WBC counts were depressed at 200 ppm at both treatment periods and at 50 ppm after 14-day exposure. RBC counts did not show treatment-related effects. The absolute numbers of B- and T-lymphocytes in blood and spleen were depressed related to the doses at 7 and 14 days of exposure in both dose groups. Spleen and blood percentages of B-lymphocytes were depressed in both dose groups. The depression was dose dependent. The T-lymphocyte ratio increased in the high dose group after 7 days of exposure and in both dose groups after 14 days of exposure. Effects on the humoral and cellular immune responses were reported in Section 4.1.2.6.1 B.

Toft et al. (1982) reported benzene vapor effects on male NMRI mice at continuous or intermittent exposure. Groups of 5 animals exposed to 21 ppm (61 mg/m³), 50 and 95 ppm (~16.24 and 308.5 mg/m³) benzene for 4-10 days (24 hr/d) showed reduction in bone marrow cellularity, number of colony-forming unit granulopoietic stem cells (CFU-C) and an increase in the frequency of micronucleated polychromatic erythrocytes (MN-PCE). No effects were seen at 1 and 10 ppm (~3.247 and 32.47 mg/m³). Mice exposed continuously to 14 ppm (45 mg/m³) for 1-8 weeks had significant increased number of MN-PCE.
Intermittent exposures on 8 hr/d, 5 d/w during 2 weeks to 10, 21, 50, 95, or 107 ppm (~32.47, 68.19, 162.35, 308.5, 347.43 mg/m³) revealed that exposure to 21 ppm was the lowest dose tested yielding suppressed CFU-C content and elevated frequency of MN-PCE. Bone marrow cellularity was depressed at doses of ≥50 ppm. No effect on these parameters were obtained in mice exposed to 14 ppm for up to 8 weeks. Authors concluded that percentage of granulopoietic stem cells (CFU-C content) was more sensitive than the total number of bone marrow cells.
Additional experiments included exposure to 95 and 201 ppm (~308.5 and 652.6 mg/m³) on 0-8 h/d, 5 d/w for 2 weeks. At 95 ppm depressive effects on bone marrow cellularity and CFU-C content were observed at the 6 hr/d regimen, the number of MN-PCE were increased at 4 h/d exposure time. 201 ppm for 2 hr/d suppressed cellularity and increased numbers of MN-PCE, but did not alter significantly CFU-C content indicating that at high exposures of short duration bone marrow cell numbers were the most sensitive parameter. At the 4 hr/d dose regimen 201 ppm caused changes of all three parameters.

Male and female C57B1/6 BNL mice (5-10 animals/group) were exposed to benzene vapor at concentration of 0, 10, 25, 100, or 400 ppm (32, 80, 320, or 1280 mg/m³) for 2 weeks (6 hr/d, 5 d/w) (Cronkite et al. 1985). At 100 ppm reduced bone marrow cellularity (no data on higher doses) was reduced. A decreased number of pluripotent stem cells in bone marrow and a higher fraction of stem cells in DNA synthesis were reported at 100 and 400 ppm. In peripheral blood hematocrit was reduced at ≥100 ppm and lymphocyte counts were depressed at 25 ppm and

higher. No effect on the granulocytes was seen in all dose groups. Hemosiderin deposits in the spleen were reported in exposed animals, however no exact data are available.

Indicating strain-specific differences in the response to benzene, susceptibility was higher in Swiss Webster mice than in C57B1/6J mice. Male mice of each strain were exposed to 300 ppm benzene (960 mg/m³) for 6 hours per day, 4 days per week, for 2 weeks. They had reduced numbers of bone marrow cells and a reduced development of CFU-E (colony-forming unit-erythroid) with a more severe reduction in the Swiss Webster mice (Neun et al. 1992).

Inhalation exposure/mouse/subchronic and chronic studies (>14 days)

Benzene effects after intermittent or continuous exposures of C57B1/6 mice were investigated by Gill et al. (1980). Intermittent exposures of 6 males/group on 5 days per week, 6 hr/day for up to 6 weeks resulted in a concentration-related leukopenia at dosages of 1000, 2000, and 4000 ppm (63247, 6494 and 12988 mg/m³). Decreased numbers of white blood cells were evident on the third day and reached the minimal number by the 5th or 6th day of exposure. Mortality from continuing the treatment up to 6 weeks was negligible. Mice of the 4000 ppm group experienced tremulousness and were nearly immobilized during the 6-h exposure. Animals recovered quickly after the return to room air. Differential blood counts performed on the high dose animals after counts stabilized during treatment revealed decreased numbers of lymphocytes (1.34x versus 5.94x10³/cells/µl in controls) and granulocytes (0.5x versus 2.37x10³/cells/µl in controls). Cellularity of femural marrow was not altered at 4000 ppm concentration. However, number of splenic colonies of transplantable colony forming units (CFU-S) representing marrow precursors of granulocytes was reduced to about 55% after 1- and 4-week exposure and to 30% after 6-week exposure. (Comment: In general, CFU-S represents a heterogeneous group of progenitor cells including the myelocytic cell lineage. It is otherwise characterized as multipotential hematopoietic stem cell (Green et al. 1981a,b).
Continuous exposure of mice to concentrations of 4000 ppm and 2000 ppm resulted in death of the mice within 24 hours. Causes were reported to be unrelated to the hematopoietic system (no further data). Continuous exposures to 1000 and 500 ppm caused death after 3 or 4 days of exposure. Exposure to 100 ppm were tolerated for longer than 1 week. A decline of white blood cell numbers occurred in the 100, 500, and 1000 ppm (~324.7, 1623.5 and 3247 mg/m³) groups beginning already after 24 hours. Bone marrow cellularity exposed continuously to benzene at concentrations of 500 and 1000 ppm was not altered during the first 24 h, but at the end of 48 h to about 30% of the control values.

In a recent study, Farris et al. (1997) demonstrating the progression of effects in relation to treatment duration exposed male B6C3F1/CrlBR mice (24 animals/group) to 0, 1, 5, 10, 100, and 200 ppm (~3.25, 16.2, 32.5, 324.7, 649.4 mg/m³) benzene for 6 hr/d, 5 days/week for 1, 2, 4, or 8 weeks. A subset of mice from the 4-week exposure was kept for 4, 11, 18, and 25 days of recovery. There was no significant effect on hematopoietic parameters from exposure to 10 ppm or less. Exposure of mice to 100 or 200 ppm benzene reduced the number of total bone marrow cells at all time points. A tendency to recover was obvious at the 4th week of the treatment in the 100 ppm group, but the decrease progressed in the 200 ppm animals. Bone marrow nucleated cells were within control values by 4 days after the end of exposure to 100 and 200 ppm for 4 weeks. CFU-HPP representing highly proliferative potential primitive progenitor cells of all three lineages (comparable to CFU-S of other studies) were decreased at all time points in the 200 ppm group and at 2, 4, and 8 weeks in the 100 ppm group. The number remained decreased in the 200 ppm recovery group and returned to control values by day 11 in the 100 ppm recovery group.

Replication of primitive progenitor cells, measured as the percentage of these cells in S-phase of the cell cycle, increased during the exposure period as a compensation for the cytotoxicity induced by 100 and 200 ppm benzene. In mice exposed to 200 ppm benzene, the primitive progenitor cells maintained an increased percentage of cells in S-phase through 25 days of recovery compared to controls. At the 100 ppm recovery group, percentages of cells in S-phase remained high until day 11 postexposure. Exposure to 100 or 200 ppm benzene induced an increase in the number of erythrocytic bone marrow colony forming units (CFU-E) after 1 week of exposure and, at the high dose, a decrease after 2 and 8 weeks of exposure. While the absolute numbers of differentiating erythropoietic cells, characterized by immunostaining to be rubriblasts, rubricyts, and metarubricytes, were decreased at 100 and 200 ppm benzene, the percentage of immunolabelled cells increased by exposure to 100 ppm for 4 weeks and 200 ppm for 8 weeks. A decrease in the percentage of PCE in the blood was severe at 5 days of exposure to 100 or 200 ppm benzene. The absolute numbers and percentages of PCE were decreased in the high dose group through week 4 and in the 100 ppm group through week 2 (no data on week 1). Erythrocytes in the blood were diminished from the second week onwards in the 100 ppm group and at all time points in the 200 ppm group. The mean corpuscular volume increased at week 8 of treatment with 100 and 200 ppm. The number of granulocyte-macrophage colony-forming units (CFU-GM) was reduced by 100 and 200 ppm benzene with exposure for 2, 4, or 8 weeks. The absolute numbers of granulocytic marrow cells recognized by immunolabelling and morphologically classified to be myeloblasts, promyelocytes, myelocytes, band cells, and segment neutrophiles, were decreased by 100 ppm benzene at week 4 and 200 ppm benzene at all time points, whereas the percentages of these cells increased by exposure to 100 or 200 ppm benzene for 2 weeks and by exposure to 100 ppm for 8 weeks. In mice recovering from 200 ppm benzene, the number of granulocytic cells increased above controls at 4 days postexposure and thereafter returned to the control values. The numbers of blood leukocytes were lowered at from week 2 onwards (no data on week 1) in mice exposed to 100 and 200 ppm benzene. The numbers of platelets were reduced in mice exposed to 200 ppm from week 2 through week 8 and in mice exposed to 100 ppm at week 2.

Green et al. (1981a,b) conducted 3 experiments using different exposure regimens and concentrations to evaluate the interaction of inhaled benzene with hematopoietic stem cells (multipotential hematopoietic stem cell CFU-S, granulocyte/macrophage progenitor cell CFU-GM), marrow and spleen cells. In experiment 1, male CD-1 mice (11-19 animals/dose group) were exposed for 6 hr/d for 5 days to 3.5, 32, 320, 979, 1930, 4083, 7731, or 15558 mg/m³ (1.1, 10, 100, 306, 603, 1276, 2416, or 4862 ppm). Experiment 2 was designed to compare the effects of 32 mg/m³ (10 ppm) exposure delivered over 50 days (6 hr/d, 5 d/w) to effects from 320 mg/m³ (100 ppm) exposure delivered over 5 days (experiment 1). In experiment 3, mice were exposed to 966 mg/m³ (302 ppm) for 6 hr/d, 5 d/w for 26 weeks. There were no exact data on the number of animals/group in experiments 2 and 3, number of animals for organ cellularity and weight determination was 12 males/group.
Results from experiment 1 showed that spleen weight, femoral and splenic cellularities (total number of nucleated cells, granulocytes, lymphocytes and nucleated red cells), total number of CFU-S in femur and spleen, and the number and concentration of splenic CFU-GM were significantly reduced at concentrations ≥ 320 mg/m³ (100 ppm). In femur, absolute numbers of CFU-GM were marginally reduced at 100 ppm and significantly lower at all higher doses, whereas the fraction of CFU-GM was increased to variable amount in most doses of 100 ppm and higher. Exposure to 306 ppm resulted in reduced concentration of splenic and marrow CFU-S. In peripheral blood, WBC, neutrophiles and lymphocytes were depressed ≥ 320 mg/m³ (100 ppm). RBC counts were depressed only at the two highest exposure levels.

Experiment 2 showed that exposure to 32 mg/m³ (10 ppm) over 50 days resulted in higher spleen weight, elevated splenic cellularity and increased number and concentration of CFU-S, but no changes in the CFU-S content of bone marrow were detected. CFU-GM were not evaluated in this experiment. No differences in the peripheral blood, bone marrow, or body weight were detected in exposed mice.
Results from experiment 3 showed lower spleen weight, marked depression in marrow and spleen cellularity with depressed marrow and spleen CFU-S (total number and concentration) and marrow CFU-Gm (total number and concentration) and spleen CFU-GM (total number). Marked changes in the peripheral blood included depressed WBC counts, RBC counts and percentages of lymphocytes, while the number of neutrophiles appeared to be elevated. Morphologically neutrophiles were abnormal exhibiting pyknosis and hypersegmentation. Red cell morphology was characterized by polychromasia, anisocytosis, poikilocytosis, stippling, and numerous Howell-Jolly bodies. Marrow differentials revealed reduced numbers of granulocytes, lymphocytes and nucleated red cells. In spleen number of lymphocytes were more drastic reduced than granulocytes, while the number of nucleated red cells were equal to the control value. Morphologically, nucleated marrow and spleen cells displayed a variety of nuclear/cytoplasmic dyscrasias including nuclear and cytoplasmic blebbing, vacuolization, and atypical mitotic figures. In addition, asynchronous nuclear/cytoplasmic maturation was observed in myeloid precursors.

Effects of benzene inhalation on mouse pluripotent hematopoietic stem cells have also been evaluated in the study of Cronkite and coworkers (1982). Male Hale Stoner BNL mice were exposed to 400 ppm benzene for 6 hr/d, 5 d/w, for up to 9½ weeks (65 days) with a 14 day-recovery period. At various times during and after the exposure period two to four mice were sacrificed to examine WBC and RBC counts, femur and tibia were evaluated for total bone marrow cellularity, stem cell content and the percent of stem cells in DNA synthesis. Exposure to benzene caused depressions of RBC and WBC counts gaining significance on day 11 and day 4 of exposure, which continued throughout the study and for at least 14 d after exposure. Beginning at the 5th day of exposure bone marrow cellularity were also depressed in exposed animals throughout the study. Except the day 50 cellularity was decreased to 33% up to the 25th day of study and around 50% for the remaining time to the control values. After the termination of benzene exposure, the marrow cellularity increased promptly to 88% of the control values 14 days after the last exposure. The absolute stem cell content measured as colony-forming unit in spleen (CFU-S) had dropped to 23% of the control value at day 5 of exposure and remained between 13 and 43% up to 14 day after termination of exposure. This effect was explained by a large reduction in the amplifying populations of identifiable erythrocytic and granulocytic precursors. An initial decrease of CFU-S actively synthesizing DNA from 26 to 13% during the first 3 days of exposure was evident, thereafter the percentage increased ranging from 26% to 66% during the remaining time of exposure and dropped after the last exposure to 7%. 5-25% of the CFU-S of control animals were in DNA synthesis. Histological typing of splenic colonies produced by bone marrow from exposed mice revealed that immature colonies have disappeared on the day 3 of exposure followed by a short rebound and a secondary diminution. Mature erythrocytic and granulocytic colonies diminished more slowly, reaching a minimum on day 5 and remaining lower than control levels throughout the study.
In extended experiments of this study, assays of early progenitors of erythrocytic cells and granulocytic cells were performed (Cronkite et al. 1989). 2-day cultures of erythrocyte colony forming units (CFU-E) from bone marrow cell suspensions were not changed after one and four exposures, but after 29, 48 and 65 days of exposure there was a significant diminution in the number of CFU-E. Bone marrow derived eight-day burst forming units (BFU-E-8) cultured in erythropoitin and pokeweed-mitogen were reduced markedly by day 29 of exposure (<10% of control levels) and recovery was incomplete 12 days after termination of exposure. Units of

granulocyte-macrophage aggregates in agar cultures were decreased compared to controls. The decrease was smaller (<20%) than that of BFU-E-8 with recovery to nearly that of the control levels 12 days after termination of exposure.

Exposure to 300 ppm (974.1 mg/m³) for 2, 4, 8, and 16 weeks produced a lower level of pluripotent stem cells in bone marrow of male and female C57B1/6 BNL mice which returned to those of controls 2 weeks after benzene exposure for 2 and 4 weeks, 16 weeks after exposure for 8 weeks, and to 92% of controls 25 weeks after 16 weeks of exposure (Cronkite et al. 1985). There was a more rapid return of blood lymphocytes to control level. Mice exposed to 300 ppm for 16 weeks had a shorter latency period of mortalities than control animals.

Bone marrow hemopoietic stem cell compartments and peripheral blood cell counts were studied in female BDF1 mice (9 animals/group) exposed for 16 weeks to 100, 300, and 900 ppm (~324.7, 974.1 and 2922.3 mg/m³) of benzene, 6 hours per day, 5 days per week (Seidel et al. 1989). Dose-dependent depressive effects were observed on all stem cell compartments. Only the erythroid colony-forming units (CFU-E) compartment was depressed during exposures to 100 ppm. CFU-E were more sensitive than the erythroid burst-forming units (BFU-E), spleen CFU (CFU-S), or CFU-GM, which were depressed by exposure to 300 ppm or 900 ppm. In peripheral blood, lymphocytopenia developed in mice exposed to 300 and 900 ppm benzene. At these dose groups, erythrocyte counts were depressed at week 4, did not further progress and showed a tendency to recover at week 13 and 16. After benzene-free intervals, a regeneration of lymphocyte numbers and slow normalisation of stem cell numbers was seen. Complete recovery from the 16 weeks exposure to 300 ppm was seen between 73 and 185 days.

To compare benzene effects of short term exposure with high dosages with longer exposure regimen at lower doses, Cronkite et al. (1989) exposed male and female CBA/Ca BNL mice (no data on number of animals/group) to 316 ppm (1011 mg/m³), of benzene vapor on 6 hr/d, 5 d/w, for a total of 19 exposures. Another group received 3000 ppm (9600 mg/m³), 6 hr/d, for two successive exposures. After termination of exposure and up to 214 days after termination of exposure, lymphocyte and neutrophil counts were reduced in either treatment group. However, lymphopenia and neutropenia were more drastic in the longer exposure regimen at most periods of recovery. At day 214 after exposure, only neutrophilic counts had recovered in the 3000 ppm group. Similarly differential leukocyte counts demonstrated reduction of all cell types except large unstained cells. Bone marrow cellularity was reduced in both treatment groups on day 1 after treatment and recovered at day 32. The content of marrow colony forming unit-spleen (CFU-S) were reduced in both treatment groups at day 1 of recovery. Whereas this parameter remained lowered up to 214 days in the 316 ppm group, it recovered at day 32 in the 3000 ppm group.

In the Baarson et al. (1984) study, C57B1/6J male mice were exposed to 32 mg/m³ (10 ppm) benzene for 6 hr/day, 5 days/week for up to 178 days (no number on animals tested). In vivo and in vitro evaluations of hematopoiesis, specifically erythropoiesis, were performed at 32, 66 and 178 days of exposure. There were significant depressions in the numbers of circulating RBC and lymphocytes in benzene-exposed mice. The levels of circulating neutrophiles, however, were unaffected by the exposures (data not shown). At 178 days, benzene-exposed mice exhibited depressions in splenic nucleated cellularity and in splenic nucleated RBC numbers. Marrow cellularity and marrow-nucleated RBC counts were unaffected by the exposures (data not shown). In vitro, progenitor cells from benzene-exposed mice showed reduced ability to form colonies compared to cells from control mice. Benzene exposed mice showed a progressive decline in bone marrow and splenic colony-forming unit-erythroid

(CFU-E) colonies during the exposure period, reaching 5% and 10%, respectively, of control values after 178 days.

Exposure to benzene showed decreased WBC counts in CD-1 mice exposed to 960 mg/m³ (300 ppm) for 2 to 13 weeks (Ward et al. 1985). In this study, 150 mice were exposed to benzene vapor (whole body exposure) at concentrations of 3.2, 32, 96 or 960 mg/ m³ (1, 10, 30 or 300 ppm) for 6 hr/day, 5 days/week for up to 13 weeks, 20 mice/sex/group sacrificed after 7, 14, 28, 56, and 91 days of treatment (study design in accordance to the requirements of 412). No exposure-related mortality or effects on mean body weight and clinical signs were seen. At 960 mg/ m³ (300 ppm), mice exhibited statistically significant decreases in hematocrit, Hb, RBC count, WBC count, platelet count, myeloid/erythroid ratio and the percentage of lymphocytes at day 14 of treatment and later. Mean cell volume (MCV), mean corpuscular hemoglobin (MCH), and the incidence and severity of red cell morphologic cell changes were increased in mice. These changes included anisocytosis, poikilocytosis, acanthocytosis, hypochromasia, nucleated red blood cells, Howell-Jolly bodies, polychromasia, echinocytosis and basophilic stippling. Gross pathology observations in mice included a slight increase in the incidence of small thymuses (day 56 and 91) and small spleens (day 56) in the 300 ppm group. At several sacrifices, animal of this dose groups showed lower organ weights in the testes, female mice had higher liver weights. Histopathology changes in 300 ppm mice of all sacrifice groups were first seen at day 7 of treatment and increased in severity with time. They included myeloid hypoplasia of the femoral marrow, depletion of the periarteriolar lymphoid sheaths in the spleen, lymphoid depletion in the mesenteric lymph nodes, and increased extramedullary hematopoiesis in the spleen. Plasma cell infiltration in the mandibular lymph nodes occurred in some mice at day 28 and thereafter. Additional, the final sacrifice revealed centrilobular hypertrophy of hepatocytes (three males). Degenerative lesions of the testes and the ovaries occurred in mice of the 300 ppm group as well as at lower dose groups. The NOAEL for hematological effects on peripheral blood circulation in this study was 96 mg/ m³ (30 ppm). The NOAEL for all adverse effects was not clearly estimated. Lesions resembling those seen in the high dose mice were thymic atrophy, increased extramedullary hematopoiesis, plasma cell infiltration in mandibular lymph nodes in some animals of the 10 and 30 ppm dose groups.

Luke et al. (1988a) evaluated the ability of benzene to damage and suppress erythropoiesis in mice, as measured by the percentage of polychromatic erythrocytes (PCE), and the frequency of micronuclei in polychromatic erythrocytes (MN-PCE) and normochromatic erythrocytes (MN-NCE) in the peripheral blood (no other test parameters). Groups of 6 male and female DBA/2 mice were exposed to 960 mg/m³ (300 ppm) benzene for 6 hr/day for 13 weeks using two different exposure regimens: Exposure was for either 5 consecutive days/week or for 3 consecutive days/week. Frequency of MN-PCE (lifetime of PCE in mice: 24 h) was increased without regimen and exposure duration relationship. Exposure to benzene resulted in a duration-dependent increase of MN-NCE (lifetime in mice of around 30 days). The increase was more slowly in the exposure regimen on 3 consecutive days. Males were more sensitive than females to both effects. An analysis of % PCE data (3% in controls) revealed an initial severe depression in the rate of erythropoiesis in both sexes (almost 0%), with a return of the PCE production to control levels being dependent to both sexes and exposure regimen. The effect was more persistent in males, exposure on 3 consecutive days were more depressive than on 5 days (only in males). However, during the later weeks of exposure there was a high variability of frequencies among individual control and exposed animals.
Luke et al. (1988b) conducted similar studies as in the Luke et al. (1988a) study using DBA/2, B6C3F1 and C57Bl/6 male mice (6 animals/group). The frequency of MN-PCE increased in all strains. The magnitude was strain specific (DBA/2> C57Bl/6=B6C3F1), independent from

exposure regimen and, except for exposure on 3 consecutive days in B6C3F1 mice, of exposure duration. There was an exposure duration-dependent increase in the frequency of MN-NCE in exposed mice of all strains (5 exposure days > 3 exposure days). The magnitude of MN-NCE accumulation were different between the strains, however differences were inhomogeneous between treatment regimen (5 exposure days: C57Bl/6=B6C3F1>DBA/2, 3 exposure days: C57Bl/6>B6C3F1=DBA/2). PCE levels were markedly depressed in the peripheral blood of mice of all strains. The extent and duration was dependent on both strain (more pronounced in DBA/2 mice) and exposure regimen (3 exposure days > 5 exposure days). The group mean percentage of PCE varied throughout the course of the study, variability was even greater within individuals from one week to another particularly evident near the final weeks of the study.

In another inhalation study (Rozen and Snyder 1985) groups of ten C57B1/6J male mice were exposed to 300 ppm (974.1 mg/m³) via inhalation for 6 exposures on 6 consecutive days (6 hr/d) or for 30, and 115 exposures (6 hr/d, 5 d/w). In peripheral blood, total lymphocytes and RBC were depressed after 6, 30, and 115 exposures. Depressions in mean counts of lymphocytes and RBC intensified with exposure progression. Mean spleen and thymus weights were also lower after all exposure periods compared to air-exposed controls. Thus, spleen and thymus weight of benzene-exposed mice increased with time. Nucleated cells in spleen, bone marrow and thymus from benzene-exposed mice were depressed after all periods of exposure. However, exposed mice exhibited a 15-fold increase in thymic cellularity and a 3-fold increase in marrow cellularity between 6 and 30 exposures. The total number of B-lymphocytes in bone marrow and spleen and the numbers of T-lymphocytes in thymus and spleen were found to be markedly reduced after all three periods. The numbers of splenic B-lymphocytes were continuously declining during exposure reaching less than 1% of control values, the marrow B-lymphocyte numbers were depressed to 6%, 11%, and 28% of corresponding air controls during the exposure periods. Similarly, the splenic T-lymphocytes were reduced progressively, the number of T-lymphocytes in thymus increased 15-fold in the period between 6 and 30 exposures.
Although depressed in comparison to control values, the relative increase of lymphocytes with exposure duration may reflect the efforts to repopulate the bone marrow and the thymus. No comparable increases were observed in the spleen. Other than the bone marrow and thymus, the spleen, however, has no B-cell or T-cell restorative capacities. The authors did not explain the underlying mechanism (e.g. extramedullary hematopoiesis, histiocytosis or hemosiderosis) of spleen weight increase. Histopathology was not performed.

Chronic exposure to benzene caused persistent lymphopenia and depressed RBC counts beginning after 1 exposure week in male AKR/J mice and C57Bl/6J mice exposed to 100 ppm (320 mg/m³) (50 AKR/J mice) or 300 ppm (974.1 mg/m³) (40 C57Bl/6J mice) on 6 hr/d, 5 d/w for a lifetime (Snyder et al. 1980). AKR mice transiently showed a tendency toward neutrophilia whereas in C57Bl mice neutrophilia was evident after 17 weeks and persisted until the end of study. Morphologic changes of RBC were observed in C57Bl mice consisting in anisocytosis and poikilocytosis which began after 4, respectively 15 weeks of exposure. Hyperlobulated, mature neutrophiles were observed and a neutrophilic left shift with increased appearance of metapyelocytes, myelocytes, promyelocytes, and giant platelets were evident concurrently with the neutrophilia. Where 20% of the exposed AKR mice developed bone marrow hypoplasia and no increased neoplasm rate, 33% of C57Bl/6J mice developed bone marrow hyperplasia limited to granulopoietic elements and increased rate of hematopoietic neoplasms.
Hematotoxicity in long term studies were also investigated by another study of Snyder and coworkers (1988). Groups of males C57Bl and CD-1 mice were exposed to benzene vapor

using two different exposure protocols. One protocol consisted of repetitive weeklong exposures of 60 mice/strain to 300 ppm (974.1 mg/m³) benzene, 6 hr/d, 5 d/w interrupted by 2 weeks of non-exposure until death. The second protocol consisted of exposures of 80 mice/strain to 1200 ppm (3896.4 mg/m³) benzene, 6 hr/d, 5d/w, for 10 weeks. After termination animals were allowed to live out their lifes. This regimen produced peripheral blood lymphocytopenia and a mild anemia during the 10 weeks of exposure, but after cessation of exposures, blood counts returned to control values. The 300 ppm (974.1 mg/m³) benzene exposures induced lymphocytopenia and anemia throughout the study. (The exact tumor data of both studies are cited in section 4.1.2.8).
Ten-week old male CBA/Ca mice were exposed to 300 ppm (974.1 mg/m³) benzene via inhalation for 6 hr/day, 5 days/week, for 16 weeks and held 18 months after the last exposure. Bone marrow smears of 24 benzene-exposed mice surviving and 24 sham-exposed male mice at terminal euthanasia at the study end of 20 months, revealed minimal to marked granulocytic hyperplasia in 14/24 benzene-exposed mice (maximal myeloid to erythroid ratio was 16:1, average ratio 3:1) and minimal granulocytic hyperplasia in the bone marrow of 2/24 sham-exposed mice (maximum myeloid to erythroid ratio was 2.4:1, mean ratio 1:1). The morphology and cell counts from the blood smears of these animals reflected bone marrow findings with a high segmented leukocyte count in those animals with granulocytic hyperplasia. The average absolute neutrophil counts for benzene-exposed mice was double that of the sham-exposed mice. The average ratio of segmented cells to lymphocytes in the benzene-exposed mice was 58:29 and in the sham-exposed was 48:39. The tumors observed were reported in section 4.1.2.8 (Farris et al. 1993). Authors concluded that granulocytic response was not a direct benzene effect due to the presence of inflammation or necrotic processes associated to superficial tumors (therefore study was not part of the Table 4.19). However, it is not clear whether the surviving animals were tumor bearing. No exact data on this are available.

Inhalation exposure/rat/subacute studies (<14 days)

A short-term study focussed on leucocytic alkaline phosphatase (LAP) activity and leukocyte counts in female Wistar rats (5-6 animals/group) exposed to 20, 50, 100, and 300 ppm (~64.94, 162.4, 324.7, 974.1 mg/m³), 8 hr/d, for 7 days (Li et al. 1986). Exposure to 100 and 300 ppm resulted in a dose-dependent increase in LAP; leukocyte counts and body weight were reduced. Exposure at higher concentrations at 1000 ppm and 3000 ppm for 7 or 14 days did not cause any additional elevation in LAP. An additional group of rats exposed to 300 ppm benzene vapor confirmed the findings in LAP, serum alkaline phosphatase remained unchanged.

Inhalation exposure/rat/subchronic-chronic studies (>14 days)

The findings of Li et al. (1986) were in conformance with the results of a 20-week study on male and female rats (6 animals/group, no data on the strain) exposed to 14.6 mg/l benzene (4 hours/day, 6 days/week) (Songnian et al. 1982). Leukocyte alkaline phosphatase activity was increased and WBC counts were decreased (no exact data on WBC counts were reported).

A recent study documented the effects of benzene vapor at concentrations of 0, 30, 200, or 400 ppm (0, 97, 649, 1299 mg/m³) for 6 hr/d, 5 days/week for 2 weeks (8 males/group) or 4

weeks (8 males/group) on Sprague-Dawley rats (Robinson et al. 1997). The number of splenic B-lymphocytes and the absolute spleen weight were significantly reduced after 2 weeks at 400 ppm. Non-significant dose-related lower spleen weight were observed in the low and mid dose groups after 2 weeks and in all treatment groups after 4 weeks. Lowered spleen cellularity was observed in all treatment groups at week 4 of treatment showing significance only at the high dose level. After 4 weeks of 400 ppm, there was a significant reduction in absolute and relative thymus weight and spleen B- and T-lymphocytes. There was no effect on the bone marrow cellularity at any time or treatment group.

Exposure to benzene showed a decrease in WBC counts in Sprague-Dawley rats exposed to 960 mg/m³ (300 ppm) for 2 to 13 weeks (Ward et al. 1985). In this study, 50 rats/sex/group were exposed to benzene vapor (whole body exposure) at concentrations of 3.2, 32, 96 or 960 mg/m³ (1, 10, 30 or 300 ppm) for 6 hr/day, 5 days/week for up to 13 weeks, and 10 rats/sex/group sacrificed after 7, 14, 28, 56, and 91 days of treatment. No exposure-related mortality or effects on mean body weight and clinical signs were seen. At several sacrifices, female rats of the 300 ppm dose groups showed lower organ weights of the thyroid. Rats of the 300 ppm dose groups exhibited decreased WBC counts, percentages of lymphocytes and, on day 7 only, decreased femoral marrow cellularity. This study was the most reliable study on rats. It was performed in accordance to the requirements of the EU-method B.29 and used for the delivery of the NOAEC. The NOAEC for hematological effects on peripheral blood circulation in this study was 96 mg/m³ (30 ppm). Also, the NOAEC for all adverse effects was 30 ppm in rats.

In an early less documented study of Deichmann et al. (1963) groups of 40 Sprague-Dawley rats were exposed for 5 hr/d on 4 d/w for 6 to a maximum of 31 weeks to benzene vapor (whole body exposure). Hematology was done at weekly or biweekly intervals in 10 male and 10 female randomly picked animals. Rats exposed to a mean concentration of 831 ppm (~2698 mg/m³) on 32 days over a period of 46 days had reduced number of WBC in males and females after one week of exposure and thereafter. Another treatment with mean exposure to 65 ppm (~211 mg/m³) on 26 days over a total period of 39 days showed reduced number of WBC beginning at the treatment week 2 in females and week 4 in males. Leucopenia became also apparent in rats exposed to 47 ppm (~152 mg/m³) of benzene for 7 hr/d on 180 days over a total of 245 days. A mean benzene vapor concentration of 44 ppm (~143 mg/m³) induced leucopenia gaining significance in males at week 7 and in females at week 5. Animals were sacrificed at week 8 after 45-54 periods of exposure. Concentrations of 31 ppm (~101 mg/m³) on 126 days (7 hr/d, 4 d/w), 29 ppm (~94 mg/m³) on 88 days (7 hr/d, 4 d/w) or 15 ppm (~49 mg/m³) on 154 days (5 d/w) did not induce changes in WBC counts. The spleen of rats of the 15 ppm, 31 ppm and 47 ppm groups examined microscopically revealed a higher incidence and severity of hemosiderosis (females>males). The authors summarized that the degree of leucopenia was similar in rats exposed to 65 ppm or 831 ppm, but exposure to higher concentration induced an earlier response. The leucopenia was less severe in rats exposed to 44 and 47 ppm. Female rats were more susceptible to leucopenia than males. The NOAEL for effects on peripheral blood was 31 ppm. However, no clear NOAEL for all adverse effects was established due to increased incidence/severity of splenic hemosiderosis at doses ≥15 ppm (~249 mg/m³).

Oral exposure/mouse/subchronic and chronic studies (4 weeks and longer)

In adult CD-1 mice (5 males/group) administered orally via drinking water to 8, 40, or 180 mg/kg bw/d benzene for 4 weeks, peripheral RBC, blood leukocyte and lymphocyte counts were significantly reduced in a dose-responsive fashion, whereas numbers of neutrophiles and other WBC were not altered (Hsieh et al. 1988b) (special immune effects see 4.1.2.8.B). At all dose groups, MCV values increased in a dose-related manner. Benzene produced a dose-related decrease in spleen weight and increase in kidney weight at all dose groups gaining significance at the high dose level. Thymus weight was reduced at all dose groups but not significantly. The total number of recovered splenocytes was significantly reduced related to the dose level at all dose groups.

In a National Toxicology Program (NTP) study (NTP 1986; Huff et al. 1989), B6C3F1 mice were evaluated to cumulative toxicity of benzene in 17 week studies and two-year studies. In the seventeen-week study, groups of 10 mice/sex were administered 0, 25, 50, 100 or 400 mg/kg benzene in corn oil by gavage. Groups of 15 mice were administered 0, 200, or 600 mg/kg bw/d, 5 animals of each of these groups were killed on day 60. Mice receiving 100 mg/kg bw or more had lower final body weights. Tremor was observed intermittently in 400 and 600 mg/kg groups. Dose-related leucopenia and lymphocytopenia were registered in male mice at 50 mg/kg or more and in female mice at 400 mg/kg bw or more.
In the cancer study, mice of each sex were administered to 0, 25, 50, or 100 mg/kg bw benzene by gavage, 5 d/w for 103 weeks. Blood was withdrawn from 10 animals/sex/group at 12, 15, 18, and 21 months. Additional groups of 10 animals of each sex and species were treated at the same doses for 51 weeks, blood was withdrawn at 0, 3, 6, 9, and 12 months. Weight gain reductions occurred in high dose male and female mice. Hematological effects were limited to lymphocytopenia and associated leukocytopenia in all mouse dose groups (males from 3 to 18 months, female mice from 12 to 18 months). Benzene increased the frequency of micronucleated normochromatic peripheral erythrocytes in male and female mice of all dose groups, males were more sensitive than females.
Hematopoietic hyperplasia in the bone marrow and splenic hematopoiesis was observed in all dosed mice groups. (Tumor data and survival rates were reviewed in section 4.1.2.8)

Oral exposure/rat/chronic studies (60 days and longer)

In a National Toxicology Program (NTP) study (NTP 1986; Huff et al. 1989), Fischer 344 rats were evaluated to cumulative toxicity of benzene in 17 week studies and two-year studies. In the seventeen-week study, groups of 10 rats were administered 0, 25, 50, 100 or 400 mg/kg benzene in corn oil by gavage. Groups of 15 rats were administered 0, 200, or 600 mg/kg bw/d, 5 animals of each of these groups were killed on day 60. In rats, final body weight were depressed in both sexes that received ≥200 mg/kg bw. A dose-related leucopenia and lymphocytopenia was observed in male rats at ≥200 mg/kg bw and in female rats at ≥25 mg/kg bw. In the spleen, lymphoid depletion of B-cells was evident in both sexes at ≥200 mg/kg, increased extramedullary hematopoiesis was seen in male and female rats at 600 mg/kg bw/d.
In the cancer study 50 male rats were administered to 0, 50, 100, or 200 mg/kg bw and female rats were administered to 0, 25, 50, or 100 mg/kg bw benzene by gavage, 5 d/w for 103 weeks. Blood was withdrawn from 10 animals/sex/group at 12, 15, 18, and 21 months. Additional groups of 10 animals of each sex and species were treated at the same doses for 51 weeks; blood was withdrawn at 0, 3, 6, 9, and 12 months. Weight gain reductions occurred in mid and high dose males rats, and high dose female rats. Hematological effects were limited to lymphocytopenia and associated leukocytopenia in all male rat groups from 3 to 18

months; a similar but less pronounced response was observed in dosed female rats during the same time period. The frequency of micronucleated normochromatic peripheral erythrocytes was not examined in rats. Histopathology revealed increased incidences at all dose groups of lymphoid depletion in the spleen (male and female rats) and the thymus (male rats). (Tumor data and survival rates were reviewed in section 4.1.2.8)

Subcutaneous administration/rabbit/short-term studies (<14 days)

A group of 9 rabbits (female 2-4 kg bw) was administered subcutaneously to 0.5 mg/kg bw/d of benzene on 10 consecutive days, another group of 8 animals received 0.25 mg/kg bw/d (Irons and Moore 1980). 4, respectively 2 animals were allowed to recover for up to 30 days.

Treatment resulted in a dose-related rapid loss of circulating lymphocytes up to 80%. At the end of the treatment period, circulating immunglobulin-positive lymphocytes representing B-lymphocytes were depressed. Recovery of lowered values was incomplete at the end of the recovery period. The percentage of immunglobulin-negative lymphocytes at the high dose level were also decreased in relation to the base line values on day 0. The authors concluded that circulating lymphocytes were decreased due to a selective toxic effect on B-cells. The conclusion that negative cells, presumably T-lymphocytes, were relatively unaffected, remains unclear.

Intraperitoneal application/mouse/short-term studies (<14 days)

Short-term treatment with 600 mg/kg bw of benzene, twice a day on 2 days, injected intraperitoneally to four male C57B1/6J mice caused a significant depression of the total number of nucleated bone marrow cells per femur on day 3 (Niculescu and Kalf 1995). Depression of the nucleated erythroid cells started at day 3 and remained constant until day 7 of monitoring. Reduction of lymphocyte counts also started on day 3 and progressively decreased until day 7. Conversely, the numbers of intermediate and terminally differentiated granulocytes progressively increased over 7 days.

Dermal exposure

No information was found on the hematotoxicity of benzene after dermal exposure.

4.1.2.6.1. B. Effects on the immune system

In addition to immunological effects associated with altered leucopoiesis, there is experimental evidence that benzene and its metabolites can influence immune function (see Table 4.22).

Effects on lymphocyte subpopulations

In the inhalative study (Rosenthal and Snyder 1987) C57BL/6 mice were exposed 6 hr/d for 5d/w to 100 ppm (325 mg/m³) benzene twenty times. The data show that the relative proportions of splenic leukocytes, the percentages of splenic T-cell subsets and the ratio of splenic helper/suppressor cells are not affected.

Lymphoproliferative response to mitogens

Rozen et al. (1984) performed studies in which male C57Bl/6J mice were exposed to 10, 31, 100 or 300 ppm benzene vapor on 6 days (6 hr/d) demonstrating reduced RBC counts and numbers of T- and B-lymphocytes (see Section 4.1.2.6.1.1 A) at dosages of 100 ppm (320 mg/m³) and above. Levels of circulating lymphocytes and lipopolysaccharide (LPS)-induced B-colony forming ability of femoral B-lymphocytes were depressed at all dose groups. At 31 ppm (99 mg/m³) splenic phytohemagglutinin (PHA)-induced blastogenesis of T-lymphocytes was also depressed.

Inhalative exposure to vapor concentrations of benzene of 300 ppm (960 mg/m³) for periods of 6, 30, or 115 days resulted in decreased number and proliferative capacity of T- and B-lymphocytes (Rozen and Snyder 1985) in male C57Bl/6J mice. Mitogen-induced proliferation in a B-lymphocyte colony forming assay to bone marrow and splenic B-lymphocytes exhibited a progressive depression throughout the exposure period reaching a point of no observable mitogen-induced response after 115 exposures. Splenic T-cell mitogen-induced proliferation in the PHA-stimulation index assay was also markedly depressed throughout the exposures, but there was no evidence of a progressive decline in this response during the exposures.

Following four weeks of oral benzene treatment via the drinking water, the proliferative response of either mitogen-stimulated or nonstimulated splenic lymphocytes were elevated in male CD-1 mice at 8 mg/kg bw and depressed at 40 and 180 mg/kg bw/d (Hsieh et al. 1988b). This biphasic alterations in proliferation of T- and B-lymphocytes was observed using LPS, PWM, ConA and PHA.

In *in vitro* studies supernatants from splenic T-lymphocyte cultures stimulated with ConA were assayed for Interleukin-2 (IL-2) content by their ability to enhance proliferation of the murine T-helper cell line HT-2. Splenic IL-2 production was suppressed in the 40 and 180 mg/kg bw treated benzene groups (Hsieh et al. 1991).

Cell-mediated immune responses

Mixed lymphocyte reaction and cytotoxic T-lymphocyte reaction to allogenic cells

Inhalative exposure of male C57Bl/6J mice to 100 ppm benzene (320 mg/m³) (6 hr/d for 5d/w) on 10 consecutive days were performed before starting the tumor cell inoculation (Rosenthal and Snyder 1987). Reduced tumor lytic abilities of splenic cytotoxic T-lymphocytes were demonstrated. Splenic T-lymphocytes taken from mice treated with 10 ppm (960 mg/m³) and 100 ppm (~325 mg/m³) for 20 days showed a delayed mixed lymphocyte reaction (MLR) to alloantigens. This delayed MLR response was not due to the presence of benzene-induced suppressor cells. The authors suggested that benzene impaired the functional abilities of alloreactive T-cells.

In a further study, cell mediated immunity was measured in splenic lymphocytes of 4 weeks orally exposed male CD-1 mice by mixed-lymphocyte culture response to allogenic cells and cytotoxic T-lymphocyte (CTL) activity to YAC-1 tumor cells. Both immune reactions were inhibited at benzene doses of 40 and 180 mg/kg bw/d, but increased in the 8 mg/kg bw/d dose group (Hsieh et al. 1988b).

Suppressor cells

Cell-mediated immune response was measured by contact sensitivity (CS) to picryl chloride (PCl) in BALB/c male mice exposed to 50 or 200 ppm (~162 or 649 mg/m³) benzene vapor (6 hr/d) for 14 consecutive days. Mice were immunized with PCl on day 7 or 9 and challenged to PCl on day 14 (Aoyama 1986). The CS response expressed as the increase of ear thickness after 6, 24, and 48 hr was enhanced in the 200 ppm group. It was concluded that the activity of T-lymphocytes in the induction and expression of CS was not depressed at the exposure levels.
The activity of suppressor cells was evaluated in spleen by the suppressive effect on splenic passive transfer of CS. Spleen cells from 14-days exposed mice which were immunized with PCl on day 7 and killed on day 14 were injected into irradiated recipients which received effector cells from immunized nonexposed animals. The response was measured as the increase of ear swelling at 24 h after challenge to PCl of the recipients.
Ear thickness increased at 200 ppm to comparable percentages of the positive controls assuming that suppressor cell activity in mice exposed to 200 ppm was significantly lowered.

Humoral immune responses

Antibody production

Humoral immune response to sheep red blood cells (SRBC) was depressed in animals exposed by inhalation or by ingestion with benzene. In the study of Aoyama (1986), male BALB/c mice which were exposed to 50 or 200 ppm (~162 or 649 mg/m³) of benzene vapor for 14 consecutive days showed reduced numbers of IgG- and IgM- plaque-forming cells per spleen in the plaque-forming cell assay (PFC).

Hsieh et al. (1988b) assessed the primary antibody response to SRBC after benzene exposure. The number of PFCs in male CD-1 mice receiving 40 and 180 mg/kg bw/d of benzene was

reduced, when expressed on either specific activity of PFC/10^6 spleen cells or whole spleen basis. However, there were more PFC per 10^6 spleen cells at the low level of benzene. The titers of SRBC antibodies corresponded to the numbers of PFC.

In male Sprague-Dawley rats, no significant effect on the humoral immune response was measured in an ELISA of serum anti-SRBC IgM (Robinson et al 1997). SRBC was injected four days prior to the completion of 2 or 4-week exposure to 30, 200, or 400 ppm benzene vapor (6 hr/d, 5 d/w).

Immune response in host resistance models

Continuous exposure to concentrations as low as 30 ppm (96 mg/m³) of benzene resulted in a delay in immune response of T-cells and macrophages after induction of bacterial infection in C57BL/6 mice (Rosenthal and Snyder 1985).
Preexposure of male C57Bl/6J mice (5-7 animals/group) to benzene at 10, 30, 100, or 300 ppm for 5 days followed by infection with Listeria monocytogenes with continuous exposure on 7 days or without continuing the exposure increased the bacterial counts in mice of the 300 ppm group of the preexposure group and in mice at 30, 100, and 300 ppm (~97, 325, 974 mg/m³) of the continuous exposure groups on day 4, but not days 1 or 7. Nucleated cells, lymphocytes, T- and B-lymphocytes and monocytic/macrophagic cells per spleen increased from day 1 to day 7 of infection in air control groups. Significant depressions of the mentioned cell types except the monocytic/macrophagic cells were observed in each exposure regimens at 30 ppm or higher concentrations from day 1 through day 7 of bacterial infection.

Reduced tumor resistance mediated via T-lymphocytes was observed in 9 out of 10 male C57Bl/6J mice exposed to 100 ppm benzene (320 mg/m³) for a total of 100 days (6 hr/d, 5 d/w, 20 weeks) and challenged with 10.00 polyoma virus-induced tumor cells/mouse. These mice developed tumors that were lethal. Lethal tumor incidences in air controls and mice exposed to 10 or 30 ppm benzene concentrations were 3/10 or less (Rosenthal and Snyder 1987).

Immune response to toxin

Concentration of 200 ppm (649 mg/m³) for 10 or 20 exposures or 400 ppm (1299 mg/m³) for 5, 12, or 22 exposures (6 hr/d, 5 d/w) suppressed the T-cell dependent primary antibody response to tetanus toxin in female BNL mice (15 animals/group) on day 21 after immunisation (Stoner et al. 1981). No effect at 50 ppm (160 mg/m³) after 5, 10, or 20 exposures and at 200 ppm after 5 exposures was measured.

Nonspecific immune response

Subcutaneous injection on 3 days with 800 mg/kg bw/d of benzene or a combination of 50 mg/kg bw phenol and hydroquinone to BALB/c mice (no data on number and sex of experimental animals) were found to activate bone marrow derived macrophages and granulocytes measured as an increased production of hydrogen peroxide after stimulation

(Laskin et al. 1989). The number of cells recovered from the bone marrow of the femur and tibia was decreased in each of the treatment groups to 30-40% of the control values.

Immune response in rats

In the inhalative study of Robinson et al. (1997) the immunotoxicity of benzene was evaluated in male Sprague-Dawley rats by exposure to 0, 30, 200 or 400 ppm (~97, 649, 1299 mg/m³) benzene for 6h/day, 5 days/ for 2 and 4 weeks. In the two-weeks study a reduction in the number of splenic B-lymphocytes was induced in the highest dose group of 400 ppm, whereas after 4 weeks treatment the number of B- and T-lymphocytes was effected. The humoral immune response measured with the antigen SRBC was not influenced by benzene inhalation as tested with 30, 200 and 400 ppm. Overall, the data suggest that immune functions are not influenced by exposure of rats with 200 ppm benzene or less.

4.1.2.6.1 C Other effects

Benzene is also reported to possess neuromodulatory effects.
Oral administration of 8, 40 or 180 mg/kg bw/d of benzene via drinking water to male CD-1 mice (5 animals per group) for four weeks markedly stimulated the hypothalamic-pituitary-adrenocortical activity (Hsieh et al. 1991). Treated animals did not elicit mortality or any overt clinical symptom of toxicity. At the end of treatment, concentrations of hypothalamic norepinephrine and its metabolite vanillylmandelic acid were elevated in homogenized brain tissue accompanied by increased ACTH/corticosterone releases into peripheral blood. At all dose groups, serum corticosterone levels collected at day 2, 7 and 14 of the treatment period were increased on day 7, declined to control level on the 14th day and reelevated in the high dose group only at the termination of the study.

In an earlier study, Hsieh et al. (1988a) observed increased concentrations of norepinephrine (NE) in the hypothalamus, medulla oblongata and cerebellum of CD-1 mice fed continuously with drinking water containing 31, 166 and 790 mg/l benzene for four weeks. Dopamine (DA) concentrations increased significantly in the hypothalamus and corpus striatum. Increases of several catecholamine metabolites and the indoleamine serotonin (5-HT) were seen in a number of brain regions. The authors concluded that benzene induced increased rates of synthesis and catabolism of neurotransmitters NE, DA, and 5-HT. Besides of direct toxic effects on the immune system, the increases in brain catecholamines can act indirectly on the immune system via hypothalamus-pituitary-adrenal axis. Increased metabolisms of catecholamines can result in increased adrenal corticosteroid levels.

Ten 3-months old male Sprague-Dawley rats were administered by intraperitoneal injections on three consecutive days to 0.5 ml/kg bw/day of benzene (purity 99%) (De Gandarias et al. 1992). The activity of aminopeptidase, which is proposed to regulate the activity of several neuroactive peptides, was measured by the hydrolysis rate of Lys- and Leu-2-naphthylamides in several brain regions. Both enzyme activities were decreased in the thalamus, hypothalamus, hippocampus, and amygdala after benzene treatment suggesting that central neuropeptide transmission may be activated.

Neurobehavioral function and changes in acetylcholinesterase (AChE) activity at low level exposure to benzene were investigated by Li and coworkers (Li et al. 1992). Adult male

Kunming mice were exposed to 0, 0.78, 3.13, and 12.52 ppm (~0, 2.5, 10 and 41 mg/m³) of benzene for 2 hours per day for 30 days. Neurobehavioral function was measured in tests on the limb grip strength, rapid response (learning/memory functions) and locomotor activity. Depressed neurobehavioral function was recorded at the high dose level, whereas the mid dose animals did not show consistent effects and low dose animals responded with higher activities compared to the controls. Decreases of AChE activity in blood and brain were noted with increase of benzene exposure dose, especially in the mid and high dose groups. Values of AChE activity only gained significance in the brain of the high dose group.
Body weight and consumption of food and water were not affected, relative weights of the liver were increased and of the spleen were decreased in high dose animals. Microscopically, percentages of most precursors of WBC and RBC in the bone marrow decreased with increase of the inhaled benzene level, some cell precursors showed increased values in the mid and low dose groups.

Summary Table 4.19 Animal toxicity data after repeated exposure to benzene (Sections 4.1.2.6.1 A,B,C)

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
Inhala-tion	mouse/ DBA/2J (males)	10, 30, 100 ppm 6 hr/d, 5 days	no	-	10 ppm	≥10 ppm: depression of marrow erythroid progenitor cells (BFU-E, CFU-E) on day 1 after exposure and recovery on day 5 after exposure, splenic erythroid progenitor cells (CFU-E) increased on day 5 of recovery	Dempster and Snyder, 1990
	mouse/ C57B1/ 6J (males)	10, 31, 100, 300 ppm 6 hr/d, 6 d	no	-	10 ppm	≥10 ppm: depressed Ly counts, reduced mitogen response of femoral B-Ly to LPS ≥31 ppm: reduced mitogen response of splenic t-Ly to PHA ≥100 ppm: lower RBC counts, reduced numbers of B-Ly (femur) and T-Ly (spleen)	Rozen et al., 1984

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
	mouse/ BALB/c (males)	50, 200 ppm, 6 hr/d, 7 or 14 days	no	-	50 ppm	≥50 ppm: lower relative weights of spleen and thymus, reduced WBC, reduced No. of T- and B-Ly in blood and spleen, depressed antibody response in the Plaque-forming assay, reduced suppressor cell activity in a contact sensitivity test	Aoyama, 1986
Inhala-tion	mouse/ NMRI (males)	continuous: 24 hr/d: 1, 10, 21, 50, 95 ppm, 4-10 days	no	10 ppm	21 ppm	≥21 ppm: depressed bone marrow cellularity and granulopoietic stem cells (CFU-C), increased MN-PCE	Toft et al., 1982
						14 ppm: increased marrow MN-PCE	
		14 ppm, 1-8 weeks		-	14 ppm		
	mouse/ NMRI (males)	Intermittent: 8 hr/d: 1, 10.5, 21, 50, 95, 107 ppm, 5 d/w,		10.5 ppm	21 ppm	≥21 ppm: depressed granulopoietic stem cells, increased marrow MN-PCE ≥50 ppm: depressed bone marrow cellularity	

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
		2 weeks 14 ppm, 1-8 weeks		14 ppm	-	- 95 ppm/≥4 hr/d: increased MN-PCE	
Inhala-tion		0, 2, 4, 6, 8 hr/d: 95, 201 ppm, 5 d/w 2 weeks		-	95 ppm	95 ppm/≥6 hr/d: reduced bone marrow cellularity, granulopoietic stem cells (CFU-C) 201 ppm//≥2 hr/d: suppressed bone marrow cellularity, increased MN-PCE, 201 ppm//≥4 hr/d: reduced granulopoietic stem cells (CFU-C)	
	mouse/ B57B1/ 6 BNL	10, 25, 100, 400 ppm 6 hr/d, 5d/w 2 weeks	no	10 ppm	25 ppm	25 ppm: depressed Ly counts all groups ≥100 ppm: depressed Ly counts and hematocrit, bone marrow: lower No. of nucleated cells and stem cells and higher fraction of stem cells in DNA synthesis	Cronkite et al., 1985
	mouse/	300 ppm, 6	no	-	300 ppm	reduced bone marrow cellularity and development of	Neun et al., 1992

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
	Swiss Webster & C57B1/ 6J (males)	hr/d, 4 d/week, 2 weeks				CFU-E in both strains (Swiss>C57B1/6J)	
Inhala-tion	mouse C57B1 /6 (males)	Intermittent: 1000, 2000, 4000 ppm, 6 hr/d, 5 d/w, up to 6 weeks continuous 24 h/d: 100, 500, 1000, 2000, 4000 ppm up to 8 days	no	-	100 ppm	≥2000 ppm: lower WBC counts from day 3 on 4000 ppm: tremor during exposure, reduced no. of Ly and PMN, reduced no. progenitor cells (CFU-S) in femur marrow ≥2000 ppm: death within 24 hr 500+1000 ppm: death within 3 or 4 d, lower WBC counts beginning after 24 hr 100 ppm: reduced WBC counts after 24 hr and thereafter, reduced bone marrow cellularity after 48 hr	Gill et al., 1980
	mouse B6C3F1	1, 10, 100, 200 ppm, 6 hr/d, 5	no	10 ppm	100 ppm	≥100 ppm: bone marrow: reduced No. of bone marrow cells (reversible), decreased No. of stem cells (non-	Farris et al., 1997

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
Inhala-tion	/CrlBR (males) mouse B6C3F1 /CrlBR (males)	d/w, 1,2,4*,8 weeks, * with 4, 11, 18, or 25 days of recovery				reversible at 200 ppm) increased No. of replicating stem cells in S-phase (non-reversible at 200 ppm), initially increased and thereafter decreased No. of erythrocytic progenitor cells (CFU-E), decreased No., but increased percentages of differentiating erythrocytic cells (rubriblasts-metarubricytes), reduced No. of granulocyte-macrophage colony-forming units (CFU-GM), reduced No. and increased percentages of differentiating granulocytic cells (myeloblasts-segmented neutrophiles); blood: decreased No. and percentages of PCE and RBC, increased MCV, reduced WBC counts and platelets	
	mouse CD-1 (males)	1.1, 10, 100, 306, 603, 1276, 2416, 4862 ppm 6 hr/d, 5 days	no	10 ppm	100 ppm	≥100 ppm: increased spleen weight, depressed WBC, Ly, PMN in peripheral blood, in spleen/femur bone marrow: reduction in cellularity (total cell number, Ly, PMN, nucleated red cells), No. of hematopoietic stem cells (CFU-S), No. of granulocytic/macrophage progenitor cells (CFU-GM)	Green et al., 1981a,b

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
Inhala-tion		9.6 ppm 6hr/d, 5 d/w, 50 days 302 ppm 6 hr/d, 5 d/w 26 weeks			9.6 ppm 302 ppm	increased fraction of CFU-GM in femur ≥306 ppm: in spleen & marrow: reduced concentration of CFU-S ≥2416 ppm: reduced RBC 9.6 ppm: increase of spleen weight, splenic cellularity, No. &concentration of CFU-S 302 ppm: lower spleen weight, depressed WBC, RBC, Ly %, increased PMN and altered red cell and PMN morphology in peripheral blood, depressed marrow and spleen cellularity with reduced Ly, PMN and (in femur only) nucleated red cells, lower No. & concentration of CFU-S in spleen/marrow and of CFU-GM in marrow, lower No. of spleen CFU-GM	
	mouse/ Hale Stoner	400 ppm 6 hr/d, 5 d/w up to 65 d & 14	no	-	400 ppm	depressed peripheral RBC and WBC counts, cell No. and stem cell content (CFU-S) in bone marrow, initially decreased and thereafter increased percentage	Cronkite et al., 1982

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
	BNL (males)	d recovery				of marrow stem cells (CFU-S) with active DNA production	
	mouse/ B57B1/ 6 BNL	300 ppm 6 hr/, 5 d/w 2,4,8,16 weeks	no	-	300 ppm	Reduced No. of pluripotent stem cells in bone marrow at all time periods, incomplete recovery of reduced stem cell No. after 16 weeks of exposure at week 25 of recovery	Cronkite et al., 1985
Inhala-tion	mouse BDF1 mice (female)	100, 300, 900 ppm, 6hr/d 5 d/w, up to 16 weeks	no	-	100 ppm	≥100 ppm: depressed colony-forming units (CFU-E) in bone marrow ≥300 ppm: depressed erythroid burst-forming cells (BFU-E), spleen CFU (CFU-S), or CFU-GM in marrow; blood: lymphocytopenia, anemia; recovery between 73 and 185 days	Seidel et al. al., 1989
	mouse CBA/Ca BNL	316 ppm 6 hr/d, 5d/w 19 days or 3000 ppm 6 hr/d, 2 days	no	-	316 ppm	both dose groups: nonreversible reduction of blood WBC, Ly, neutrophils up to 214 d after exposure (except neutrophils in 3000 ppm group), bone marrow cellularity (reversible at day 32 postexposure) and stem cell content (recovered at day 32 at 3000 ppm, no	Cronkite et al., 1989

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
						recovery in 316 ppm)	
	mouse/ C57B1/ 6J (males)	10 ppm ($32mg/m^3$) 6hr/d, 5d/w up to 178 d	no	-	10 ppm	Depressed RBC, lymphocytes and splenic nucleated red cells, lowered splenic and marrow colony forming units-erythroid (CFU-E)	Baarson et al., 1984
Inhala-tion	mouse CD-1	1, 10, 30, 300 ppm 6hr/d, 5d/w up to 13 w	B.29	30 ppm for hematol ogy	300 ppm for hematolo gy	300 ppm: Blood: decreased RBC, WBC, Hb, Htk, Ly %, platelets, increased MCV, MCH, altered red cell morphology femoral myeloid hypoplasia, thymic atrophy, Ly depletion of splenic PALS and mes. lymph nodes, splenic extramedullary hematopoiesis 10/30 ppm: some animals with thymic atrophy and extramedullary hematopoiesis	Ward et al., 1985
	mouse/ DBA/2	300 ppm 6 hr/d, 13 w	no	-	300 ppm	blood: increased frequency of MN-PCE and MN-NCE, initially depressed polychromatic erythrocytes (PCE)	Luke et al., 1988a

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
		3 d/w or 5 d/w					
	mouse/ C57B1/ 6J (males)	300 ppm 6 hr/d, 5 d/w 6, 30, 115 d	no	-	300 ppm	all exposure periods: lower circulating Ly and RBC counts, decreased spleen and thymus weight, depressed nucleated cells in bone marrow, thymus, spleen, depressed thymus and spleen T-Ly, depressed spleen and marrow B-Ly; depressed mitogen-induced proliferation in B-Ly of spleen and bone marrow and in T-Ly in spleen	Rozen & Snyder 1985
Inhala-tion	mouse/ AKR/J (males) C57Bl/ 6J (males)	100 ppm lifetime 300 ppm lifetime	no	-	100 ppm	AKR/J mouse/100 ppm: lymphopenia, lower RBC, tendency to neutrophilia. Bone marrow hypoplasia. C57Bl/6J mouse/300 ppm: reduced weight gain, lymphopenia, lower RBC, neutrophilia/left shift, altered RBC morphology, myeloid hyperplasia. Granuolopoietic or myeloid bone marrow hyperplasia, spleen hyperplasia due to extramedullary hematopoiesis	Snyder et al., 1980
	mouse/	Intermittent:	no	-	300 ppm	300 ppm/intermittent exposure: persistent	Snyder et al., 1988

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
	C57Bl and CD-1 (males)	300 ppm 6 hr/d, 5d/w, interrupted by 2 weeks unexposed, until death 1200 ppm 6 hr/d, 5 d/w 10 weeks, untreated until death				lymphocytopenia, anemia 1200 ppm/continuously on 10 w: lymphocytopenia and anemia, reversible after exposure cessation	
Inhala-	C57Bl /6J mouse/ (males)	10, 30, 100,300 ppm, 6 hr/d, preexposure 5 days prior to infection, 10, 30, 100,300	no	10 ppm	30ppm	≥30 ppm: spleen: reduced increase of nucleated cells, lymphocytes, T-Ly, B-Ly on day 1 through day 7 postinfection 300 ppm: spleen: increased bacterial counts on day 4 postinfection ≥30 ppm: spleen; increased bacterial counts on day 4	Rosenthal and Snyder, 1985

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
tion		ppm, 6 hr/d, 5 d prior and 7 days during infection				postinfection, reduced increase of nucleated cells, lymphocytes, T-Ly, B-Ly on day 1 through day 7 postinfection	
	mouse/ BNL (female)	50, 200 ppm 6 hr/d, 5 d/w 5, 10, 20 exposures 400 ppm 6 hr/d, 5 d/w 5,12, or 22 exposures	no	50 ppm	200 ppm	≥200 ppm: suppressed primary antibody response to tetanus toxin	Stoner et al., 1981
	mouse Kun-ming (males)	0.78, 3.13, 12.52 ppm 2hr/d, 30 d	no	3.13 ppm	12.52 ppm	12.52 ppm: significant depression of neurobehavioral functions in test on limb grip strength, rapid response, locomotor activity , relative weights of liver: increased, of spleen: decreased, AChE activity in blood (nonsig) and brain (sig) lowered, reduced No. of bone marrow precursor cells of all lineages	Li et al., 1992

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
						3.13 ppm: some minor nonsignificant effects on all test parameters	
Inhala-tion	rat/ Wistar (female)	20, 50, 100 and 300 ppm 8hr/d, 7 d 1000 and 3000 ppm, 8 hr/d, 7 or 14 d	no	50 ppm	100ppm	≥100ppm: increased activity of leukocytic alkaline phosphatase, depressed WBC counts, lower body weight gain	Li et al.. 1986
	rat	14.6 mg/l, 4 hr/d, 6 d/w, 20 weeks	no	-	14.6 mg/l	increased leukocyte alkaline activity, reduced WBC counts	Songnian et al., 1982
	rat/Sprague-Dawley (male)	30, 200, 400 ppm, 6 hr/d, 5 d/w, 2 or 4 weeks	no	200 ppm	400 ppm	400 ppm/2 weeks: reduction of abs. spleen weight and no. of splenic B-lymphocytes 400 ppm/4 weeks: reduction of spleen cellularity, of abs./re. thymus weight, and of spleen B- and T-lymphocytes	Robinson et al., 1997
	rat/	1, 10, 30, 300	B.29	30 ppm	300 ppm	Decreased WBC and Ly %, decreased femoral	Ward et al., 1985

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
	Sprague -Dawley	ppm 6hr/d, 5d/w up to 13 w				cellularity	
Inhala-tion	rat/ Sprague -Dawley	5 hr/d, 4 d/w: 46 d/831 ppm 39 d/65 ppm 154 d/15 ppm 7 hr/d, 4 d/w: 245 d/47 ppm 54 d/44 ppm 126 d/31 ppm 88 d/29 ppm	no	-	15 ppm	All treatment groups ≥44ppm: decreased WBC counts Histopathology performed in rats from the 15, 31 and 47 ppm groups revealed increased incidence and severity of hemosiderosis of the spleen	Deichmann et al., 1963
oral oral drink-	mouse/ CD-1 (males)	8, 40, 180 mg/kg bw/d 4 weeks	no	-	8 mg/kg bw/d	≥8 mg/kg: reduced counts of RBC, leukocytes, lymphocytes, increased level of MCV lower weight of spleen and thymus, elevated kidney weight, reduced splenic cellularity elevated concentrations of hypothalamic norepinephrine and vanillylmadelic acid, increased	Hsieh et al., 1988a, b, 1991

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
ing water						levels of ACTH and corticosterone in the blood 8 mg/kg: spleen: elevated mitogen proliferation responses of T-Ly and B-Ly to LPS, PWM, ConA, PHA; increased mixed lymphocyte reaction and cytotoxic T-Ly reaction to allogenic cells; increased primary antibody response to SRBC ≥40 mg/kg: reduction of all immune responses cited above, depressed IL-2 production of stimulated T-Ly	
oral gavage	mouse/ B6C3F1	25, 50, 100, 200, 600 mg/kg bw/d 60 days or 17 weeks	no	25 mg/kg bw/d	50 mg/kg bw/d	≥50 mg/kg: leucopenia and lymphocytopenia in males ≥100 mg/kg: lower body weight gain, ≥400 mg/kg: intermittently tremor leucopenia and lymphocytopenia in females	NTP, 1986, Huff et al., 1989
	mouse/ B6C3F1	25, 50, 100 mg/kg bw/d, 51 and 103 weeks	453	-	25 mg/kg bw/d	≥25 mg/kg: lymphocytopenia, leucocytopenia, increased frequency of micronucleated normochromatic erythrocytes, hematopoietic hyperplasia in bone marrow, splenic hematopoiesis ≥100 mg/kg: reduced body weight gain	NTP, 1986, Huff et al., 1989

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
oral	rat/ Fischer-344	25, 50, 100, 200, 400, 600 mg/kg bw/d 60 days or 17 weeks	no	100 mg/kg in males, none in females	25 mg/kg in females 200 mg/kg in males	≥25 mg/kg: leucopenia and lymphocytopenia in females ≥200 mg/kg: reduced body weigh gain in both sexes, leucopenia and lymphocytopenia in males, lymphoid depletion in the spleen, ≥600 mg/kg: extramedullary hematopoiesis	NTP, 1986, Huff et al,. 1989
oral	rat/ Fischer-344	25, 50, 100 mg/kg bw/d in females, 50, 100, 200 in males, 51 and 103 weeks	453	-	25mg/kg bw/d in females 50mg/kg bw/d in males	≥25 mg/kg/females & ≥50 mg/kg:/males: leukocytopenia, lymphocytopenia lymphoid depletion in the spleen and the thymus (males only) ≥100 mg/kg/males & females: reduced body weight gain	NTP, 1986, Huff et al., 1989
subcutaneous inject.	mouse Balb/c (sex?)	800 mg/kg bw/d 3 d	no	-	800 mg/kg bw/d	decreased bone marrow cellularity, activated bone marrow derived macrophages and granulocytes showing increased production of hydrogen peroxide after stimulation	Laskin et al., 1989

Route	Species *	Study design	Study design acc. to B. 7, 8, 29, 32, 33,	NOAEL	LOAEL	Results	Reference
	rabbit (sex?)	0.25, 0.5 mg/kg bw/d, 10 d	no	-	0.5 mg/kg bw/d	≥0.25 mg/kg: lymphocytopenia	Irons and Moore, 1980
ip injection	mice C57B1/6J (males)	600 mg/kg bw/d, 2x/d, 2 d	no	-	600 mg/kg bw/d	monitoring on day 3 to day 7 of recovery: lowered bone marrow nucleated cells, depression of nucleated erythroid and lymphocyte marrow cells, stimulation of differentiation to intermediate and differentiated granulocytes	Niculescu and Kalf, 1995
ip injection	rat SD (males)	0.5 ml/kg bw/d	no	-	0.5 mg/kg bw/d	reduced enzyme activity of aminopeptidase involved in the regulation of neuroactive peptides, in several brain regions	Gandarias et al., 1992

Abbrevations:

∗ sex were reported when a single sex was tested, otherwise when no sex is named then each sex was tested

AChE	Acetylcholine esterase
ACTH	Adrenocorticotropine
B-Ly	B-lymphocyte
ConA	Concanvalin A
DNA	Desoxyribonucleic acid
IL-1	Interleukin-2
LPS	Lipopolysaccharide
MCV	Mean cell volume
MN-NCE	Micronucleated normochromatic erythrocyte
MN-PCE	Micronucleated polychromatic erythrocyte
PALS	Periarteriolar lymphoid sheath
PCE	Polychromatic erythrocyte/reticulocyte
PHA	Phythemagglutinine
PMN	neutrophilic granulocyte
PWM	pokeweek mitogen
RBC	red blood cell
T-Ly	T-lymphocyte
WBC	white blood cell

4.1.2.6.1 D Summary

Most relevant adverse effects in animals repeatedly exposed to benzene were observed in the haematopoietic system. These included immunotoxicity occurring subsequently after primary damage of haematopoiesis. Effects on other target organs (e.g., kidney, nervous system) were of minor toxicological significance; for reason of completeness data were included in this report.

Mortality and clinical signs

Repeated or prolonged exposure to high doses of benzene may result in mortalities or serious health damage. Mice died after 24 hours of continuous inhalation of benzene vapor from 2000 ppm (6400 mg/m³). Continuous exposure on 24 hours per day with benzene concentrations of 500 ppm (1600 mg/m³) resulted in premature deaths on day 4 of exposure (Gill et al. 1980).

Reduction of body weight gain was seen in mice after lifetime treatment with 300 ppm (960 mg/m³) of benzene vapor (Snyder et al. 1980). Also, mice and rats given 100 mg/kg bw/d by oral administration in subchronic and chronic toxicity studies showed reduced body weight gain (NTP 1986). At higher doses from 400 mg/kg bw/d administered by gavage, intermittently tremor became obvious in mice (NTP 1986). Tremor during the exposure time were also observed at high doses of 4000 ppm (12800 mg/m³) of benzene vapor (6 hours/day, 5 days/week) (Gill et al. 1980).

Effects on haemopoiesis (see 4.1.2.6.1 A)

Mouse

Irrespective of the exposure route, the primary target organ of benzene treatment is the hematopoietic system. Repeated inhalation exposure was effective at concentrations from 10 ppm (~ 32 mg/m³) benzene, the lowest observed effect level in chronic oral studies was 25 mg/kg bw/d (see Table 4.23 N(L)OAEL/C).

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 hematopoietic multipotential stem cells, early progenitor cells and intermediate stages of differentiation. Morphologically, anemia in mice, the species with the most extended database, can be classified as macrocytic and hypochromic (Ward et al. 1985; Hsieh et al. 1988b).
Platelets depression was only reported in the mouse study of Ward et al. (1985). Other studies did not report effects on platelets, probably because this parameter was not examined.

Various studies have reported that prolonged exposure to benzene in vivo depresses the number of hemopoietic progenitor cells as quantitated in functional tests of colony formation (Cronkite et al. 1982; Toft et al. 1982; Neun et al. 1992; Farris et al. 1997; Green et al. 1981a,b; Seidel et al. 1989; Baarson et al. 1984). Marrow progenitor cells seemed to be a more sensitive parameter of benzene effects than the bone marrow cellularity. In the studies of Toft et al. (1982) and Gill et al. (1980) the number of transplantable colony 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 (~ 649 mg/m³) 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 hemopoiesis confirmed that there is an increased demand for erythrocyte production. No morphologic signs of scavenger of degenerated erythrocytes, such as increases of hemosiderin deposits or stainable intracellular iron deposits in the spleen or other organs, were reported in most animal studies on benzene effects. Cronkite et al. (1985) reported splenic hemosiderin deposits in exposed animals without giving exact data on a dose response. Deichman et al. (1963) found excess splenic hemosiderosis in a long-term rat study. Anemia is not primarily caused by peripheral loss or destruction of mature erythrocytes, it results due to a reduced bone marrow production.

Main toxic effects of benzene on the hematopoietic system from repeated dose studies in mice were summarized in Summary Table 4.19 (overview on effects in mice, see Table 4.20). Some of the summarized parameters in the table seem to respond contrarily, e.g., the spleen weight and cellularity could increase or decrease. The diversity of responses can be explained by the concomitant cytotoxicity of benzene and the thereby induced organ response. Inhomogenous reactions of stem cell content during the course of treatment may also be associated to a physical response. Whereas at the beginning of the benzene exposure or at short-term exposure, toxic effects may be predominating, later on cells simultaneously responded with an increased attempt to repopulate the damaged marrow. The progression and recovery of lesions during the course of benzene exposure were dose-related, an influence by other factors (species, strain) can be discussed.

Rat

Only few hematology data on rats were available (see Summary Table 4.19 and separate overview on effects in rats, see Table 4.21). Leucopenia and lymphocytopenia was also found in benzene-treated rats. Myeloid hypoplasia of the bone marrow was registered, too. However, the cell lineages affected were not investigated in this species (Ward et al. 1985). Robinson et al. (1997) did not find altered bone marrow cellularity, however, showed reduction of spleen and thymus weight, spleen cellularity, and number of T- and B-lymphocytes in rats exposed to benzene.

Any effect on the erythrocytic cell lineage was observed after inhalative and oral administration in the rat. Reduced WBC counts were correlated to an increased activity of leukocyte alkaline phosphatase activity, which was proposed to be a useful score of chronic benzene poisoning in rats and humans (Songnian et al. 1982).

Effects on the immune system (see 4.1.2.6.1 B)

Besides of leukocytopenia and other effects on the lymphocyte cellularity reported in Section 4.1.2.6.1A (Summary Table 4.19), 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 (Rozen et al. 1984; Hsieh et al. 1988b). Occasionally, immune stimulatory responses were seen at a low dose of 8 mg/kg bw/d, 4 weeks, in the mouse study of Hsieh et al. (1988b). 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 (Laskin et al. 1989). Results from in-vitro immune response were confirmed by host resistance tests.
At present experimental data are lacking allowing firm conclusion on specific influences of different functional immune cell subtypes. The main effects were summarized in the Table 4.22.
Scarce data from the rat did not reveal any relevant effect on the humoral immune response (Robinson et al. 1997).

Neurological effects (see 4.1.2.6.1 C)

Oral administration to mice at doses from 8 mg/kg bw/d, for four weeks; induced increased catecholamine concentrations of the brain, increased adrenocorticotropin (ACTH) and corticosterone release into the blood (Hsieh et al. 1991). An indirect action on the immune system via the hypothalamus-pituitary-adrenal axis was supposed. The oral studies did not include any data on behavioral dysfunctions or morphological abnormalities. Therefore they were not considered for the delivery of a NOAEL or LOAEL for the oral route. Inhalation of benzene vapor on 30 days to mice resulted in changes of neurobehaviur functions and depressed activity of acetylcholinesterase at a concentration of 13 ppm (~ 42 mg/m³) (Li et al. 1992).

Other effects (see 4.1.2.6.1 A, B)

In cannot be excluded that the kidney may also be affected by benzene treatment. A 4-week study in mice revealed altered kidney weights, but no corresponding morphological or functional change (Hsieh et al. 1988b). Other effects in mice possibly attributable to benzene exposure were plasma cell infiltration in the mandibular lymph nodes, centrilobular hypertrophy and weight increase of the liver, lower weight and degeneration of the testes, and degenerative lesions in the ovaries (Ward et al. 1985).

Table 4.20 Benzene effects on hemopoiesis in mice:

Weight/morphology	**Cellularity**
Bone marrow (BM)	
myeloid hypoplasia, myeloid hyperplasia, granulopoietic/myeloid hyperplasia, hematopoietic hyperplasia, BM cells with nuclear/cytoplasmic dyscrasias	Cellularity/nucleated cells: No.↓ stem cells: No.↓ stem cells in S-phase: %↑, or initially ↓ and thereafter ↑ hematopoietic stem cells (CFU-S, CFU-HPP): No./% ↓ hematopoietic stem cells (CFU-S) in S-phase: % ↑ granulopoietic stem cells (CFU-C): No.↓ erythroid progenitor cells (BFU-E/CFU-E):No.↓,or initially↑and thereafter↓ granulocytic/macrophage progenitor cells (CFU-GM): No/%↓ or %↑ Micronucleated polychromatic erythrocytes (MN-PCE): No↑ Nucleated red cells: No↓ Differentiating erythrocytic cells: No. ↓, %↑ Intermediate and differentiated granulocytes: No.↑ or No. ↓ and %↑ Lymphocytic cells↓ B-lymphocytes↓ PMN↓

Peripheral blood	
altered PMN and RBC morphology	WBC: No. ↓ Lymphocytes: No./% ↓ T-lymphocytes: No. ↓ B-lymphocytes: No.↓ Micronucleated polychromatic erythrocytes (MN-PCE)↑ Micronucleated normochromatic erythrocytes (MN-NCE)↑ Polychromatic erythrocytes(PCE)/reticulocytes: No. ↓ initially or Persistent, % ↓ RBC: No. ↓ MCV: ↑, MCH: ↑: Hematokrit↓, hemoglobin↓ PMN: No.↓ or No.↑ ,%↓ PMN: left shift Platelets: No. ↓
Spleen	
weight↓ or ↑ lymphocytic depletion of the PALS region, extramedullary hemopoiesis↑ cells with nuclear or cytoplasmic dyscriasis	Cellularity ↓ or ↑ Nucleated cells: No./%↑ or No.↓ Erythroid progenitor cells (CFU-E): No.↓ or No.↑ Hematopoietic stem cells (CFU-S): %↓ or No./%↑ Granulocytic/macrophage progenitor cells (GM-CFU-C): No./% ↓ Nucleated red cells: No. ↓ Lymphocytes: No. ↓ T-lymphocytes: No. ↓ B-lymphocytes, No. ↓ PMN: No. ↓
Thymus	
weight↓, atrophy	Nucleated cells: No. ↓ T-lymphocytes: No. ↓
Mesenteric lymph nodes	
lymphocytic depletion	

(Details are given in Summary Table 4.19)

Table 4.21 Benzene effects on hemopoiesis in rats:

Weight/morphology	Cellularity	Subcellular effects
Bone marrow		
cellularity↓		
Peripheral blood		
	WBC: no. ↓ Lymphocytes: no./% ↓	leukocytic alkaline phosphatase: activity↑
Spleen		
weight↓ extramedullary hemopoiesis↑ hemosiderosis lymphoid depletion	Cellularity↓ T- and B-lymphocytes↓	
Thymus		
weight↓ lymphoid depletion		

(Details are given in Summary Table 4.19)

Table 4.22 Immune response to benzene treatment in mice

Treatment schedule and effective doses	Target cell Compartment	Response	Reference
inhalation, ≥31 ppm,6d,6hr/d	T-lymphocyte	response to mitogens↓	Rozen et al. 1984 Rozen&Snyder1985
oral, ≥40 mg/kg bw/d, 4 weeks	T-lymphocyte	response to mitogens↓,	Hsieh et al. 1988b
oral, ≥40 mg/kg bw/d, 4 weeks	T-helper cell	IL-2 production↓	Hsieh et al. 1988b
inhalation, 100 ppm 5 d/w,6 hr/d, 10 d	cytotoxic T-cell	cytotoxic activity↓	Rosenthal & Snyder 1987
oral, ≥40 mg/kg bw/d, 4 weeks	cytotoxic T-cell	cytotoxic activity↓	Hsieh et al. 1988b
inhalation, 100 ppm 5	Alloreactive T-cell	mixed-lymphocyte	Rosenthal & Snyder

d/w,6 hr/d, 10 d		response↓	1987
inhalation, 200 ppm, 6 hr/d, 14 d	Suppressive T-cell	suppressive activity↓	Aoyama 1986
inhalation, 100 ppm, 5 d/w,6 hr/d, 20 weeks	T-cells	tumor resistance↓	Rosenthal & Snyder 1987
inhalation, 5d/w, 6hr/d, 200 ppm, ≥10d or 400 ppm, ≥5d	T-cell dependent B Cells	antibody production to tetanus toxin↓	Stoner et al. 1981
inhalation,≥30 ppm, 5 d preinfection and 7 d postinfection	T-cells and Macrophages	resistance to Listeria monocytogenes↓	Rosenthal & Snyder 1987
inhalation, ≥10 ppm,6d,6hr/d	B-lymphocyte	response to mitogens↓	Rozen et al. 1984 Rozen&Snyder1985
oral, ≥40 mg/kg bw/d, 4 weeks	B-lymphocyte	response to mitogens↓	Hsieh et al. 1988b
inhalation, ≥50 ppm, 6 hr/d, 14 d	B-lymphocyte	antibody production↓	Aoyama 1986
oral, ≥40 mg/kg bw/d, 4 weeks	B-lymphocyte	antibody production↓	Hsieh et al. 1988b
sc. injection, 800 mg/kg bw/d, 3 d	Macrophages and Granulocytes	activation	Laskin et al. 1989

NOAEL(C)/LOAEL(C)

From numerous animal studies, the NOAEL/C, or otherwise the LOAEL/C, if no NOAEL/C could be established, for the main effects of benzene on the hematopoietic system was derived as shown in the following Table 4.23

Table 4.23 N(L)OAEL/C for the inhalation and oral routes

Exposure route	Exposure duration	Species	NOAEL/C	LOAEL/C	Reference
inhalation	6 to 178 days	mouse	-	10 ppm (32 mg/m³)	Dempster and Snyder, 1990, Rozen et al. 1984, Baarson et al., 1984, Green et al., 1981a,b, and other studies (see Table 4.20)
inhalation	13 weeks	rats	30 ppm (97mg/m³)	300 ppm (947 mg/m³)	Ward et al., 1985
oral	103 weeks	mouse	-	25 mg/kg bw/d	NTP, 1986
oral	103 weeks	rat	-	25 mg/kg bw/d in females, 50 mg/kg bw/d in males	NTP, 1986

For quantitative risk assessment procedures, the lowest N(L)OAEL/C in experimental animals characterizing the most sensitive adverse effect of benzene after repeated exposure was estimated to be the LOAEC of 10 ppm for subchronic and chronic inhalation exposure and the LOAEL of 25 mg/kg bw/d for chronic oral ingestion.

4.1.2.6.2. Repeated dose toxicity / Human data

High and medium level exposures

High benzene [usually > 320 mg/m^3 (100 ppm) as TWA for months to years] concentration effects include several reports of severe haematologic effects, such as pancytopenia and aplastic anemia (Aksoy et al. 1971, 1972; Paci et al. 1988; Vigliani and Forni, 1976; Greenburg et al. 1939). These are based on cross-sectional studies or case series in which dose-response evaluations were not performed. Also, several of the reports applied to earlier dates in which reliable industrial hygiene tools for measuring benzene in air were not available. Thus, the precise levels of benzene which are associated with the more severe forms of marrow depression (i.e. pancytopenia, aplastic anemia) are somewhat uncertain. However, these studies are briefly reviewed below and are informative in demonstrating which haematologic parameters are affected by benzene, but may not be useful in determining a LOAEL or NOAEL. Ultimately, the NOAEL was determined from studies at relatively low exposures where less severe haematopoietic effects were noted.

Greenberg et al. (1939) suggested that both RBC counts and mean corpuscular volume (MCV) may be more sensitive indicators of potential benzene haematotoxicity since effects on RBC appeared to occur earlier and in less severe cases than reductions in WBC. In this study, most haematologic abnormalities were resolved within a year following cessation of benzene exposure. The study involved workers employed in three printing plants (A, B and C). The medians of benzene concentrations were 585 mg/m³ (183 ppm) in plant A, 435 mg/m³ (136 ppm) in plant B and 205 mg/m³ (64 ppm) in plant C. Observations included blood cells reductions in (RBC, platelets, and WBC), haemoglobin (Hb) concentrations, and lymphocyte counts and increases in MCV. Follow-up examinations were performed 8-10 weeks after exposure ceased on 35 employees from plant A deemed to have been poisoned by benzene where recorded exposures were between 160 and 3.392 mg/m^3 (50 and 1.060 ppm). These examinations showed that haematologic changes were resolved in 13 employees, had improved in 3, were the same in 15, and were worse in 4. In plant B, 46 of 47 workers exposed to between 77 and 2160 mg/m³ (24 and 675 ppm) improved one year after exposure ceased while one remained relatively the same.

Other investigators suggest RBC reduction may not be the most sensitive effect of benzene haematotoxicity (Aksoy et al. 1971; Savilhati 1956). Aksoy et al. (1971) studied a group of 217 workers reported to have been exposed to between 96 and 672 mg/m³ (30 and 210 ppm) for up to 17 years. Haematologic abnormalities were observed in 51 workers (23.5%) including 6 with pancytopenia and no cases of aplastic anemia. The extent of haematologic changes did not correlate with the duration of exposure. Thrombocytopenia (reduced number of platelets) was observed as the most frequent finding in chronic benzene poisoning and benzene appeared to influence WBC more frequently than RBC. Aksoy et al. (1971) were unable to determine whether WBC, RBC, or platelet counts were the most sensitive indicator of benzene exposure in this study.

Aksoy et al. (1972) reported 32 cases of aplastic anemia in Turkish shoe workers who were exposed to high, unspecified levels of benzene for four months to 15 years. Jandl (1977) reviewed the early U.S. literature on case reports of benzene exposure and found 880 cases of cytopenia or pancytopenia, and 101 cases of aplastic anemia. Exposures in most cases were estimated to exceed 320 mg/m³ (100 ppm) based upon general impressions of workplace exposure guidelines and practices during the time that exposures occurred.

Other studies concerning an association between short term exposure and hematologic alterations were not considered because there is no relevance for risk characterisation. Midzenski et al. (1992) showed that exposure to benzene of 5 days up to 3 weeks led to haematological alterations such as decreased WBC, large granular lymphocytes in blood smears, which did not correlate with either duration or frequency of exposure

Table 4.24

HUMAN DATA ON HAEMATOLOGIC EFFECTS FROM LOW EXPOSURES TO BENZENE

Author	Sample size	Exposure characteristics	Critical parameter(s)	Comments	LOAEC	NOAEC
Kipen et al., 1988 and 1989	264	35-137 ppm (mean=75 ppm); 15-20 ppm (1940-48)				
			WBC, RBC (Crump)	Statistically significant or near-significant correlations between exposure and blood parameters (annual means)	75 ppm (35-137 ppm)	15-20 ppm
			WBC, RBC (Rinsky)	-	-	6-19 ppm
Fishbeck et al., 1978	10	37-132 ppm TWA, then <25 ppm		Small sample, subjects served as own controls over time	-	
			RBC, Hb		35 ppm	<10 ppm
			WBC		-	35 ppm

Table 4.24 (contin.)

HUMAN DATA ON HAEMATOLOGIC EFFECTS FROM LOW EXPOSURES TO BENZENE

Author	Sample size	Exposure characteristics	Critical parameter(s)	Comments	LOAEC	NOAEC
Tsai et al., 1983	303	<5 ppm		96% of total samples were below 5 ppm		
			WBC, lymphocytes, RBC, platelets, Hb, Hct		-	<5 ppm
Hancock and Moffitt, 1984	70 exposed 21 controls	Average of 10.5 ppm		Controls matched for gender - averaging exposures may limit ability to detect transient effects of higher exposure		
			RBC, WBC, Hb		-	10 ppm
Yardley-Jones et al., 1988	66 exposed 33 controls	<1-10 ppm (TWA)		Controls matched for gender; occasional levels (duration not specified in report, but less than full shift) of 100 ppm		
			Hb			<1-10 ppm
Yardley-Jones et al., 1988			MCV	Statistically signif. results, but within clinical range	<1-10 ppm	

Author	Sample size	Exposure characteristics	Critical parameter(s)	Comments	LOAEC	NOAEC
Collins et al., 1991	200 exposed 268 controls	0.01-1.4 ppm		Well controlled multivariate analysis		
			RBC, WBC, Hb, platelets			0.01-1.4 ppm
			MCV	Statistically significant results judged by authors as clinically non-significant	0.01-1.4 ppm	
Chang, 1972	119	10-20 ppm		Studied unspecified industrial workers (Korea)		
			WBC, RBC		-	10-20 ppm
Doskin, 1971	365	10-40 ppm		Poor reporting of exposure data		
			Platelets	"Mild" cytopenia	10-40 ppm	-
Rothman et al., 1996a	44	1 - 328 ppm	WBC, lymphocytes, platelets MCV	Case control study, comparison of exposure > 31 vs < 31 ppm		1 ppm

Author	Sample size	Exposure characteristics	Critical parameter(s)	Comments	LOAEC	NOAEC
Rothman et al., 1996b	44	1 – 328 ppm	GPA Somatic cell mutation frequency	Case control study		1 ppm
Dosemeci et al., 1997	44	1 - >400 ppm	Relative risk (RR)	Increase of RR from 1 (exposure of <5 ppm) to 2.2 (exposure 5-19 ppm)		< 5 ppm
Dosemeci et al., 1997 Rotman et al., 1996a/b	22	Subcollectives < 30.6 ppm (median 13.6 ppm),	WBC, lymphocyte and platelet counts	Significant decrease		
	11	1.6 – 20 ppm, median 7.6 ppm.	Lymphocyte count	Significant decrease		1 ppm

Low level exposures

A study of 10 ethyl cellulose manufacturing workers, who were among the more highly exposed (duration of exposure was about one year or more) workers included in the Townsend et al. (1978) study, were examined separately by Fishbeck et al. (1978). In 1963, all of the employees were exposed to benzene TWA concentrations between 118 and 422 mg/m³ (37 and 132 ppm). Prior to 1963, some employees were also exposed to TWA concentrations of 112 mg/m³ (35 ppm). By 1966, all employees were either no longer being exposed or were being exposed to more moderate levels <80 mg/m³ (<25 ppm). All employees had enlarged RBC (macrocytosis), transient anemia, and 90% had low Hb. No effects on WBC or other haematologic parameters were reported. All of the affected parameters tended to resolve as exposures fell below 80 mg/m³ (25 ppm). Most TWA exposures during these later years of employment were between 0 and 32 mg/m³ (0 and 10 ppm). The study showed effects on RBCs and Hb for exposures above 112 mg/m³ (35 ppm), but no evidence of any effects in RBCs for exposures below 32 mg/m³ (10 ppm). The study also suggests a higher no effect level for WBC counts, but this judgment is limited by the size of the study population.

In a study on 39 workers occupationally exposed to benzene, toluene and xylene for 55 to 122 months lymphocyte-associated immunity was examined using such parameters as total lymphocyte count, T and B cell count, blastic transformation test, tuberculin test, distreptase skin test, IgA, IgG and IgM concentrations in the serum antistreptolysin <<0>> titer in the serum, direct and indirect Coombs test, antinuclear antibodies in the serum, HbsAg and antiHBs antibody presence in the serum (Moszczynski and Lisiewicz (1983). The only abnormal findings in the exposed workers (benzene concentration of 12 mg/m³ (arithmetic mean, range 5 – 17 mg/m³, in 1978) were significant reductions in the number of total lymphocytes and in the number of E_a and the E_{18h} rosettes (T cells) compared with the control group (n=38). The total number of lymphocytes in the subjects exposed of 2.208 [± 0.623] x 10^9/l was significantly diminished when compared with the number of the control group of 2.694 [±0.790] x 10^9/l (mean ± sd, p=0.01). However, it should be emphasized that the quantitative alterations of T-cell counts were not accompained by a reduction in functions of these cells since both the blastic transformation capacity after stimulation with PHA and the cellular immunity reactions against distreptase and tuberculin were normal in the subjects exposed. According to the authors, the diminished numbers of T lymphocytes in the blood of workers exposed to benzene and its homologues may be regarded as an early marker of intoxication by these compounds, which preceeds the appearence of other disturbances in cellular immunity reactions.

Hancock and Moffitt (1984) reported a study which compared 70 male employees of a coke oven by-product recovery facility with TWA benzene exposures of 33.6 mg/m³ (10.5 ppm) to 21 unexposed males from the same facility. A cumulative exposure index was calculated and categorized as <64 mg/m^3-years (<20 ppm-years), 64-640 mg/m^3-years (20-200 ppm-years), and >640 mg/m³-years (>200 ppm-years). WBC, RBC, and Hb values in exposed workers were similar to unexposed controls. A slight non-statistically significant trend towards lower Hb values was evident. The authors concluded that levels of about 32 mg/m³ (10 ppm) had no effect on the haematologic parameters studied. Again, this design averaged both exposures and time-sensitive blood counts, such that transient effects of higher exposures [which reached an average of 534 mg/m³ (167 ppm)] may have gone undetected.

Yardley-Jones et al. (1988) examined 66 workers exposed to TWA concentrations of <3-32 mg/m³ (<1 - 10 ppm), although peaks of 320 mg/m³ (100 ppm) were sometimes experienced during a work day (time period not specified). There were 33 controls matched for gender. Hb and MCV were examined. Although MCV showed a statistically significant elevation in exposed workers [93.1 femtoliters (fL)] versus controls (91.5 fL), the authors noted that the range of values in exposed workers (87 to 99 fL) were largely within the normal clinical range (76 to 96 fL). Therefore, this effect was not considered in establishing the NOAEL/LOAEL.

Kipen et al. (1988, 1989) examined peripheral blood counts (RBC, WBC, Hb) in 459 rubber hydrochloride workers. This population is part of the study reported by Rinsky et al. (1987), often referred to as the Pliofilm® cohort. A job exposure matrix consisting of 493 job versus time period entries was constructed, 86 (17%) of which were filled with actual exposure monitoring information. All entries prior to 1947 (i.e., from 1939) were done through extrapolation of more recent measurements. In the 1989 report, Kipen et al. used two exposure extrapolation schemes (A and B) and related each to blood counts which included RBC, WBC and Hb. To obtain reliable trends for each worker, the authors analyzed those with more than five blood tests (264 workers and 16841 tests). The authors reported an increase in blood counts in the 1940's, and a leveling off thereafter. When using extrapolation scheme B, Kipen et al. (1989) found a strong correlation between benzene exposures between 112-438 mg/m³ (35-137 ppm) [mean: 240 mg/m³ (75 ppm)] and decreased WBC counts (between 1940-48). There also was a strong correlation for decreased RBC counts, but the correlation with Hb values was lower. For 1949-75, when the mean exposure (long-term average concentrations) was about 48-64 mg/m³ (15-20 ppm), no such correlation could be observed with any of the three haematology measures. Extrapolation scheme A, which predicted lower exposures, particularly in 1940-48, did not correlate with decreases in WBC, RBC, nor Hb in either time period. This scheme predicted exposures from 19.2 to 60.8 mg/m³ (6 to 19 ppm) in 1940-48. In either case (extrapolation scheme A or B), the data suggest that exposures of 64 mg/m³ (20 ppm) or less have no effect on WBC, RBC, or Hb.

Collins et al. (1991) also reported on 200 chemical workers and 268 controls exposed to benzene levels between 0.032 and 4.48 mg/m³ (0.01 and 1.4 ppm). No differences in RBC, WBC, Hb, platelets, or MCV were found when benzene was treated as a continuous exposure. A small difference in MCV was found for "current" exposure. Several confounders were controlled, and it was shown that smoking had significant effects on most studied parameters. The authors judged that since the MCV effect was only 0.4%, it was not of clinical significance.

Marcus (1987) summarized studies performed by Doskin (1971) and Chang (1972), from the former Soviet Union, and Korea, respectively. These studies attempted to discern a NOAEL for haematologic parameters. Doskin (1971) evaluated 365 chemical workers exposed to benzene in a new plant. Exposures were between 32-128 mg/m³ (10-40 ppm) 64% of the time in year 1, 37% of the time in year 2, and 3% of the time in year 3. Exposures were under 32 mg/m³ (10 ppm) the remainder of the time. The study reported that in the first year, 40% of the workers exhibited mild cytopenias, most commonly, thrombocytopenia. Effects from year 2 onward at the lower exposures were not reported. The Chang (1972) study reported 28 workers with leucopenia, anemia, or both from a population of 119 unspecified industrial workers. No haematologic abnormalities were reported for workers between 32 and 64 mg/m³ (10 and 20 ppm). The author implied a threshold of 32 mg/m³ (10 ppm) for cytopenia. There is a lack of information concerning the basis for the reported exposure concentrations.

Data published by Lange et al. (1973) are considered to be not sufficient for defining a NOAEL or LOAEL since it is not possible to follow which exposure levels were responsible for the effects. Furthermore, this study was not considered due to potentially confounding exposures to other substances in the collective.

Yin et al. (1987) reported 24 cases of aplastic anemia in 508818 Chinese workers, 26319 of them were exposed to benzene and 502410 to benzene-containing mixtures at estimated exposures of 1035 mg/m³ (333 ppm). The overall prevalence of benzene poisoning leading to leucopenia was 0.5%, with 0.94% in workers exposed to benzene, and 0.44% in workers exposed to benzene-containing mixtures. The highest prevalence was in the shoe-industry (1.25%) where benzene concentrations ranged from 0.06 to 844 mg/m³ (0.02 to 264 ppm) with a median concentration of 40 mg/m³ (12.5 ppm). There was significant correlation between benzene air-concentrations and prevalence of leucopenia (<4000 cells/mm³) among workers. Leucopenia cases were noted in work places where benzene concentrations were lower than 40 mg/m³ (12.5 ppm), but it is unknown whether the prevalence of leucopenia was greater than expected in these work places.

In an update and expansion of the Yin et al. (1987) study, hematopoietic disorders in 74828 Chinese workers exposed to various levels of benzene (exposure levels not reported) were compared to a control population of 35805 workers (Travis et al., 1994). Of particular interest, Travis et al. (1994) reported 9 cases of aplastic anemia and 7 cases of MDS in exposed workers vs. none in unexposed workers.

Further case-control studies in sub-collectives from the studies described by Yin et al (1996) in rubber industry, manufacturing of adhesive tapes, and paint-and varnish factories were performed by Rothman et al. (1996a, 1996b) and Dosemeci et al. (1997). In these studies workers exposed to benzene were compared to a cohort of non-exposed individuals who had no history of benzene exposure and other marrow-toxic chemicals, or ionizing radiation. They were frequency-matched to the exposed subjects on 5 year age intervals and gender. The exposure level was 1 - 328 ppm (Rothman et al., 1996a) for a period of at least six months. There was a significant difference between cases and controls in the following parameters: WBC, lymphocytes, platelet and RBC counts were significantly reduced. APA somatic cell mutation frequency was about as twice as high in the benzene exposed individuals as compared to controls. Sub-collectives of these cohorts were further studied: In a group of persons (n=22) that were exposed to levels below 31 ppm of benzene (range 1.6 – 30.6 ppm, median 8-hr TWA 13.6 ppm), a significant decrease of WBC, lymphocyte and platelet counts remained. Workers came from factories that used benzene to solubilize natural rubber and manufacture adhesive tape, as well as a factory that used a benzene-based paint to varnish and paint wooden toys. According to industry (Aromatic Producers Association (2006) COM063_hh_Ind15) these operations have been linked to very high benzene exposures in the past which were not addressed within the study and might have been expected to have affected the observed blood effects. A further subgroup of persons (n=11) exposed to 1.6 – 20 ppm, median 8-hr TWA 7.6 ppm, showed a significantly decreased absolute lymphocyte count of 1.6 [±0.4] x 10^3/µl as compared to that of controls of 1.9 [±0.4] x 10^3/µl (mean ± sd, p=0.03; Rothman et al., 1996b). There was an increase in the relative risk for benzene induced health impairment from 1 to 2.2 in persons exposed to < 5 ppm compared to 5-19 ppm, respectively (Dosemeci et al., 1997).

The clinical relevance of the statistically significant reduction in lymphocyte counts may be questioned. According to results of the study by Moszczynski and Lisiewicz (1983) a diminished numbers of lymphocytes in the blood of workers exposed to benzene may be regarded as an early indicator of intoxication, which preceeds the appearence of other

disturbances in cellular immunity reactions. In a study by Lee et al. (1996) reference ranges for lymphocyte subpopulations in an Asian population from Singapore (with 80% Chinese) have been established. The results of this study confirm variation of lymphocyte subpopulations with age and sex. Absolute lymphocyte counts of 1.3 (1.1-1.5) and 1.5 (1.2-1.9) x 10^3/µl blood were observed for adult males (n=33) and females (n=38), respectively (median; lower and upper quartiles in brackets). Taking into consideration information on changes in lymphocyte counts from all these studies a NOAEC for depression of lymphocytes by benzene can be deduced to be 1 ppm.

It should be noted that the Commission of the European Communities (CEC 1993) also reported on the preliminary results of an unpublished study (Van Damme et al. 1991). This study suggested an increased prevalence of leucopenia (defined as <4000 cells/mL) for exposures of 0.64 to 1.92 mg/m³ (0.2 to 0.6 ppm) and is well below the NOAEL estimate of 64 mg/m³ (20 ppm) for WBC effects reported by other investigators. However, since this study has not appeared in the published literature, it could not be adequately evaluated. Because it also conflicts with other published studies (Kipen et al. 1988; Fishbeck et al. 1978; Tsai et al. 1983; Collins et al. 1991), it was considered to be inappropriate for defining a LOAEC or NOAEC.

In a cross-sectional repeat survey on 387 workers with daily 8-hr time weighted exposures averaging 0.55 ppm benzene and 553 unexposed workers (Collins et al., 1997) no indication was found that workers exposed to low levels of benzene were at increased risk of developing lymphopenia or other hematologic outcomes. No increase in the prevalence of lymphopenia among benzene-exposed workers (Odds ratio 0.6; 95% confidence interval, 0.2 – 1.8), taking into account smoking, age and sex. Decreases in the lymphocyte counts among workers with higher exposure to benzene were reported by Moszczynsky and Lisiewicz (1983) and Rothman et al. (1996b).

As the study "Lympho-hematopoietic cancer and exposure to benzene in the Australian Petroleum Industry" (API, 2001) demonstrates even very low life time exposures (ranging from 0.005 to 57.3 ppm - years with a mean of 4.9 ppm-years) were strongly associated with acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL). Hence, it might be assumed that the NOAEC for hematopoietic effects is lower than observed in the previous studies.

Conclusion

It can be concluded from the above discussed data, that chronic benzene exposure leads to depression of white blood 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) of benzene for about a 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 anemia which can be fatal. Jandl's (1977) review suggests a fatal outcome in 13% of the cases (as opposed to 85% for idiopathic aplastic anemia).

The prevalence of leucopenia correlates with the concentration of benzene as shown by data of Yin et al. (1987) as well as by Kipen et al. (1988, 1989). Taken 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 above 320 mg/m³ (100 ppm).

The case control studies presented recently by Rothman et al. (1996a, 1996b) and Dosemeci et al. (1997) have shown, that the most sensitive reaction in humans to chronic benzene exposure is lymphopenia. The data show that a collective of workers exposed to benzene concentrations in a range between 1.6 and 30.6 ppm had significantly reduced lymphocyte counts as compared to a cohort of non-exposed workers. Thus, for blood cell depression an overall LOAEC is suggested to be 32 mg/m³ (10 ppm). Taking into consideration information on changes in lymphocyte counts from all studies with benzene exposure a NOAEC of 3.2 mg/m^3 (1 ppm) can be derived for depression of lymphocytes by benzene.

In conclusion, the NOAEC for non-neoplastic effects of benzene is assumed to be 3.2 mg/m^3 (1 ppm).

Conclusion: Classification and labelling

The present classification according to Annex I to Directive 67/548/EEC which includes the required R-phrases characterizing health risks after repeated exposure is confirmed. Benzene is classified as toxic and labelled with T, R 48/23/24/25.

4.1.2.7 Mutagenicity

4.1.2.7.1 In vitro data

A detailed overview over the genotoxicity data for benzene up to 1990 is given in the EHC report 150 (1993). According to this report, benzene is negative in routine bacterial gene mutation tests; however, weak positive effects were obtained when, in presence of S-9 mix, bacteria were incubated with benzene in a desiccator to enhance exposure. Mammalian cell gene mutation tests resulted in mixed results. There is some evidence for in vitro clastogenicity, although again mixed results were obtained. It is discussed that with negative findings may have been due to low activities of benzene-activating enzymes.

4.1.2.7.2 In vivo data

In the following data on the in vivo mutagenicity of benzene are summarized:

A Somatic cell studies after oral administration

B Somatic cell studies after administration per inhalation

C Transplacental mutagenesis

D Mammalian germ cell tests

E Human data

F Data on structurally related substances

Main emphasis is put on recently published data and on positive studies with low benzene exposure.

A Somatic cell studies after oral administration (see also Table 4.25)

Chromosomal aberrations

Ciranni et al. (1991) investigated time- and dose-effect relationships for the induction of chromosomal aberrations by benzene in bone marrow cells of mice. First, the analysis was performed by administering 1 ml/kg (880 mg/kg bw) of benzene as a single oral dose and sampling either cell type after a wide range of times (6, 12, 18, 24, 30, 36, 42 and 48 h). At this dose benzene showed high clastogenic activity in bone marrow cells at all sampling times with a peak at 24 and 30 hours (approx. 20% aberrant cells (excl. gaps) versus 1% in controls). The number of aberrations per 100 cells at 24h/30 hours were as follows: gaps 8.8/19.5 (control 2.4), breaks 33.3/39.5 (control 1.1), exchanges 1.0/2.5 (control 0), highly damaged cells, i.e. cells with more than 10 alterations, 2.2/2.2 (control 0). Second, the dose-response was determined 24 h after treatment with 0.1, 0.5 or 1.0 ml/kg benzene (equivalent to 88, 440 and 880 mg/kg bw). All three doses were clearly positive and a dose-dependency was established.

Fujie et al. (1992) conducted comparative studies with regard to clastogenic effects of benzene in rat bone marrow cells in vivo. They examined dose-effect and time-effect relationships and sex and strain differences. After oral benzene administration the incidence of aberrant cells increased progressively with time and reached a maximum 12 hours after administration. Also clear dose-response relationships was observed. Male rats were more sensitive than females and Long-Evans rats were more sensitive than Wistar or Sprague-Dawley rats. Benzene-induced chromosomal aberrations consisted mainly of gaps and breaks. The maximum response was observed 12 h after oral administration of 750 µl/kg (660 mg/kg bw) benzene in male Long-Evans rats. Under these conditions benzene induced 65% aberrant cells as compared to 1% in negative controls. The LOED after oral administration was 150 µl/kg (132 mg/kg bw).

Micronuclei

Au et al. (1990) investigated the induction of micronuclei in normochromatic blood erythrocytes of mice. After oral administration for 2, 8 or 14 days, all tested doses - 26.6 to 146.6 mg/kg bw - gave positive findings in a dose- and time-dependent manner. Further analyses after the end of treatment showed further increase of micronuclei frequencies (strongest effects 36 days after start of the treatment).

The potency of benzene for induction of micronuclei after oral long-term exposure was investigated by MacGregor et al. (1990) in normochromatic erythrocytes of mice. After 4 months of exposure a dose-dependent increase on micronuclei frequencies was found in the dose range 25 to 600 mg/kg bw. In males the effect was more pronounced than in females. With 25 mg/kg bw a weak effect was found for males, females were negative at this dose (exact frequencies cannot be derived from the figure of the publication). With 50 mg/kg bw a clear effect was observed in males (approximately 0.40% as compared to 0.13% in the

controls) and in females a small increase was described (approximately 0.20% as compared to 0.13%). Longer exposure times of 1 and 2 years were only investigated in males; although micronuclei frequencies decreased with exposure time, the effect was still clearly positive.

Chen et al. (1994) have characterized in mice the origin of the micronuclei that are formed in bone marrow erythrocytes and spleen lymphocytes of benzene treated mice using two molecular cytogenetic approaches: fluorescence in situ hybridization with a centromeric DNA probe (FISH) and immunofluorescent staining with the CREST antibody (CREST). Following oral administration of benzene (220 or 440 mg/kg bw) to male mice, significant increases of micronuclei were observed in the bone marrow erythrocytes: 1.8% at 220 mg/kg bw and 1.5% at 440 mg/kg bw (0.05% in the negative controls). The FISH and CREST technique indicated that the micronuclei in bone marrow erythrocytes were formed from both chromosome loss and breakage. The majority of the micronuclei originated from chromosome breakage. An increase in micronucleated cells was also observed in splenocytes established from these benzene treated mice (2 to 3-fold increases in micronucleated cells). In contrast to the bone marrow erythrocyte results, in splenocytes the majority of benzene induced micronuclei were labeled with the CREST antibody indicating that these micronuclei were the result of whole chromosome loss.

DNA damage

Tuo et al. (1996) investigated in mice benzene genotoxicity and the role of CYP2E1 protein with the alkaline comet assay, a technique for detecting DNA damage such as single and double strand breaks as well as alkali-labile sites of the DNA. In the alkaline comet assay, treated cells are embedded in a gel and subjected to an electric field after lysis of the membrane. Increased levels of DNA damage will allow the DNA to move more easily in the field, which can be detected as so-called comet tails after fluorescence staining of DNA.
Benzene exposure of male mice in single oral doses of 40, 200 or 450 mg/kg bw resulted in dose-related DNA damage (indicated by increased comet tail length) in peripheral lymphocytes and bone marrow cells sampled 6 h after exposure. After a dose of 40 mg/kg bw, there was a 1.6-fold increase of tail length in bone marrow cells as compared to the negative control. There was no significant increase in DNA damage in peripheral lymphocytes in the same animals. At 200 mg/kg bw, the tail length was increased 4.8-fold and 4.0-fold in the two cell types, respectively. At 450 mg/kg bw, the tail length was further increased to 5.4-fold and 6.6-fold of the control values, respectively.

Pre-treatment with propylene glycol (which inhibits CYP2E1), reduced the increase in the tail length by about 50% at all doses in both cell types.

B Somatic cell studies after administration per inhalation (see also Table 4.25)

Chromosomal aberrations

Fujie et al. (1992) investigated clastogenic effects of benzene in rat bone marrow cells after administration per inhalation for 2 weeks (2h/day, 5 days/week). A dose-dependent effect was observed in the dose range 10 to 60 ppm (32.5-196 mg/m^3), already 10 ppm (32.5 mg/m^3), gave a clear positive finding. A different response in the two sexes was not observed.

Another chromosomal aberration assay with rats after inhalation exposure was performed by Styles et al. (1984). After single of 6-h exposure to 100 or 1000 ppm benzene (325 or 3250 mg/m^3), increased frequencies of chromosomal aberration were found in bone marrow cells, exposure to 1 or 10 ppm (3.25 or 32.5 mg/m^3), led to negative results.

Genetic effects of extremely low benzene doses were investigated in mouse tissues other than bone marrow by Au et al. (1988; lung macrophages) and Au et al. (1991; spleen lymphocytes). Exposure to 0.04 ppm (0.14 mg/m^3, only spleen lymphocytes), 0.1 ppm or 1.0 ppm (0.325 or 3.25 mg/m^3), 7 days per week, lasted for 6 weeks; the daily exposure period was given as 24 h in the 1988 publication and as 22 h in the 1991 publication.

For investigation of the effect on macrophages a new test system was developed by Au et al. (1988). For accumulation of mitotic macrophages it included intraperitoneal treatment with the spindle poison vinblastine 4 h before cell preparation. Nevertheless, only relatively few macrophages were arrested in metaphase; in the 1 ppm-group only 15 out of 24 animals were analyzable and for some animals less than 25 metaphases were analyzed. The vinblastine dose is not given, but it seems that an extremely high dose was used. In a pre-experiment for range finding of an appropriate vinblastine dose, no dose-dependency was observed for macrophages in the dose range 0.14 to 87.5 mg/kg bw, whereas in the bone marrow the highest dose was most effective. (In the parallel experiments on spleen lymphocytes the spindle poison colchicine was used in the extremely high dose of 150 mg per mouse.) Au et al. (1988) reported on a significant dose-dependent increase in aberration frequencies after inhalation of 0.1 and 1 ppm benzene: negative control, 1.2 +/- 2.3% (standard deviation); 0.1 ppm, 5.3 +/- 5.5%; 1 ppm, 6.5 +/- 5.9%. Due to the methodological problems associated with the test system, co-exposure to vinblastine and extremely high standard deviations of aberration frequencies, the result is evaluated as being equivocal.

In the study on spleen lymphocytes (Au et al. 1991) two experiments were performed, in each of them between 6 and 12 animals were analyzed per sex. Four hours before sacrifice the animals were treated with colchicine (experiment I) or vinblastine (experiment II); colchicine, which is clastogenic high doses, was given in an extremely high dose of 150 mg per mouse; the vinblastine dose in experiment II is not given. Numbers of chromatid breaks per 100 cells are given in the following table (other cell types and frequency of aberrant cells are not given in the paper):

chromatid breaks per 100 cells

sex	Expt.	neg.co.	0.04 ppm	0.10 ppm	1.00 ppm
male	I	2.0		6.4	9.0
	II	2.6	4.7	4.0	2.0
female	I	2.5		8.2	8.7
	II	0.4	1.7	2.7	1.4

These findings are evaluated as positive by the authors. However, on the basis of the high variation of 'effects' and some methodological insufficiencies the overall finding is equivocal (no positive control, no blinding before analysis, often analysis of less than 100 mitoses, co-exposure to colchicine or vinblastine).

Micronuclei

The effect of 6-h inhalation of benzene on rats and mice was analyzed by Erexson et al. (1986). In mice, clear and dose-dependent increases of micronucleated bone marrow cells were obtained for all doses tested ranging from 10 to 1000 ppm (32.5 to 3250 mg/m^3). In rats, the effect was not as strong as in mice. Doses ranging from 1 to 30 ppm (3.25 to 97 mg/m^3) led to significant increases in the frequencies of micronuclei per 1000 polychromatic erythrocytes (frequencies of micronucleated cells were not given).

Farris et al. (1996) investigated in mice the mutagenicity of benzene at relatively low inhalative concentrations. The frequencies of micronucleated polychromatic erythrocytes in the bone marrow and blood and micronucleated normochromatic erythrocytes in the blood of male mice were measured following inhalation of benzene at 1.0 to 200 ppm (3.25 to 650 mg/m^3), during exposure periods for 1, 2, 4 and 8 weeks. Only 100 and 200 ppm (325 and 650 mg/m^3) benzene induced an increased frequency of micronucleated erythrocytes in the bone marrow and blood. The micronucleus frequency in polychromatic erythrocytes plateaued at week 2 with 4.2% (100 ppm) and 8.6% (200 ppm) in the bone marrow as compared with 1.0% for controls. The micronucleus frequency in normochromatic erythrocytes (in the blood) progressively increased to 1.34% (100 ppm) and 3.25% (200 ppm) at week 8 as compared to 0.18% for controls. Cytotoxic effects were observed at 100 and 200 ppm (325 and 650 mg/m^3).

Valentine et al. (1996) investigated the reduction of benzene toxicity in mice that lack CYP2E1 protein expression. Transgenic knockout mice (cyp2e1-/-), wild-type mice and B6C3F1 mice were exposed by whole-body inhalation to 0 ppm (control) and 200 ppm benzene (650 mg/m^3), 6 h/day for 5 days. Benzene exposure resulted in decreases in bone marrow cellularity in the wild-type and B6C3F1 mouse strains to 31% and 50% of air-exposed controls, respectively. Furthermore, there was an increase (5-fold to 4-fold, respectively) in the frequency of micronucleated polychromatic erythrocytes in these two mouse strains after benzene exposure. In contrast, neither bone marrow cellularity nor frequency of micronucleated polychromatic erythrocytes were altered in benzene-exposed cyp2e1-/- mice as compared to air exposed controls. Transgenic CYP2E1 knockout mice

(cyp2e1$^{-/-}$), compared with wildtype and B6C3F1mice, were used to investigate the involvement of CYP2E1 in the in vivo metabolism of benzene and in the development of benzene-induced toxicity. The results of the study demonstrate the causal role of CYP2E1 for in vivo benzene metabolism and benzene-induced myelotoxicity in mice.

Gene mutations

The potential of benzene for induction of gene mutations (HPRT variants) in spleen lymphocytes was investigated by Ward et al. (1992) after exposure of mice by inhalation. Doses of 0.04, 0.10 and 1 ppm (0.14, 0.33 and 3.25 mg/m^3) were given for 6 weeks (22 h per day, 7 days per week). This non-routine study was performed with the same animals which were analyzed for chromosomal aberrations by Au et al. (1991); 3 animals were analyzed per sex. Four hours before sacrifice animals were treated with vinblastine in an extremely high dose of 700 mg/kg bw; possible interference with the following stimulation of lymphocytes by the mitogen concanavalin A was not investigated.

Mutant cells were detected by their ability to incorporate tritiated thymidine in the presence of 6-thioguanine (6-TG). Quantification of mutation frequencies was done by the following procedure: In cultures without 6-TG the proportion of labelled cells was determined for each animal (labelling index, LI). The number of cells (nuclei) scored from 6-TG containing cultures was corrected by the LI of the same animal to give the number of 'evaluable nuclei' (N). The mutant frequency (Vf) is determined by dividing the number of labelled nuclei (M) by (N). Quantitative data on VF, M and LI per group are given in the following table; Vf values are given in 10 E-6 (M and LI data per group were not included in the paper).

	males			females		
	VF(1)	M	LI	VF(1)	M	LI
unexposed	15.3	10.7	0.071	13.2	14.3	0.081
air exposure	5.7	5.0	0.089	7.2	14.7	0.166
0.04 ppm	24.7	8.3	0.028	29.2	21.3	0.066
0.10ppm	40.2	12.0	0.031	62.5	25.7	0.052
1.00 ppm	17.0	12.6	0.064	25.0	14.0	0.057

According to the authors the doses of 0.04 and 0.10 ppm (0.14 and 0.33 mg/m^3) gave positive results for both sexes. However, the 'effects' are not paralleled by clear increases in numbers of labelled cells (M values). On the other hand, the labelling indices (LI) between groups vary by a factor of 6 and the increases in VF values might artificially be caused by this variation. Considering furthermore the co-exposure to vinblastine and the lack of a positive control, the overall finding of the study is equivocal.

Mullin et al. (1995) investigated the mutagenic potential of benzene by using a transgenic mouse assay in which bacteriophage lambda lacI transgenes are rescued from mouse genomic DNA as infectious phage and scored for their LacI phenotype. With this assay DNA-base substitutions and small insertions or deletions can be detected. Eight mice were exposed by inhalation to a concentration of 300 ppm (974 mg/m^3) of benzene for 6 h/day x 5 days/week x

12 weeks. Mutant frequencies were calculated as the ratio of LacI-/total phage recovered from organs of interest. The mean mutant frequency measured in lung tissues of exposed mice was 10.6 x 10-5, which is about 1.7-fold higher than that of the unexposed controls (P>0.05). In spleen tissues from exposed mice the mean mutation frequency was 12.6 x 10-5, which is about 1.5-fold higher as compared to controls (P>0.05). In liver tissues, however, the mean mutant frequencies of benzene-exposed mice and unexposed mice are not significantly different.

Sister chromatid exchanges (SCE)

Induction of sister chromatid exchanges (SCE) by inhalation exposure to benzene was investigated by Erexson et al. (1986) in peripheral lymphocytes of rats and mice. As compared to the analysis of micronuclei in bone marrow cells which was performed in parallel (see above) relatively weak effects were found. In mice, a doubling of the spontaneous SCE frequency was achieved only by the highest dose tested, 1000 ppm (3250 mg/m^3). In rats, the highest dose tested of 30 ppm (97 mg/m^3) led to a marginal increase (11.1 SCE/metaphase as compared to 8.6 in the negative control group).

C Transplacental mutagenesis

The potential of benzene for induction of transplacental mutagenic effects was investigated by Harper et al. (1989), Ning et al. (1991) and Xing et al. (1992). Increased frequencies of micronucleated polychromatic erythrocytes were found in fetal liver cells of mice after intraperitoneal administration of doses ranging from 219 to 874 mg/kg bw (Ning et al. 1991) or from 878 to 1318 mg/kg bw (Xing et al. 1992). According to Harper et al. (1989) no clear effects were observed after i.p. or oral administration of doses from 880 to 1760 mg/kg bw.

Although in these studies with intraperitoneal administration an artificial route of exposure was used, they give some indication that benzene has the potential for induction of transplacental mutagenesis.

D Mammalian germ cell tests (see also Table 4.26)

Some data are available concerning the potential of benzene for induction of germ cell mutations but most of them are of low reliability.

Ciranni et al. (1991) investigated time- and dose-dependency the induction of chromosomal aberrations in spermatogonia of mice after single oral treatment. After administration of 1 ml/kg (880 mg/kg bw) the maximum response was obtained 24 h after treatment (6.3% aberrant cells versus 1.2% in negative controls). In the dose-response study, all doses tested (0.25, 0.5 and 1.0 ml/kg bw, equivalent to 220, 440 and 880 mg/kg bw) increased the aberration frequency in a dose-dependent manner; at 880 mg/kg again 6.3% of the spermatogonia were aberrant. Since bone marrow clastogenicity was investigated in parallel (see part A), it can be concluded that clastogenicity in bone marrow cells and spermatogonia was induced in the same dose range, although effects were less pronounced in spermatogonia.

In an abstract without detailed information Rithidech et al. (1987) reported on the induction of chromosomal aberrations in spermatogonial stem cells after oral treatment of mice.

Induction of dominant lethal effects was investigated in mice after oral administration of benzene (1.0 - 4.0 ml/kg up to 48 days) in a dominant lethal test ring study (GSF Bericht, 1977; also reported in Ehling et al. 1978). The authors conclude that it was impossible to draw an overall unequivocal conclusion out of the separate studies.

A dominant lethal test with rats showed after inhalation exposure (1.0 - 300 ppm for ten weeks, 3.25 - 975 mg/m^3) also an equivocal result (Biodynamics, 1981). The ten-week treatment period was followed by two immediate mating periods of one week each. However, later mating periods were not analysed. Furthermore, for the high dose group (300 ppm, 975 mg/m^3) weak increases of the mean number of dead implants and mean mutagenic ratio values were reported for both mating periods. Therefore, the dominant lethal test is to be assessed as equivocal.

Further dominant lethal tests with mice (oral administration; Feldt et al. 1985) and rats (intraperitoneal administration; Lyon 1975, cited in Dean et al. 1978) were described as negative; however they were without adequate information on methodology and result. Therefore no relevant conclusion can be drawn.

Topham (1980) found an induction of sperm head abnormalities after treatment of mice with benzene; this test system, however, is not specific to mutagenicity.

E Human data

In principle, human data are of high relevance for evaluation genotoxic risks for man. However, reliable data on germ cell mutagenicity in man are not available for any compound, and data on somatic cells, in general, are critical in their interpretation because of methodological problems (Ashby and Richardson 1985; Carrano and Natarajan 1988; Speit et al. 1994).

An overview on the human genotoxicity studies with benzene is given in Table 4.27, nearly all studies were performed with peripheral lymphocyte cultures. A fully reliable conclusion, however, cannot be drawn from these data because of poor exposure information and methodological insufficiencies:

All human genotoxicity studies on benzene were performed retrospectively, i.e. effects in exposed groups are compared to non-exposed groups. Thus the problem arises to collect adequate negative control groups which are identical to the exposed groups in all aspects but benzene exposure. It is required that exposed and control groups are matched not only according to age and sex but also according to confounding factors (in the past and in the present) like smoking history, medication, exposure to physical and chemical agents at work and at home, nutrition, personal and family cancer incidences (Carrano and Natarajan 1988). None of the benzene studies considered here meets these criteria strictly. Furthermore, in none of the studies a positive control group was established.

In most studies exposure is described insufficiently, e.g., peak benzene concentrations are lacking or exposures to other chemicals are not excluded.

In the following the investigations mentioned in Table 4.27 are shortly discussed according to the genetic endpoints analyzed. Emphasis is put on those studies with low benzene exposure.

Chromosomal aberration tests

In the majority of chromosomal analyses the authors concluded that a positive effect was obtained which was caused by benzene, however, also negative findings were described (for details see Table 4.27). However, due to the methodological insufficiencies a fully reliable conclusion cannot be drawn.

Those studies with low mean exposures up to 10/20 ppm (32.5 / 65 mg/m^3) are of special interest. In this dose range six investigations were evaluated as positive (Karacic et al. 1995; Major et al. 1994; Picciano 1979; Sarto et al. 1984; Sasiadek 1992; Tompa et al. 1994) and four investigations were evaluated as negative (Jablonicka et al. 1987; Jong et al. 1988; Tough et al. 1970; Watanabe et al. 1980).

In the positive studies, in general, weak effects were obtained. Only in the study of Türkel and Egeli (1994) a moderate effect was found (7.1% aberrant cells as compared to 0.8% in the control group). However, this study suffers from major methodological insufficiencies (no quantification of exposure, co-exposure at least to other benzene derivatives, no adequate control group).

Micronucleus tests

In both studies on micronucleus frequencies the authors concluded positive results. Weak effects were obtained by Högstedt et al. (1991) and by Liu et al. (1996) in the low-exposure group (<12 ppm, 39 mg/m^3). In the two higher exposure groups of the Liu et al. study (12-60 and >60 ppm, 39-195 mg/m^3 and >195 mg/m^3) micronucleus frequencies were increased by a factor of approximately 3. The reliability of both studies is limited by methodological insufficiencies (poor exposure data, no matched control groups, in the Liu et al. study the methodology for analysis of micronuclei is not given).

Aneuploidy tests

Ding et al. (1983) and Erdogan and Aksoy (1973) reported on the induction of aneuploidy after benzene poisoning. However, quantitative data on the effect are not given.

Glycophorin A mutation assay

Rothman et al. (1995) investigated bone marrow cells of workers which were heavily exposed to benzene (daily mean concentration 72.2 ppm, 235 mg/m^3) in the glycophorin A mutation assay, in which a wide spectrum of genetic effects can be detected (gene and chromosome mutations as well as mitotic recombination). As compared to a matched negative control group, a doubling of the frequency of glycophorin A variant cells was found in workers.

SCE tests

All SCE studies were negative or led to increases of the SCE frequencies by factors ranging from 1.1 to 1.3. These marginal increases are probably due to unspecific cytotoxicity (prolongation of S phase) and not to direct effects on DNA.

SSB tests (DNA single strand breaks)

Nilsson et al. (1996) and Popp et al. (1992) reported on the induction of DNA single strand breaks (SSB) after exposure to low benzene concentrations. In both papers peak benzene concentrations are not given and co-exposure (other gasoline components, toluene) is mentioned.

In the Nilsson et al. study the 8-h time-weighted average exposure to benzene was 0.13 ppm (range 0.003 to 0.6 ppm; 0.42 mg/m^3, range 0.01 to 1.95 mg/m^3). SSB were measured by means of the alkaline elution technique and quantified by NAAC values (normalized area above the curve). As compared to a matched negative control group, SSB frequencies were decreased in the exposed group. However, comparing SSB frequencies before and after working shifts, an increase by a factor of 1.25 was found (which is very similar to the factor by which the pre-shift control value is increased as compared to the pre-shift value in the exposed group). A specific methodological problem arose from the fact that NAAC values were strongly dependent on the storage time of blood samples which varied from 0-59 to 120-240 days. It may be deduced that pre-shift/post-shift changes are at the limit of the resolution of the methodology and have no biological relevance.

In the study of Popp et al. (1992) the mean benzene exposure was 1.3 ppm (4.2 mg/m^3) (range 0.2-4.8 ppm). For indirect quantification of SSB, DNA elution rates were measured using polycarbonate filters and polyvinylidene filters. Using polycarbonate filters the elution rate was increased statistically significant as compared to the control group, using polyvinylidene filters there was no statistical significance.

8-Hydroxy-deoxyguanine tests

Effects of benzene exposure on 8-hydroxy-deoxyguanine (8-OH-dG) levels were investigated by Liu et al. (1996; lymphocytes) and Nilsson et al. (1996; urinary levels). 8-OH-dG is used as an indicator for oxidative DNA lesions.

Liu et al. reported on a weak increase of these lesions in a low exposure group (<12 ppm; 39 mg/m^3; increase by a factor of 1.3), in high exposure groups (12-60 and >60 ppm; 39-195 mg/m^3 and >195 mg/m^3) clear increases were found. The biological relevance of such effects are a matter of debate. Since exposure data are poor (no peak benzene concentrations, no exposure periods, co-exposure to at least toluene and xylene) and matched controls are lacking, the effects cannot be put down to benzene exposure.

Nilsson et al. (1996) found a small decrease in urinary 8-OH-dG levels (µmol/mol creatinine) in an exposed group as compared to a control group. Furthermore, the 8-OH-dG levels did not vary pre- and post-shift, but in the late evening and the next morning increases by factors of 1.4 and 1.3 were found; details on urine collection are not given. Similar to the SSB analysis of the authors (see above), again the changes are based on going beyond reasonable limits of the test system.

F Data on structurally related substances / metabolites

Phenol is a weak inducer of micronuclei in mouse bone marrow cells in vivo (Ciranni et al. 1988; McFee et al. 1991; Shelby et al. 1993). However, the effect is bound to high doses in the toxic range.

Hydroquinone is an in vivo mutagen in mammals. In mice after intraperitoneal administration of high doses, chromosomal aberrations and micronuclei are induced in bone marrow cells (Xu and Adler 1990; Pacchierotti et al. 1991; Marrazzini et al. 1994). Furthermore, chromosomal aberrations are induced in spermatogonia and spermatocytes (Ciranni and Adler 1991).

Catechol and 1,4-benzoquinone are relatively weak inducers of micronuclei in mouse bone marrow cells after intraperitoneal administration (Ciranni et al. 1988; Marrazzini et al. 1994).

Witz et al. (1990) investigated in vivo effects of trans,trans-muconaldehyde in bone marrow cells of mice after three daily intraperitoneal administrations. Sister chromatid exchanges (SCE) were induced in the dose range 3 to 6 mg/kg bw; however, there was no effect on micronucleus frequencies in polychromatic erythrocytes (PCE), although doses from 3 mg/kg bw upwards depressed the percentage of PCE (as compared to normochromatic erythrocytes).

In vivo mutagenicity of mixtures of the benzene metabolites hydroquinone, phenol and catechol was determined by (Marrazzini et al. 1994) in the micronucleus assay with mice after intraperitoneal administration. Mixtures of two or three metabolites in varying concentrations led to different results, causing increase or decrease in MN induction. For mixtures of all three metabolites, the genotoxicity was mainly the result of hydroquinone and catechol.

4.1.2.7.3 Conclusion

Benzene has been widely studied regarding its mutagenicity. An overview over the in vitro data, given in the EHC report 150 (1993), presents mainly negative findings in bacteria and mixed results in mammalian cell culture assays.

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 with mice). Concerning chromosomal effects after inhalation exposure, according to one report a single low dose of 1 ppm (~3.25 mg/m³) induced micronuclei in bone marrow cells of rats. However, in investigations on chromosomal aberrations in rats positive effects were

obtained only for doses of 100 ppm (~ 325mg/m³) and higher (single exposure) or 10 ppm (32.5 mg/m³) and higher (repeated exposure). In mice, the lowest dose with observed effect is reported to be 10 ppm (~ 32.5 mg/m³) (micronuclei after single exposure).

Although only intraperitoneal studies are available, it seems that benzene has the potential for induction of transplacental genetic effects.

There are only few valid data on germ cell mutagenicity in mammals. In mice chromosomal aberrations are induced in spermatogonia by oral doses ranging from 220 to 880 mg/kg bw. No clear conclusions can be drawn from dominant lethal tests with mice and rats. Concerning human studies 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.

Overall, benzene obviously is an in vivo somatic cell mutagen for mammals and man. Concerning germ cell mutagenesis dominant lethal tests were without clear conclusion. Based on the positive data regarding 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. Therefore, benzene should be classified as mutagen of category 2.

Table 4.25 In vivo studies (somatic cells)

Test	**Species** (tissue)	**Dose groups**	**Harvest time**	**Observations and remarks** (include route of administration)
Oral administration				
Chromosomal aberration test	mouse (bone marrow)	88- 440 - 880 mg/kg	6 to 48 h	**positive** (Ciranni et al., 1991)
Chromosomal aberration test	rat (bone marrow)	up to 660 mg/kg	up to 24 h	**positive** (Fujie et al., 1992)
Micronucleus test	mouse (bone marrow)	26.6 to 146.6 mg/kg	2 - 8 - 14 days	**positive** (Au et al., 1990)
Micronucleus test	mouse (bone marrow)	25 to 600 mg/kg	4 to 24 months	**positive (**MacGregor et al., 1990)
Micronucleus test	mouse (bone marrow)	220 - 440 mg/kg	24 h	**positive** (Chen et al. 1994)
Comet assay	mouse (peripheral lymphocytes, bone marrow)	40 - 200 - 450 mg/kg	6 h	**positive** (Tuo et al., 1966)
Transplacental micronucleus test	mouse (fetal liver)	880 to 1760 mg/kg	24 h	**positive** (Harper et al., 1989)
Inhalation administration				
Chromosomal aberration test	rat (bone marrow)	10 to 60 ppm	2 weeks	**positive** (Fujie et al., 1992)
Chromosomal aberration test	rat (bone marrow)	1 to 1000 ppm		**positive** (Styles et al., 1984)
Chromosomal aberration test	mouse (lung macrophages)	0.1 - 1.0 ppm	6 weeks	**inconclusive** (Au et al., 1988)
Chromosomal aberration test	mouse (spleen lymphocytes)	0.04 - 1.0 ppm	6 weeks	**inconclusive** (Au et al., 1991)
Micronucleus test	rat & mouse (bone marrow)	rats, 0.1 to 30 ppm;		**positive** (Erexson et al., 1986)

Test	Species (tissue)	Dose groups	Harvest time	Observations and remarks (include route of administration)
		mice, 10 to 1000 ppm		
Micronucleus test	mouse (bone marrow & blood)	1 to 200 ppm	1 to 8 weeks	**positive** (Farris et al, 1996)
Micronucleus test	mouse (bone marrow)	200 ppm	5 days	**positive** (no effect in cyp2e1$^{-/-}$ mice; Valentine et al, 1996)
Gene mutation test	mouse (spleen lymphocytes)	0.04 to 1 ppm	6 weeks	**equivocal** (Ward et al., 1992)
Gene mutation test - transgenics	mouse (lung, spleen, liver)	300 ppm	12 weeks	**positive** (Mullin et al., 1995)
SCE test	rat & mouse (peripheral lymphocytes)	rats, 0.1 to 30 ppm; mouse, 10 to 1000 ppm		**positive** (Erexson et al., 1986)
Intraperitoneal administration				
Transplacental micronucleus test	mouse (fetal liver)	880 to 1760 mg/kg	24 h	**inconclusive** (Harper et al., 1989)
Transplacental micronucleus test	mouse (fetal liver)	109 to 874 mg/kg	21 h	**positive** (Ning et al., 1991)
Transplacental micronucleus test	mouse (fetal liver)	439 to 1318 mg/kg	40 h	**positive** (Xing et al., 1992)

Table 4.26 In vivo studies (germ cells)

Test	Species (tissue)	Dose groups	Harvest time	Observations and remarks (include route of administration)
Oral administration				
Germ cell chromosome aberration test	mouse (spermatogonia)	0.25 - 0.50 - 1.0 ml/kg (220 - 440 - 880 mg/kg)	up to 48 h	**positive** (Ciranni et al., 1991)
Germ cell chromosome aberration test	mouse (spermatocytes)	36.6 to 146.4 mg/kg	2 weeks	**positive** (Rithidech et al., 1987; abstract without detailed information)
Dominant lethal assay	mouse	1.0 - 4.0 ml/kg	up to 48 days	**equivocal** (GSF Bericht, 1977; also mentioned in Ehling et al., 1978)
Dominant lethal assay	mouse	Not given	5 weeks	**negative** (Feldt and Zhurkov, 1985; no detailed information on methodology and results)
Intraperitoneal administration				
Dominant lethal assay	rat	0.5 ml/kg	not given	**negative** (Lyon, 1975; cited in Dean, 1978; no detailed information on methodology and results))
Sperm abnormality test	mouse	0.4 to 1.0 ml/kg	5 days	**positive** (Topham, 1980)

Test	**Species** (tissue)	**Dose groups**	**Harvest time**	**Observations and remarks** (include route of administration)
Inhalative administration				
Dominant lethal assay	rat	1.0 - 300 ppm	10 weeks	**equivocal** (Biodynamics, 1981)

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen- tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Clare 1984	N.I.	N.I.	N.I.	acute exp.	10	no	CAb SCE	neg neg	
Ding 1983	N.I.[*13]	N.I.	N.I.	6 (1-28)	21[*17]	no	CAb Aneu	pos pos	N.I. N.I.
Erdogan 1973	N.I.(150-210)[*14]	N.I.	N.I.	long-term	13	no[*8]	CAb Aneu	pos pos	N.I. N.I.

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(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Forni 1971a	N.I.[*13]	N.I.	N.I.	N.I.	25[*18]	no[*15]	CAb	pos	1.89/1.22% (0.49/0.04)[*16]
Forni 1971b	N.I. (125-532)	N.I.	toluene	N.I. (<1-22)	10[*17]	no[*15]	CAb	pos	1.66/0.62% (0.61/0.09)[*16]
Fredga 1979	0.08 (0.02-0.31)	N.I.	N.I.	N.I. (4-43)	9	no	CAb	inconcl	
	0.40 (0.01-4.13)	N.I.	N.I.	N.I. (4-25)	11	no	CAb	inconcl	
				N.I. (4-18)	12	no	CAb	inconcl	

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
	6.56 (0.33-22.80)	N.I.	N.I.	N.I. (0.1-12)	9	no	CAb	inconcl	
	5.0-10.0	N.I.	N.I.	N.I. (2-14)	12	no	CAb	inconcl	
Högstedt 1991	0.31 (N.I.)	6.2	N.I.	N.I.	15	no	MN	pos[*3]	0.53% (0.34)
Jablonicka 1987	N.I. (0.45-11.25)	N.I.	N.I.	N.I. (3-18)	66	no	CAb	neg	

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Jong 1988	< 0.09 (<0.03-0.75)	N.I.	N.I.	N.I. (1-13)	32	no	CAb	neg	
Karacic 1995	8.0 (1.7-15.2)	N.I.	toluene	13.4 (2-31)	38	no no	CAb SCE	pos pos	0.55/0.16% (0.23/0.00)[*4] 7.2 (5.6)
	5.0 (1.9-12.8)	N.I.	toluene	17.7 (1-33)	45	no no	CAb SCE	pos neg	0.18 % (0.00)[*5]
Liu 1996	<12 (N.I.)	N.I.	toluene, xylene	N.I.	35	no	MN 8-OH-dG	pos pos	0.40% (0.26) 4.7 (3.7)[*10]
	N.I. (12-60)	N.I.	toluene, xylene	N.I.	24	no	MN 8-OH-dG	pos pos	0.80% (0.26) 26.1 (3.7)[*10]

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
	>60 (N.I.)	N.I.	toluene, xylene	N.I.	28	no	MN 8-OH-dG	pos pos	0.82% (0.26) 29.8 (3.7)[*10]
Major 1994	2.2 (0.3-14:7)	N.I.	N.I.	N.I.	42	yes	CAb	pos	3.5% (1.6)
						yes	SCE	pos	6.4 (5.6)
Nilsson 1996	0.13 (0.003-0.6)	N.I.	gasoline components	N.I.	33	yes yes	SSB 8-OH-	pos[*22] pos[*22]	

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Picciano 1979	2.1 (N.I.)	N.I.	aromatic hydrocarb.	4.7 (0.1-26)	52	yes	CAb	pos	0.67/0.19% (0.35/0.06)[*7]
Popp 1992	1.3 (0.2-4.8)	N.I.	toluene	18 (3-N.I.)	20	yes	SSB SCE	pos pos	1.17/3.8 (0.95/3.4)[*2] 6.55 (6.05)
Sarto 1984	N.I. (0.2-12.4)	N.I.	N.I.	N.I. (3-35)	22	no	CAb SCE	pos neg	2.6% (1.9)[*11]

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Rothmann 1995	72.2 (2.4-301.1)	N.I.	minimal	6.9 (0.7-16.5)	24	yes	gene-dupl[*9]	pos	13.9 (7.4)[*25]
Sasiadek 1989	<31 (N.I.)	N.I.	N.I.	N.I. (10-26)	33	no	CAb	pos	4.7% (1.7)[*12]
Sasiadek 1992	<10 (N.I.)	N.I.	organic solv.	N.I. (10-20)	56	yes	CAb	pos	2.7% (0.9)[*12]
Seiji 1990	50 (3-210)	N.I.	N.I.	5.5 (N.I.)	36	yes	SCE	neg	

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Tompa 1994	N.I. (0.9-21.5)	N.I.	N.I.	N.I. (0-2)	10	yes	CAb	pos	2.5% (1.5)
							SCE	pos	6.6 (5.8)
				N.I. (2-10)	22	yes	CAb	pos	3.8% (1.5)
							SCE	pos	6.9 (5.8)
				>10 (N.I.)	17	yes	CAb	pos	3.0% (1.5)
							SCE	pos	6.4 (5.8)

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen- tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
Tough 1970	N.I. (25-150) N.I. (25-150) 12 (N.I.)	N.I. N.I. N.I.	N.I. N.I. N.I.	N.I. (2-16) N.I. (4-23) N.I. (2-26)	20[*19] 12[*20] 20	no no no	CAb CAb CAb	pos neg neg	1.5/1.0% (0.6/0.4)[*16]
Türkel 1994	N.I.	N.I.	b. derivatives	N.I. (5-50)	58	no	CAb	pos	7.1% (0.8)
Watanabe	N.I. (3-50)	177	N.I.	N.I. (2-12)	7[*21]	no	CAb SCE	neg neg	

Table 4.27

BENZENE MUTAGENICITY: OVERVIEW ON HUMAN STUDIES WITH PERIPHERAL LYMPHOCYTES

(N.I. = No information; pos = positive; neg = negative; inconcl = inconclusive)

Reference[*23]	Daily benzene concentration (ppm) mean (range)	Peak concen-tration	Co-exposure	Exposure period (years) mean (range)	No. of subjects	Matched negative control?	Genetic endpoint[*24]	Authors' conclusion	Quantitative effect (negative control)
	N.I. (0-9)	N.I.	N.I.	N.I. (1-20)	9[*21]	no	CAb SCE	neg neg	
Yardley-J. 1988	N.I. (<1-10)	>100	N.I.	>5 (N.I.)	66	yes	SCE	neg	
Yardley-J.	N.I. (<1-10)	>100	N.I.	>5 (N.I.)	48	yes	CAb	inconcl[*6]	

Explanations

*1 Urinary levels of DNA adduct 8-hydroxy-deoxyguanosine
*2 Arbitrary units of DNA elution rate through polycarbonate/polyvinylidene fluoride filters
*3Positive in B-lymphocytes (stimulation with pokeweed mitogen) but negative in T-lymphocytes (phytohemagglutinin stimulation)

*4 Acentric fragments/dicentrics, other types of aberration were negative
*5 Dicentrics, other types of aberrations were negative
*6 1.6% in exposed group, 1.0% in controls; borderline using parametric statistical tests, significant with Fisher's exact test
*7 Chromosome breaks/marker chromosomes, negative for chromatid breaks and abnormal cells
*8 Number negative control group at all
*9 Gene duplication
*10 Number of 8-OH-dG per 105 dG
*11 % aberrant metaphases incl. gaps (chromosome type aberrations excl. gaps: 1.1% (0.5))
*12 Including gaps
*13 Chronic benzene poisoning
*14 10 out 13 subjects suffered from pancytopenia
*15 Matched with respect to age and sex, smoking habit, however, not considered
*16 Unstable/stable chromosomal aberrations
*17 Analysis 10 or more years after exposure
*18 Analysis 1 to 18 years after exposure
*19 Analysis 2 to 3 years after exposure
*20 Analysis 4 to 6 years after exposure
*21 Analysis 0.5 years after exposure
*22 Negative in comparing the exposed group with negative control group; however, positive in comparing exposed subjects before shift and after shift; SSB (normalized area above the curve): 24.9 pre-shift, 31.3 post-shift; 8-OH-dG (µmol/mol creatinine): 0.72 pre-shift, 0.75 post-shift, 0.99 late evening, 0.90 next morning
*23 For full citation see reference list
*24 Aneu, aneuploidy; CAb, structural chromosomal aberrations; MN micronuclei; SCE, sister chromatid exchange; SSB, DNA single strand breaks; 8-OH-dG, 8-hydroxy-2-deoxyguanosine
*25 Glycophorin A variant cell frequency x 10^{-6}

4.1.2.8 Carcinogenicity

4.1.2.8.1. Carcinogenicity / Animal data

Carcinogenicity-Data report

All benzene data were summarized in Table 4.28

Inhalation exposure- mouse

In 1980, Snyder et al. reported the development of malignant lymphomas in C57Bl/6J mice after the inhalative exposure for about 70 weeks to 300 ppm (960 mg/m³) of benzene. The benzene did not induce significant increased incidence of lymphomas in AKR/J-mice exposed to 100 ppm (~ 325 mg/m³) for lifetime, 29/49 malignant lymphomas were found in treated animal versus 24/50 in controls. In mice of each strain, exposure to benzene produced anemia and lymphocytopenia, but only in the group of 40 male C57Bl mice left shift neutrophilia, granulopoietic or myeloic bone marrow hyperplasia and in six cases lymphocytic lymphoma with thymic involvement, one plasmocytoma, and one hemocytoblastic leukemia was reported. Among 40 control C57Bl mice, only two developed lymphocytic lymphomas without thymus involvement.

No increased incidences of leukemia /lymphomas in two mice strains were observed in a later study of Snyder et al. (1988). However, male CD-1 mice and C57Bl/6J mice repeatedly exposed to 300 ppm (960 mg/m³) benzene on 5 days (6 hr/d) interrupted by 2 weeks of non-exposure until death exhibited increased incidences of tumors (total numbers), malignant tumors and lung tumors in CD-1 mice and Zymbal gland tumors in C57Bl-mice.
The tumor response produced by exposures to 1200 ppm (3840 mg/m³) for 10 weeks followed by non-exposure until death were different in the two strains. CD-1 mice exhibited significant increases of tumors (total number, malignant, benign), of lung adenomas and Zymbal gland carcinomas while no tumor category showed elevated incidences in C57Bl mice.

Female C57Bl/6 BNL mice exposed to 300 ppm (960 mg/m³) for 6 hr/d, 5 d/w for 16 weeks exhibited an elevated cumulative mortality rate. Mortality started at about 330 days of age in comparison to 440 days in controls. Lymphoma/leukemia rate was increased in exposed animals. The total number of lymphoma/leukemia was 20/89 in exposed females (10 thymic neoplasias (lymphocytic), 6 nonthymic neoplasias (lymphocytic), 4 leukemia not otherwise specified (NOS)) versus 8/88 in the control group (1 thymic neoplasia (lymphocytic), 2 nonthymic neoplasias (lymphocytic), 3 myelogenous leukemia, 2 leukemia NOS). An increased incidence of tumors in the Zymbal gland and ovaries compared to the control group was also found (Cronkite et al. 1984, 1985).

Exposure of CBA/Ca BNL mice to 100 (~ 325 mg/m³) or 300 ppm (~ 974 mg/m³) benzene for 16 weeks (6 hr/d, 5 d/w) resulted in myelogenous neoplasias in 19% of the male mice and 11% of the female mice at the dose of 300 ppm (960 mg/m³) versus 0% and 1.7% in control males and females. At 100 ppm (320 mg/m³), myelogenous neoplasms were observed in 2.4% of exposed males, but no case occurred in control males (Cronkite et al. 1989).

Goldstein et al. (1982) exposed three strains of mice (80 AKR mice, 40 C57Bl mice, 40 CD-1 mice without data on sex and strain specification) 6 hr/d, 5 d/w, for life to 300 ppm (960 mg/m³) benzene. Another group of 50 AKR mice were exposed to 100 ppm (320 mg/m³). Treatment resulted in four cases of myeloproliferative disease. There was one case of chronic myelogenous leukemia, one of acute myeloblastic leukemia, and one of granulocytic hyperplasia among 40 CD-1 mice exposed to 300 ppm.

The study of Farris et al. (1993) could not confirm that benzene produces granulocytic leukemia in the CBA/Ca mice strain as reported by Cronkite and coworkers (1989). 14 out of 125 CBA/CA male mice exposed to 300 ppm (960 mg/m³) at similar conditions developed lymphoma (lymphoblastic, lymphocytic, or mixed) compared to only 2/125 sham-exposed mice. Benzene-exposed mice also developed preputial gland squamous cell carcinomas (60% vs 0% in controls) and had an increased incidence of lung adenomas (36% vs 14% in controls). Fourteen cases of Zymbal gland carcinomas and nine forestomach squamous cell carcinoma were present in benzene-exposed mice compared to 1 or 0 case in the controls (microscopy of these organs was done only when gross lesions were evident). Moderate to marked granulocytic hyperplasia present in benzene-exposed mice, with a 36% incidence in the bone marrow and 6% in the spleen, as compared to the sham-exposed with 8% and 0%, respectively was not interpreted as a direct effect of benzene because of the presence of inflammatory processes, e.g. in the preputial glands.

Inhalation exposure - rat

The above cited study of Goldstein et al. (1982) also included the exposure of Sprague-Dawley rats (no data on sex) to 100 ppm (320 mg/m³) (40 animals) and to 300 ppm (960 mg/m³) (80 animals) on 6 hr/d, 5 d/w, for life. There was one case of chronic myelogenous leukemia in the low dose group.

In a series of inhalation studies by Maltoni (1982, 1983, 1985), pregnant Sprague-Dawley rats (13 week-old adults) were exposed on 5 days a week from the twelfth day of pregnancy on to 200 ppm (~649 mg/m³) for 4 hr/d, 7 week, then on 12 weeks to 200 ppm for 7 hr/d, followed by 300 ppm, (~ 974 mg/m³) 7 hr/d for 85 weeks. The 12-day old offspring have been exposed to a similar treatment schedule; treatment was stopped after 15 or 104 weeks. All groups were observed until week 150. Mortality at 104 weeks is higher in animals in which the treatment was started at the embryonic stage and lasted 104 weeks. Any of the reports contained statistical data.
The prolonged treatment up to 104 week slightly affected the body weight of male offspring at different stages. Leucopenia mainly due to lymphocytopenia was evident in male and female offspring following 104 weeks of exposure. At 150 weeks after the start of the study, benzene caused in animals treated for 104 weeks increased incidences of Zymbal gland carcinomas, oral cavity carcinomas, nasal cavity carcinomas, skin carcinomas, forestomach carcinomas, and hepatomas.
Benzene induced increased incidences of carcinomas of the Zymbal gland, oral cavity and nasal cavity and of hepatomas were also found in offspring males and females treated for 15 weeks followed by an observation period until week 150.
The US Environmental Protection Agency (EPA) Gene-Tox Carcinogenesis Panel (Nesnow et al. 1986) reevaluated the raw data from these studies including the slides used for

histopathology determinations. Their comment on this Maltoni study was that it was inconclusive (without giving any detailed reasoning).

To us, their decision seems to be explainable since the study design, data evaluation and documentation were not compliant to standard carcinogenicity bioassays. The target organs showed consistency to those of other studies, therefore the rapporteur interpreted the data from the Maltoni studies to give supportive evidence on benzene carcinogenicity via the inhalation route.

Oral application- mouse

In the oral NTP study (NTP 1986; Huff et al. 1989), increased incidences of malignant lymphomas were also reported in B6C3F1 mice given oral doses of 25, 50, or 100 mg/kg bw/d benzene in corn oil (5 d/w) for 103 weeks. Survival of dosed groups decreased with increasing dose (male: 28/50, 23/50, 18/50, 7/50, female: 30/50, 26/50, 14/50, 18/50). At week 91 for mice, survival was greater than 60% in all groups, most of the dosed animals that died before week 103 had neoplasias. Bone marrow hematopoietic hyperplasia was observed at increased incidences in dosed mice of each sex. The incidences of Zymbal gland carcinomas in mid and high dose male mice and in high dose female mice were greater than those in the vehicle controls. In the same dose groups, the incidences of epithelial hyperplasia of the Zymbal gland were also increased. Incidences of squamous cell papillomas or carcinomas (combined), hyperkeratosis, and epithelial hyperplasia of the forestomach were increased in some dosed groups of male and female mice.
Compound-related effects in the lung, Harderian gland, preputial gland, ovary, mammary gland, and liver were seen in mice, but not in rats. Administration of benzene was associated with increased incidences of alveolar epithelial hyperplasia in mid and high dose mice. Increased incidences of alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) were observed in high dose male mice. Alveolar/bronchiolar adenomas were seen at increased incidences in high dose female mice, as were alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) in mid and high dose female mice. The incidences of focal or diffuse hyperplasia of the Harderian gland were increased in dosed mice of each sex. The incidences of Harderian gland adenomas in male mice of all dose groups were greater than that in the vehicle controls. A marginal increase in the incidence of adenomas or carcinomas (combined) of the Harderian gland was seen in high dose female mice. The administration of benzene to male mice was associated with increased incidences of hyperplasia and squamous cell carcinomas of the preputial gland. Increased incidences of mammary gland carcinomas were found in mid dose and high dose female mice and carcinosarcomas in high dose female mice. Increased incidences of various uncommon neoplastic and nonneoplastic lesions of the ovary (papillary cystadenoma, luteoma, granulosa cell tumor, tubular adenoma, benign mixed tumor, epithelial hyperplasia and senile atrophy) were associated with administration of benzene to female mice. In mid and high dose female mice, the incidences of granulosa cell tumors and benign mixed tumors were greater than those in the vehicle controls. Increased incidences of hepatocellular adenomas were observed in low dose female mice and hepatocellular adenomas or carcinomas (combined) in low dose and mid dose female mice. According to the definitions of the NTP, the authors concluded, that under the condition of these 2-year gavage study, there was clear evidence of carcinogenicity of benzene in male and female B6C3F1 mice. Toxic effects reported in this study were cited in 4.1.2.6.A.

Mice of the Swiss strain (40 animals/sex/group) and the RF/J strain (45 males and 40 females/group) were exposed to 0 or 500 mg/kg bw/d for 78 and 52 weeks, respectively, in the Maltoni study (Maltoni et al. 1989).
In the Swiss mice, the administration of benzene was associated with an increase of total malignant tumors, carcinomas of the mammary glands, lung tumors, and carcinomas of the Zymbal gland. Mammary carcinomas were evident in 47.5% of females versus 5% in control females and 2.5% in control males. In comparison to controls (7.5% in males and 10% in females), pulmonary tumors were increased in treated males (42.5%) and females (37.5%). The incidence of Zymbal gland carcinomas were 10% in males and 2.5% in females and none in the control groups.
Additionally, 7.5% of the treated males and 10% of the treated females had dysplastic lesions of the Zymbal gland. Hepatomas were slightly increased in treated males (7.5% versus 5% in control males), however angiosarcomas of the liver were observed in 2.5% of the males but not in controls. Leukemia rate did not change due to benzene treatment in this strain.
A treatment of RF/J mice under similar conditions for 52 weeks revealed increased rates of total malignant tumors, mammary carcinomas (22.5% of treated females versus 2.5% in controls), lung tumors (51.1% and 45% in treated male and females versus 11.1% and 7.5% in control males and females) and leukemia NOS (57.8% and 60% in treated males and females versus 37.8% and 35% in control males and females).
No data were reported on the mortality rates and the occurrence of other tumor types. Results were only given in summary tables of tumor incidences.

Oral exposure - rat

Rats treated orally for 2 years (NTP 1986; Huff et al. 1989) received 0, 50, 100, or 200 mg/kg bw/d (males) and 0, 25, 50, or 100 mg/kg bw/d (females). As in mice, survival rate was lower in dosed groups (males: 32/50, 29/50, 25/50, 16/50, females: 46/50, 38/50, 34/50, 25/50), 60% of animals were still alive at week 92. Most of the dosed animals that died before week 103 had neoplasia. The incidences of Zymbal gland carcinomas in mid and high dose male rats and in dosed female rats were greater than those in the vehicle controls. Benzene was associated with increased incidences of neoplasms of the skin and oral cavity of rats. The incidences of squamous cell papillomas and squamous cell carcinomas of the skin in the high dose male rats were greater then those in the vehicle controls. Increased incidences of uncommon squamous cell papillomas or squamous cell carcinomas (combined) of the oral cavity were observed in dosed male and female rats. Incidences of hyperkeratosis and acanthosis were increased in high dose males.

Maltoni et al. (1989) also investigated oral exposure to benzene in Sprague-Dawley and Wistar rats. Sprague-Dawley rats were given 50 mg/kg bw/d (30 males and 30 females) or 250 mg/kg bw/d of benzene (35 males and 35 females) on 4 to 5 days/week by stomach tube for 52 weeks. In addition, 40 male and 40 female rats of Sprague-Dawley and Wistar strains were given 500 mg/kg bw/d of benzene for 104 weeks (4-5 d/w), respectively. Control groups of the 104-week study included 50 animals/sex of Sprague-Dawley rats and 80 animals/sex of Wistar rats, 30 male and 30 female Sprague-Dawley rats served as controls in the 52 week study.
In the Sprague-Dawley rats exposed to 50 and 250 mg/kg bw/d of benzene for 52 weeks, 6.5% and 22.9% of the females, respectively, developed carcinomas of the Zymbal gland, while none were present in controls and treated males. Zymbal gland carcinomas were seen in

16 percent (males 17.5%, females 15%) of the Wistar rats and in 42.5% (males 45%, females 40%) of the Sprague-Dawley rats treated with 500 mg/kg bw/d of benzene on 104 weeks.
The incidences of leukemia in Sprague-Dawley rats at week 52 treated with doses of 50 mg/kg bw mg/d were 6.7% in females (0% in males), and at 250 mg/kg bw, 11.4% of males and 2.9% of females had leukemia compared to control percentages of 3.3% in females (0% in males). After 104 weeks of treatment with 500 mg/kg bw/d, incidences of leukemia were 2.5% in males and 7.5% in females of the Sprague-Dawley rats (controls: 6% in males, 2% in females) and 5% in males and 20% of females of the Wistar strain (control: 2.5% in males, 7.5% in females).

In Sprague-Dawley rats, oral cavity carcinomas occurred in 5.7% of the females treated at 250 mg/kg bw/d (0% in other dosing groups or controls). The incidence of this tumor increased to 52.5% in males and 50% in females of this strain at 500 mg/kg bw/d at week 104. In comparison, Wistar rats had incidences of 5% in males and 10% in females of oral cavity carcinomas (control males 2.5%).
Sprague-Dawley rats treated with 500 mg/kg bw/d also had a 15% incidence of forestomach carcinomas in situ, 2.5% of invasive carcinomas were reported to occur in treated males (0% in controls). Males of this group showed a 25% incidence on acanthomas and dysplasias, the incidence in females was 17.5% (0% in controls). No data on preneoplastic or neoplastic lesions of the forestomach were reported in other treatment groups of Sprague-Dawley or Wistar rats.
Sprague-Dawley rats treated with 500 mg/kg bw/d also had increased incidences of skin carcinomas (22.5% in treated males vs 0% in control males) and increased incidences of liver tumors. 5% of males and 7.5% of females had angiosarcomas vs none of the control, 7.5% of males and 2.5% of females had hepatomas versus 6% of control males and 0% of control females.
Tumors of the nasal cavities were not seen in the 50 and 250 mg/kg bw groups. At week 104 and at 500 mg/kg bw/d of benzene carcinomas of the nasal cavity gained percentages of 7.5% of male and 2.5% of female Sprague-Dawley rats (0% in controls). 5% of male and 2.5% of female Wistar rats of this dose level had nasal cavity carcinomas (0% in controls).
Data were only given in summary tables and did not include information on survival rates or statistical significance of tumors.

Table 4.28 Data from carcinogenicity studies in experimental animals

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
Inhala-tion	mouse/C 57Bl/6J (males) AKR/J (males)	300 ppm, 6hr/d,5d/w lifetime 100 ppm , 6hr/d,5d/w, lifetime	no	reduced median survival (41 vs 75 weeks in control Ø	granulopoietic/ myeloid bone marrow hyperplasia in C57Bl mice (13/32 animals without tumors)	8/40 animals with **hematopoietic lymphoma** (six lymphocytic lymphoma, one plasmocytoma, one hemocytoblastic leukemia) 2/40 control animals with lymphocytic lymphoma no increase of tumor rate of lymphomas (29/49 in treated animals, 24/50 in controls)	Snyder et al. 1980
	mouse/ C57Bl/6J and CD-1 (males)	Intermitt.: 300 ppm, 6hr/d, 5d/w,1 w interrupted by 2 weeks unexposed, until death	no	Ø	-	C57Bl/intermittend: tumor bearing animals (TBA): total TBA 25/54 vs 8/46 controls malignant TBA 24/54 vs 2/46 controls **Zymbal gland carcinoma** 19/54 vs 0/46 controls CD-1/interrmittend: total TBA 25/54 vs 4/46 controls malignant TBA 2/54 vs 1/46 controls **lung adenoma** 4/54 vs 3/46 controls C57Bl/10 weeks: no significant tumor response	Snyder et al. 1988

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
Inha-lation		1200 ppm 6hr/d,5d/w, 10 weeks, untreated until death				CD-1/10 weeks: total TBA 45/71 vs 36/71controls malignant TBA 24/71 vs 22/71 controls benign TBA.35/71 vs 21/71 controls **lung adenoma** 33/71 vs 17/71 controls **Zymbal gland carcinoma** 4/71 vs 0/71 controls	
Inhala-tion	mouse/ C57Bl/6 BNL (female)	300 ppm, 6hr/d,5d/w, 16 weeks, observation until death	no	increased	-	**lymphomas/leukemia all types** 20/89 vs 8/88 controls **thymic lymphoma** 10/89 vs 1/88 controls **nonthymic lymphoma** 6/89 vs 2/88 controls **myelogenous leukemia** 0/89 vs 3/88 controls **leukemia NOS** 4/89 vs 2/88 controls **Zymbal tumors** 16/89 vs 1/88 controls **ovarian tumors** 8/89 vs 0/88 controls	Cronkite et al. 1984, 1985
	mouse/C BA/Ca BNL	100, 300 ppm, 6hr/d,5d/w, 16 weeks, observation until death	no	increased at 100 and 300 ppm	-	300 ppm: **Myelogenous neoplasms** males: 19.3% vs 0% control females: 11% vs 1.7% control 100 ppm: **Myelogenous neoplasms**: males: 2.4% vs 0% control	Cronkite et al. 1989

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
	mouse/ AKR, C57Bl, CD-1 (no data on sex)	6 hr/d, 5 d/w, lifetime AKR: 100 and 300 ppm, C57Bl and CD-1: 300 ppm	no	no data	CD-1 mice: granulocytic hyperplasia 1/40	CD-1 mice: **chronic myelogenous leukemia** 1/40, **acute myeloblastic leukemia** 1/40 vs none in control	Goldstein et al. 1982
	mouse CBA/Ca (males)	300 ppm, 6hr/d,5d/w, 16 weeks, observation until month 22 after start	no	increased	granulocytic hyperplasia in bone marrow (42/116 vs 9/117 controls) and in spleen (7/114 vs 0/116 controls)	**malignant lymphoma** 14/118 vs 2/119 controls **lung adenoma** 42/118 vs 17/119 controls **preputial gland squamous cell carcinoma** 71/118 vs 0/118 controls **Zymbal gland carcinoma** 14/125 vs 1/125 controls **forestomach squamous cell carcinoma** 9/125 vs 6/125 controls	Farris et al. 1993
inha-lation	rat Sprague-Dawley (no data on sex)	100, 300 ppm 6 hr/d, 5 d/w, lifetime	no	no data	-	100 ppm: **chronic myelogenous leukemia** 1/40 vs none in control	Goldstein et al. 1982

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
Inhala-tion	rat/ Sprague-Dawley adult females and male and female 12-day embryos	pregnant females + male/ female offspring: 200 ppm, 4hr/d,5d/w, 7 week, then 200 ppm 7hr/d,5d/w, 12 week, then 300 ppm, 7hr/d,5d/w, 85 week	no	increased in offspring after 104 weeks of treatment	at week 118*: liver: nodular hyperplasias in 5/48 adult females (parent), 1/74 offspring male, 5/59 offspring females nodular dysplasia 2/59 offspring females versus none of each lesions was seen in controls	increase of tumor incidences at week 150**:. No. of animals with tumors were related to the No. of animals at study begin: **Zymbal gland carcinoma**: adult females (parent) 3/54 vs 1/60 controls offspring males 6/75 vs 2/158 controls offspring females 8/65 vs 0/149 controls **oral cavity carcinomas**: adult females (parent) 2/54 vs 0/60 controls offspring males 1/75 vs 0/158 controls offspring females 10/65 vs 0/149 controls **nasal cavity carcinomas**: adult females (parent) 1/54 vs0/60 controls offspring males 1/75 vs0/158 controls offspring females 2/65 vs 0/149 controls **skin carcinomas**: adult females (parent) 0/54 vs 0/60 controls offspring males 1/75 vs 0/158 controls offspring females 1/65 vs 0/149 controls **forestomach carcinomas**: adult females (parent) 0/65 vs 0/149 controls	Maltoni, 1982, 1983*, 1985**

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
Inhala-tion		male+ female offspring: 200 ppm, 4hr/d,5d/w, 7week, then 200 ppm, 7hr/d,5h/d, 12 week, observation until death			at week 118*: liver: nodular hyperplasia 2/64 offspring males and 7/59 offspring females versus none in the controls	offspring males 0/75 vs 0/158 controls offspring females 3/65 vs 1/149 controls **hepatomas**: adult females (parent) 1/54 vs 0/60 controls offspring males 2/75 vs 1/158 controls offspring females 7/65 vs 0/149 controls **hemolymphoreticular neoplasia**: adult females (parent): 0/54 vs 2/158 controls offspring males 6/75 vs 12/158 controls offspring females 0/65 vs 1/149 controls No. of animals with tumors were related to the No. of animals at study begin: **Zymbal gland carcinoma**: offspring males 4/70 vs 2/158 controls offspring females 1/59 vs 0/149 controls **oral cavity carcinomas**: offspring males 2/70 vs 0/158 controls offspring females 6/59 vs 0/149 controls **nasal cavity carcinomas**: offspring males 1/70 vs0/158 controls	

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
						offspring females 1/59 vs 0/149 controls **hepatomas**: offspring males 2/70 vs 1/158 controls offspring females 5/59 vs 0/149 controls	
oral (ga-vage) oral	mouse B6C3F1	0, 25, 50, 100 mg/kg bw/d	yes	decreased with increasing doses	hematopoietic marrow hyperplasia males: 11/48, 0/50, 25/49 vs 0/49 control females:14/45,8/50, 13/49 vs 3/49 control hyperplasia Zymbal gland males: 4/34, 12/40,10/39 vs 0/42 control females:1/32, 2/37, 6/31 vs 1/43 control	**malignant lymphomas**: males: 9/48,9/50,15/49 vs 4/49 controls females: 24/45,24/50,20/49 vs 15/49 controls **Zymbal gland carcinomas**: males: 1/34,4/40,21/39 vs 0/43 controls females: 0/32,1/37,3/31 vs 0/43 controls **squamous cell papilloma or carcinoma (combined) of the forestomach**: males: 2/42,3/44,5/38 vs 2/45 controls females: 3/40,6/45,5/42 vs 1/42 controls **alveolar/bronchiolar carcinomas**: males: 11/48,12/50,14/49 vs 5/49 controls females: 3/42,6/50,6/49 vs 0/49 controls **alveolar/bronchiolar adenomas**: females: 2/42,5/50,9/49 vs 4/49 controls **alveolar/bronchiolar adenomas or carcinomas** (combined):	NTP, 1986, Huff et al. 1989

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
oral					alveolar/bronch. hyperplasia: males: 3/48, 7/50, 10/49 vs 2/49 control females:11/48,12 /50, 14/49 vs 1/49 control hyperplasia of preputial gland: males: 18/28, 9/29, 1/35 vs 1/21 control	males: 16/48,19/50,21/49 vs 10/49 controls females: 5/42,10/50,13/49 vs 4/49 controls **Harderian gland adenomas**: males: 9/46,13/49,11/48 vs 0/49 controls **Harderian gland adenomas or carcinomas** (combined): females: 6/44,10/50,10/47 vs 5/48 controls **squamous cell carcinomas of preputial gland** males: 3/28,18/29,28/35 vs 0/21 controls mammary gland carcinomas: females: 2/45,5/50,10/49 vs 0/49 controls **mammary gland carcinosarcomas** females: 0/45,1/50,4/49 vs 0/40 controls **ovarian granulosa cell tumors** females: 1/44,6/49,7/48 vs 1/47 controls **overian benign mixed tumors** females: 1/44,12/49,7/48 vs 0/47 controls **hepatocellular adenomas**: females:8/44,5/50,4/49 vs 1/49 controls **hepatocellular adenomas or carcinomas** (combined) 12/44,13/50,7/49 vs 4/49 controls	

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
oral	rat/ F-344	males: 0,50,100, 200 mg/kg bw/d females 0,25, 50, 100 mg/kg bw/d	yes	increased with dose	-	**Zymbal gland carcinomas**: males: 6/46,10/42,17/42 vs 2/32 controls females: 5/40,5/44,14/46 vs 0/45 controls **squamous cell papilloma of the skin**: males: 2/50,1/50,5/50 vs 0/50 controls **squamous cell carcinoma of the skin**: males: 5/50,3/50,8/50 vs 0/50 controls **squamous cell papilloma or carcinomas (combined) of the oral cavity**: males: 9/50,16/50,19/50 vs 1/50 controls females: 5/50,12/50,9/50 vs 1/50 controls	NTP, 1986, Huff et al. 1989
oral	rat/Sprague-Dawley	50, 250 mg/kg bw/d, 4-5 d/w, 52 week 500 mg/kg bw/d, 4-5 d/w, 104 week	no	no data	SD: liver acanthomas and dysplasias: males: 25%, females: 17.5% control males and control females: 0%	52 weeks: **Zymbal gland carcinomas**: 50/males: 0% 50/females: 6.5% 250/males: 0% 250/females: 22.9% control/males: 0% control/females: 0% **leukemia:** 50/males: 0% 50/females 6.7% 250/males: 11.4% 250/females:2.9% control/males: 0% control/females 3.3% **oral cavity carcinomas** 250/males: 0% 250/females: 5.7%	Maltoni et al. 1989

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
oral		in Sprague-Dawley (SD) and Wistar (W) rats				control/males: 0% control/females: 0% 104 week: **Zymbal gland carcinomas** SD-males: 45% SD-females 40% SD-control males: 2% SD-control females:0% W-males: 17.5% W-females: 15% W-control males:0% W-control females 0% **leukemia**: SD-males: 2.5% SD-females: 7.5% SD-control males: 6% SD-control females: 2% W-males: 5% W-females: 10% W-control males: 2.5% W-control females:7.5% **oral cavity carcinomas**: SD-males 52.55 SD-females: 50% SD-control males: 0% SD-control females:0% W-males: 5% W-females: 10% W-control males: 2.5% W-control females: 05 **forestomach carcinomas in situ**: SD-males:0% SD-females: 15% SD control males: 0% SD-control females: 0% **forestomach invasive carcinomas**:	

Route	Species	Study design	Study acc. to B.32 or B.33	Mortality rate	Hyperplasia related to tumor response	Tumor response	Reference
oral						SD-males:2.5% SD-females: 0% SD-control males: 0% SD-control females:0% **skin carcinomas**: SD-males: 22.5% SD-females:0% SD-control males:0% SD-control females 2% **liver angiosarcomas**: SD-males:5% SD-females 7.5% SD-control males: 0% SD-control females. 0% **liver hepatomas**: SD-males: 7.5% SD-females: 2.5% SD-control males: 6% SD-control females: 0% **nasal cavity carcinomas**: SD-males: 7.5% SD-females:2.5% SD-control males: 0% SD-control females:0% W-males: 5% W-females: 2.5% W-control males:0% W-control females:0%	

Ø no treatment-related effect NOS not other specified TBA tumor bearing animals

Summary of benzene carcinogenicity in animals

From several studies with inhalative and oral exposure there is evidence that benzene is carcinogenic in animals. 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. Target organs were similar in several studies irrespective of the application route. 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 (Snyder et al. 1980; Farris et al. 1993; NTP 1986; Cronkite et al. 1984, 1985), however not all studies could demonstrate clearly increased lymphatic tumor rates (Snyder et al. 1988). Additionally, tumor response was not homogeneous in different mouse strains (Maltoni et al. 1989).

In mice, increased rates of malignant lymphomas were seen; however, only few data existed which described the induction of myelogenous leukemia. An increased rate of leukemia without specification of the predominant cell type were found in long-term treated RF/J mice (Maltoni et al. 1989).
Some of the mice studies also demonstrated leukemia of granulocytic cell lineage. However, these studies positive for myelogenous/granulocytic leukemia revealed no significance of tumor response (Goldstein et al. 1982) or positive findings were not reproducible (Cronkite et. al. 1989; Farris et al. 1993). Even, lower rates of myelogenous leukemia were seen after benzene treatment (Cronkite et al. 1984, 1985).

In contrast to the benzene induced lymphomas in mice, no clear effect on the rate of lymphomas were observed in long term studies in the rat. Oral administration for 2 years induced no increased incidence of tumors of the lymphatic system in Fischer 344 rats (NTP 1986), and noincreased incidences in lymphomas in Sprague-Dawley and Wistar rats in the poorly documented Maltoni study (Maltoni et al. 1989).

In rats, increased frequencies of leukemia in comparison to controls were found in benzene-exposed Sprague-Dawley rats and Wistar rats of the Maltoni study (Maltoni et al. 1989) and in a rat study on the metabolite hydroquinone (Kari et al. 1992). Additionally, one case out of 40 animals of chronic myelogenous leukemia was reported in Sprague-Dawley rats exposed to benzene (Goldstein et al. 1982).

Oral cancer studies showed increased tumor rates in multiple organs, some of which were also tumor sites in the inhalation studies. The majority of tumor types at other sites than the haematopoietic system are of epithelial origin. In mice of several strains, benzene produced increased tumor incidences in Zymbal gland, (Snyder et al. 1988; Cronkite et al. 1984; 1985; Farris et al. 1993; NTP 1986; Maltoni et al. 1989), lung (Snyder et al. 1988; Farris et al. 1993; NTP 1986; Maltoni et al. 1989), Harderian gland (NTP 1986), preputial gland (Farris et al. 1993; NTP 1986), forestomach (Farris et al. 1993; NTP 1996), mammary gland (NTP 1986; Maltoni et al. 1989) and liver (Maltoni et al. 1989). A treatment-related tumor response was also found in the ovaries (Cronkite et al. 1984, 1985; NTP 1986).

Some of the organs were positive in mice and in rats. In rats, benzene treatment was associated to increased tumor incidences in the Zymbal gland (NTP 1986; Maltoni et al. 1989), oral cavity (NTP 1986; Maltoni et al. 1989), forestomach (Maltoni et al. 1989), nasal cavity (Maltoni et al. 1989), and skin (NTP 1986; Maltoni et al. 1989).

4.1.2.8.2. Carcinogenicity / Human data

Summary

There is sufficient scientific evidence to assume a causal relationship between high levels of cumulative benzene exposure and 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 (e.g. Rinsky et al. (1981) analyzing the data from the Pliofilm cohort) concluded that the leukaemia risk is increased at relatively low levels of benzene exposure (only slightly above some legal standards). 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) recent analyses assume a negligibly increased mortality attributable to benzene if the average exposure is <1 ppm over 40 years. These studies suggest the existence of a threshold level. However, the existing epidemiological data do not allow to establish such a threshold exposure level. If the exposure estimates are accepted, the statistical model sufficiently explains the data of the Pliofilm study with revised i.e. increased exposure estimates. The results, however, cannot be generalized. Additional large-scale studies are necessary to corroborate the results and conclusions. Improved methods of estimating individual benzene exposures retrospectively and of obtaining information on potential confounders would be helpful. A major disadvantage of most previous studies is the problem of non-differential misclassification which reduces any exposure-disease-association. No estimates of the magnitude of the effect of such a misclassification are available.

<u>Human epidemiological data</u>

Ott et al. (1978) performed a historical cohort study (Michigan Division Dow Chemical) on 594 individuals. In the total study sample, significantly more cases (n = 3) of acute non-lymphatic leukaemia (ANLL) were observed as compared to 0.8 expected cases (p = 0.047). However, if individuals who had been exposed to other chemicals (e.g. arsenic, asbestos) were excluded from the calculation of the Standardized Mortality Ratios (SMR) seems to be unclear; neither the total mortality nor the disease-specific mortality were increased.

The study, however, suffers from a small sample size. Furthermore the validity of the estimates for benzene exposure is debatable, the variability of the exposure measurements is very high. The average exposure is estimated by using the mean instead of the more adequate use of exposure categories or the median. Potential confounders (e.g. smoking, social class) were not considered.

Rushton and Alderson (1981) performed a historical cohort study (employees in 8 oil refineries in Great Britain) on 34 708 individuals. In this study, the SMR was not significantly increased for the leukaemia, but for malignant melanoma, and for cancers of the nasal and sinusoidal mucosa, in a few plants also for intestinal carcinomas. The SMR was adjusted for

regional differences in mortality in the general population of the same age in order to adjust for socioeconomic characteristics.
The SMR for lung cancer was significantly lower. This is probably due to the fact that a lower proportion of the study population were smokers compared to the general population.

The study, however, did not use specific estimates for benzene. Furthermore, a negative confounding effect by smoking cannot be ruled out. If smoking would increase the risk of leukaemia this would have resulted in an underestimation of the SMR for leukemia in this study. (There is some evidence that smoking increases the risk of leukaemia. However, this issue is still controversial). The study tried to adjust for social class (by using regional mortality rates). However, it is very likely that this adjustment has been incomplete. The increased SMR for several types of cancer may be due to residual confounding by social class.

Rinsky et al. (1981) performed a historical cohort study on 748 individuals with the inclusion criterion: Exposure to benzene for at least one day. The study sample is the Pliofilm cohort (employees in the rubber industry in Ohio). There have been 7 leukaemia deaths (all ANLL) with a SMR = 560 ($p < 0.001$). Among individuals who had been exposed ≥5 years, the SMR was 2100.
The leukaemia risk attributable to benzene would have been even higher if only individuals would have been included who had been exposed for much longer than one day.
In this study the methods of the exposure estimation are described in much detail. The authors conclude that benzene is carcinogenic with respect to ANLL with the risk already increased „at a range of benzene exposures not greatly above the current US-legal standard“ (at that time 10 ppm 8-hour time-weighted average (TWA)).

Much effort was put into the exposure estimates. They are based on job matrixes for each individual employee and repeated measurements (surveillance) in areas according to the different jobs. However, benzene concentrations were not measured systematically and regularly. Although the authors tried to estimate exposure meticulously non-differential misclassification of the exposure could not be avoided. For some job areas the average exposure was estimated by extrapolating the benzene concentration from one measurement over several years. The Pliofilm cohort has the big advantage that exposure to other chemicals (and the resulting potential confounding effects) can be neglected. It was not possible, however, to consider other potential confounders such as smoking or social class, because no information on these variables was available.
Other authors (Crump 1994, Paustenbach et al. 1992), Paxton et al. 1994a,b) have re-analyzed the data and concluded that Rinsky et al. (1981) had substantially underestimated the benzene exposure. This would have resulted in an overestimation of the risk of leukaemia at low levels of exposure. Rinsky et al. (1981) reviewed the new exposure estimates, and did not revise their own estimates substantially.
The study suffers from a relatively small sample size but benefits from a long follow-up.

In 1987, Rinsky et al. (1987) published a study with longer-follow up and extended data analysis of the Pliofilm cohort including 1 165 individuals. In this study, 9 observed cases of leukaemia deaths (non-lymphatic) with a SMR of 337 (95% confidence interval (CI) 154 - 641) and 4 observed cases of Multiple Myeloma with a SMR of 409 (95% CI 110 - 1047) were described.
The SMR for leukaemia increases significantly with the (cumulative) benzene exposure. This result remains unaltered if the exposure is classified differently.

The nested case-control study comprises 10 controls per case (death) of leukaemia matched for age and start of employment (exposure). The data were analyzed by conditional logistic regression. The model with the best fit (cumulative benzene exposure is the exposure variable) gives the following dose-effect-relationship: Odds Ratio (for leukaemia) = exp(0.0126 x ppm-years); the model using the exposure variable as a quadratic term resulted in a worse fit.
If the model used reflects the true relationship, the risk of leukaemia would increase by a factor of 154 at an average exposure of 10 ppm over 40 years, and by a factor of 1.7 at an average exposure of 1 ppm over 40 years. An exposure of 0.1 ppm would not be associated with an increased risk of leukaemia.

The model assumes, however, that the cumulative exposure is the product of the duration of the exposure and the average exposure rates. It does not take into account the possibility that very high exposures over a short time may have the strongest carcinogenic effect and not the cumulative exposure.
The authors assume that they underestimated rather than overestimated the exposure. This seems plausible because the benzene measurements may have been carried out predominantly in problem areas with putative high benzene concentrations.
In this study, potential confounders were not considered.

A historical cohort study was performed by Paci et al. (1988, shoeworkers in Florence, Italy, dates of exposure 1953-1964). The SMR for all leukaemia (6 cases) was 400 (95% CI 150-870). The SMR does not increase by duration of exposure. The authors, however, gave no information on the sample size. Furthermore, the validity of exposure estimates is questionable (e.g. based on estimates of the numbers of shoes produced, of the amount of glue, of the air circulation).
No information is given on the types of leukaemia. Confounders are not considered.
The historical cohort study (multicentre study in China) by Yin et al. (1989) shows the highest number of benzene-exposed individuals (28 460) and non-exposed controls (28 257). The SMR for all leukaemia was 574 (23 out of 30 observed leukaemia deaths in the exposed cohort were ANLL cases); the SMR for lung cancer was 231. The SMR for leukaemia increased significantly with the duration of exposure up to a duration of 15 years, and decreased again for longer durations. A few leukaemia deaths were also observed among employees with relatively low average exposures (6-10 ppm) and ≤50 ppm cumulative exposure. In the exposed cohort a much higher proportion of the total cases of leukaemia were ANLL cases compared to the leukaemia cases in the general population. No association was found between smoking and risk of leukaemia.

Unfortunately, no detailed information is given on the methods of the exposure estimates. The comparison of the benzene exposure (average and cumulative) between leukaemia cases and the rest of the exposed sample is missing. Data on smoking were obtained, their validity is not clear, however. Other potential confounders (e.g. exposure to other chemicals) were not considered.

The historical cohort study by Hurley et al. (1991) was performed on 6520 workers in coke works or coke departments in Great Britain. With the exposure being low in the majority of the study participants, the SMR was not increased (5 leukaemia deaths observed). Exposures are only partially based on direct measurements, therefore, it remains unclear how the exposures were estimated. Confounders were not considered.

Cox and Ricci (1992) published a mathematical modeling (Maximum-Likelihood procedures) of the dose-effect-relationship between benzene exposure and leukaemia based on data from animal experiments. A non-linear relationship for low exposures was found. However, it is questionable whether the models can be generalized to humans.

In the historical cohort study by Rushton (1993) 23306 employees in oil distribution centers in Great Britain were described. The SMR for leukaemia was increased among the employees of one company, and among drivers. The SMR for lung cancer was decreased. (This means that members of the cohort were less likely to smoke than the general population.).

Data on individual exposure, however, were not available or were not considered. As in the previous studies potential confounding effects by other variables cannot be ruled out. The reasons for the increased leukaemia risk among the drivers and the employees of one company are unclear. It is possible that the increased SMR for leukaemia in the drivers is due to their exposure to higher levels of benzene. Alternative explanations (e.g. confounding), however, cannot be ruled out.
Schnatter et al. (1993) performed a historical cohort study on 6 672 employees in the petroleum marketing and distribution industry in Canada. No significant association between benzene exposure and leukaemia was found except for the subgroup of tank truck drivers (SMR 335; 5 leukaemia deaths). This corroborates the findings by Rushton (1993). In the statistical modeling (Poisson regression), there was no association between leukaemia and the duration of employment. In this analysis, the variables socioeconomic status, and the year of the beginning of employment were included as potential confounders. In this study the benzene exposure, however, was not estimated accurately. Exposures were classified by industrial hygienists according to three (relatively crude) categories: not exposed, exposed less than daily, exposed daily. Complete data on all jobs were available only from about 50% of the employees. In some individuals, the information on the last job had to be extrapolated to the total time of employment. Thus, non-differential misclassification of the exposure is likely to be a problem. This would result in an underestimation of the true association between exposure and disease. Unfortunately no information on the benzene exposure among the drivers is provided. The authors being cautious in possible conclusions regard the study as hypothesis generating rather than hypothesis testing.

Crump (1994) again analyses the data of the Pliofilm cohort with a follow-up until 1987.

The study confirms the strong association between benzene exposure and leukaemia and the pronounced dose-response-effect. The exposure estimates are based on the paper by Paustenbach et al. (1992), whose estimates were substantially higher than those by Rinsky et al. (1987). The dose-response-effects were modeled applying maximum-likelihood methods. The model had its best fit if a quadratic dose-response-association is assumed. In this model the exposure intensity had more weight than the duration of the exposure. Assuming the model reflects reality, the additional benzene-attributable leukaemia mortality for an average exposure of 1 ppm over 45 years would be 0.02 to 0.036 per thousand exposed individuals. In the previous models with linear dose-response-associations used by Rinsky et al. (1987) the additional mortality attributable to benzene was estimated at 1.6 to 3.1 per thousand exposed individuals.
As a general rule, however, the quality of the statistical model depends on the quality of the data used. The data on benzene exposure are based on estimates the validity of which is unclear because they rely on historical measurements which cannot be repeated by better methods. It remains questionable if the more recent exposure estimates for the Pliofilm cohort

are more valid than the previous estimates by Rinsky et al. (1987). The model published by Crump (1994) may best describe the data he analyses. However, the results of this single cohort (on which different exposure estimates exist) cannot be generalized without having been confirmed in other study populations. Based on these results the hypothesis may be generated that a quadratic dose-response-relationship exists and that the risk of leukaemia from low levels of exposure may be lower as previously thought. This hypothesis appears to be biologically plausible as well. However, the results have to be confirmed by other studies among cohorts with low exposure. At present the data do not allow to draw general conclusions.

Paxton et al. (1994a), using the Pliofilm cohort with a follow-up until 1987 with 1 212 benzene-exposed employees presents the three different exposure estimates published by Rinsky, Crump/Allen, and Paustenbach. The estimates of the latter two groups are substantially higher than the one by Rinsky (due to consideration of cutaneous exposure, changes in work-time per week etc.): They are 3 to 5 times higher in the cases (deaths) of leukaemia, and 2 to 4 times higher for the individuals without leukaemia. There is a significant increase in the dose-response-curve for all three exposure estimates.
The figure on the distribution of the leukaemia deaths according to exposure dose shows that the cases (except for two cases in the Rinsky paper) occurred at cumulative exposures >1 ppm-years, and in their majority at cumulative exposures >10 ppm-years.

The more recent exposure estimates, however, were re-critised by Utterback and Rinsky (1995) (e.g. overrating of the cutaneous exposure), who hardly modified their original estimates. The conclusions of Paxton et al. imply that there exists a threshold exposure level of 50 ppm-years. The data do not provide enough evidence for such an assumption. They support the hypothesis that exposures >50 ppm-years result in a significant increase in the leukaemia risk. However, from this finding it cannot be concluded that exposures <50 do not increase the risk at all. A hypothesis could be derived which would have to be tested in further studies. If the exposure estimates by Crump (1994) and Paustenbach et al. (1992) are used, the SMRs for the exposure category >5 to 50 ppm-years is 330 (Crump) and 180 (Paustenbach), being statistically significant when based on a larger sample size.
The authors acknowledge this possibility of a lack of power in the study.

In addition, Paxton et al. (1994b) performed a statistical modeling of the extended Pliofilm data (follow-up until 1987) using proportional hazards models (applying the same matching criteria as in the nested case-control study by Rinsky et al. 1987).
This paper seems to use the adequate statistical method. However, the quality of the statistical analysis again strongly depends on the quality of the data being available.
Thus the best estimate of the dose-response-relationship arrives at 0.3 to 0.5 additional leukaemia deaths attributable to benzene per 1000 individuals with 45 ppm-years of cumulative benzene exposure.

In 1995, Wong and Rabe performed a meta-analysis calculating the leukemia risk among petroleum workers (i.e. individuals with low average exposure) based on 19 different cohorts which implies all the problems of an observational study. No a priori inclusion criteria have been defined which would give information on the quality of the different studies. In particular, no information is given which would allow to qualify the methods used to estimate exposure levels in the different studies which is the basis to calculate the mean exposure level. In some studies the exposed and the non-exposed individuals were combined (as exposed) thus diluting a possible benzene effect. The SMR for ANLL was 0.96 with SMR as

controls. It is not clear whether this control is appropriate. Unfortunately, this point has not been taken up and clarified in the discussion. The 95%-confidence interval is calculated assuming homogenicity of the studies which is rather unlikely. It is not discussed whether the 99%-confidence interval would be more appropriate as the problem is not to prove an effect but to disprove it. Due to such limitations the results of the meta-analysis have to be interpreted wisth caution. If heterogenicity of the data had been taken into account and 99%-confidence instead of 95%-confidence had been calculated much wider confidence limits for the numbers of cases than those given in the paper of Wong and Rabe (1995) would have resulted.

Ireland et al. (1995) performed a historical cohort study (large chemical plant with low to medium exposure, Illinois, USA) on 4 091 individuals. The SMR (all leukaemia) for employees with benzene exposure was 230 (95% CI 70-940), the SMR (ANLL only) was 270 (95% CI 30-1000). Using only 666 exposed individuals the sample size was small and the validity of the exposure estimates remains doubtful (no detailed data on exposure are provided). In addition no potential confounders were considered.

Rushton and Romaniuk (1995) performed a nested case-control study in employees in petroleum marketing and distribution workers in Great Britain (with mostly low levels of exposure). 91 leukaemia cases (32 ANLL cases) were reported with 4 controls matched to each case. The Odds Ratio (ANLL) was 2.8 (95% CI 0.8-9.4) for 4.5-45 ppm-years cumulative exposure compared to the group with a cumulative exposure <4.5 ppm-years. This is statistically not significant. However, a significant association was found between short-term exposure to high concentrations of benzene. The SMR for leukaemia was increased for the subgroup of drivers (all leukaemia 125, ANLL 155), albeit not significantly.
The cases of leukaemia, however, in some of the exposure categories were small. This results in a wide confidence interval and a poor fit of the regressions models. The results are not consistent when benzene exposure is used as an categorical or as a quantitative variable.
In the study, data on the potential confounder smoking were collected. However, they are obviously incomplete or were not presented in sufficient detail. The association between benzene exposure and leukaemia is likely to have been underestimated due to non-differential misclassification of the exposure.

The nested case-control study in petroleum distribution workers in Canada by Schnatter et al. (1996) is based on 14 leukaemia deaths and 4 matched controls for each case. No significant association was found between the cumulative benzene exposure and leukemia, non-Hodgkin lymphoma or multiple myeloma. The exposure levels were estimated by industrial hygienists from company records etc. Non-differential misclassification, however, of the exposure and of the potential confounder smoking is likely. The data on smoking was obtained from the employees' company medical records only.
The study has limited power due to the relatively small sample size.

Hayes et al. (1997) recently finished an epidemiological study, in which he adressed the relationship between the extent of benzene exposure and the level of risk.
A cohort of 74 828 benzene exposed and 35 805 unexposed workers employed from 1972 trough 1987 in 632 factories in 12 cities in China was identified and followed up to determined the incidence of haematological neoplasms and related disorders. Estimates of benzene exposure were derived from work histories and available historic benzene measurements. The large number of workers, factories and cities provides a high diversity of environmental scenarios. For workers historically exposed to benzene at average levels of less

than 10 ppm the RR for haematological neoplasms combined was 2.2 (95% confidence intervall (CI)=1.1-4.2), and, for the combination of acute nonlymphatic leukaemia (ANLL) and related myelodysplastic syndromes (MDS), the RR was 3.2 (95% CI=1.0-10.1). For individuals who were occupationally exposed to benzene at constant levels of 25 ppm or more, the RR for the combination of acute nonlymphatic leukaemia and related myelodysplastic syndrom was 7.1 (95% CI=2,1-23.7). Workers with 10 or more years of benzene exposure had an RR of developing non-Hodgkin´s lymphoma of 4.2 (95% CI=1.1-15.9), and the development of this neoplasm was linked most strongly to exposure that had occured at least 10 years before diagnosis. The findings suggest, that recent benzene exposure is predictive of subsequent risk for ANLL/MDS. In contrast, recent exposure was only weakly linked to non-Hodgkin's lymphoma.

In Australia, a large prospective cohort study investigates the health from employees in the petroleum industry (Health Watch, 2000). In this study 17525, working 5 years or longer in the industry are involved. The study revealed a statistically significant increase in the incidence of all leukemias combined. The risk is associated with exposure to total hydrocarbons. The relation between lympho-haematopoietic cancer and exposure to benzene was subject of a subsequent nested case-control study (Monash University, 2001). The case-control study included 79 cases of lympho-haematopoietic cancers, 33 leukemias, 31 non-Hodgkin's lymphomas, and 15 multiple myelomas. The leukemias consisted of 9 AML, 6 CML, 2 ALL, 11 CLL, and 5 other types. Individual exposure estimates were established based on 18 different job-groups. The exposure estimates in this study are probably of high reliability since they are based on more actual measurements than previous occupational studies on the leukomogenic action of benzene. Relations between cancers and various types of exposure metrics were established (cumulative exposure, exposure duration, exposure intensity, start date of exposure, influence of "peak" exposures). Lifetime cumulative exposures were low for the majority of subjects (0.005 – 57.3 ppm-years, mean 4.9 ppm-years). Nearly 85% of the subjects had an exposure < 10 ppm-years while only 3.6% had an exposure > 40 ppm-years. Average exposure intensity was less than 1 ppm for 98% of the individuals (range 0.001 to 2.07 ppm). The total incidence of lympho-haematopoietic cancers was strongly associated with total benzene exposure. The exposure group ≥ 8 ppm-years had a mean OR of 3.32. The strongest association was found with exposure between 5 to 15 years prior to diagnosis. Recent exposure within 5 years made only a small contribution. There was no association with the duration of employment nor with the starting date of employment. A very strong association was found for leukemias alone, at exposure ≥ 16 ppm-years an OR was found of about 35. No association was found with employment duration and start period of employment. A strong association was observed for leukemia subtypes AML (or ANLL) and CLL. No associations were found for chronic myeloid leukemia or other leukemia types (nor NHL and multiple myeloma) (Monash University, 2001).

Conclusion: Classification and labelling

Based on the sufficient weight of evidence of carcinogenicity in epidemiological studies and of supporting data from studies in experimental animals, benzene is considered to be carcinogenic to humans.

According to the EEC-criteria for classification and labeling of dangerous substances benzene is already classified as „carcinogen, category 1“ and labeled „T, R 45, May cause cancer“. This classification and labelling is confirmed.

4.1.2.9 Toxicity for reproduction

Fertility impairment

Animal data:
There is one inhalation fertility study on female rats available conducted by Bio/dynamics for the American Petroleum Institute and the Chemical Manufacturers Association, data of which were published by Kuna et al. (1992). In this study, female Sprague-Dawley rats were exposed to dose levels of 1, 10, 30, and 300 ppm (~ 3.3, 32.5, 97 and 974 mg/m³) benzene (6 h/day, 5 d/week) during premating and mating (10 weeks), gestation and lactation periods up to p.n. day 21. Five groups of 26 females and 13 proven fertile males were used. Animals were housed two per cage during the first week and individually during week 2. In the premating period they were individually caged during exposure and nonexposure periods. For mating, one male and two females were housed per cage. Females were housed individually during gestation, parturition and, and with litter during lactation. Chamber exposures for all study group females were conducted 6 h/day, 5 Days/week during a 10 week premating and mating period and daily from days 0 to 20 of gestation and days 5 to 20 of lactation. To determine if estrous was affected by treatment, daily vaginal smears were made and evaluated for each female beginning 2 weeks prior to initiation of mating. Observations of females for mortality and gross clinical signs were made twice daily. Detailed physical examinations were performed weekly throughout the study. Body weights were recorded once weekly through completion of the mating period. Mated females were weighed on days 0, 7, 14, and 21 of gestation and on days 0, 4, 14, and 21 of lactation. Pups were counted, weighed, and sexed on days 0, 4, 14, and 21 of lactation. Litters were observed twice daily. On day 4 of lactation, litters of more than 10 pups were randomly culled to 10 with equal number per gender where possible. Pups that died were weighed and sexed by internal examination. All dams were given a gross postmortem examination. Uteri were examined for the presence and number of implantation sites, and along with ovaries, were fixed in 10 % neutral buffered formalin and saved. Gross postmortem examinations, including internal gender determinations were performed on all pups sacrificed on day 21 of lactation and on pups found dead during lactation. The latter were also checked for the presence or absence of milk in the stomach. Liver, kidney, and in males, testes weights were recorded for each pup. Thirty-three organs and tissues along with any abnormal lesions were fixed in 10 % neutral buffered formalin from two pups per sex per litter and saved for future histopathological examination. Pups found dead prior to day 4 of lactation were preserved in 70 % ethanol.

Including the highest dose level of 300 ppm there were no effects on maternal body weight and body weight gain nor were there adverse effects on fertility as measured by percentage pregnant animals, mean gestational length, number of litters, litter size, and viability of the pups and the weanlings. A trend towards reduced mean offspring body weights during the lactation period and towards reduced mean organ weights (testes, liver, kidney) on postnatal day 21 was observed at the 30 and 300 ppm level. Except for a single data point (reduced liver weight in female pups at 300 ppm) these differences were not statistically significantly

different from corresponding control values. No treatment related effects were seen in pup survival data during lactation or at gross postmortem evaluations of these pups on postnatal day 21.

Gofmekler (1968) exposed female rats continuously to six concentrations of benzene ranging from about 1 to 670 mg/m³ (0.3 to 210 ppm) for 10 - 15 days before cohabitation with males and 3 weeks after cohabitation (gestation). A complete absence of litters was observed in female rats exposed to 210 ppm, but not at the lower exposure levels of 3 to 20 ppm. Whereas differences in individual organ weights of the dams were indicated for all exposure levels, any impairment of the newborn weight or the induction of malformations was not reported. It is not known whether observations made at the 210 ppm level were due to failure to mate, infertility, or early preimplantation losses of fertilized ova. Due to these imponderabilities and due to the very poor documentation the study is not considered valid for hazard assessment purposes.

Information relevant to possible reproductive organ toxicity can be obtained from subchronic inhalation studies (c.f.chapter 4.1.2.6). Groups of 150 CD-1 mice/sex and of 50 Sprague-Dawley rats/sex were exposed to 1, 10, 30, and 300 ppm (~ 3.3, 32.5, 97 and 974 mg/m³) benzene (>99.9% purity) vapors (whole chamber exposure; 6 h/day, 5 d/week) for 13 weeks (Ward et al. 1985). Additional groups of mice and rats of equal size were exposed under similar conditions to filtered air and served as control groups. All animals were observed twice daily, before and after exposure and on nonexposure days, for mortality and moribundity throughout the study. At weekly intervals animals were observed for signs of toxicity, weighed and individual body weights recorded. On study days 7, 14, 28, 56, and 91, blood samples were taken from randomly selected 10 rats/sex/group and 20 mice/sex/group for full range hematological and clinical chemistry examinations. Blood was collected for clinical pathology analyses from an additional 10 rats and 30 mice one day prior to the start of the study. For interim sacrifice on days 7, 14, 28, 56, and for terminal sacrifice on day 91, ten rats/sex/group and 20 mice/sex/group were randomly selected and killed. Complete necropsies were performed on all these animals and on animals found dead or sacrificed in a moribund condition during the study. With respect to reproductive organs, from each animal that was necropsied at each interval absolute testes weight and testes/terminal body weight ratios were determined. Amongst others, the following tissues from each animal necropsied at each sacrifice interval was taken and fixed: testes or ovaries, prostate or uterus, and mammary gland. Sections from the control and high-level groups of both species at each sacrifice period were subject to histopathological examinations. For the mice species, testes and ovaries of all animals at all exposure levels at the 91-day terminal sacrifice were examined microscopically. It is reported that there were no consistent exposure-related apparent trends in clinical observations or mean body weight data in either species (no data provided). In mice, at 300 ppm hematology changes occurred, consisting of decreases in red blood cell counts, white blood cell counts, platelets, hemoglobin, myeloid/erythroid ratios and hematocrit. Also femoral myeloid hypoplasia, extramedullary hematopoiesis in the spleen and thymic atrophy were reported to be seen. With respect to reproductive organs a statistically significant and exposure-time related decrease in absolute mean testes weights at sacrifices on days 28, 56, and 91 as well as in relative mean testes weights at sacrifices on days 59 and 91 was revealed at the 300 ppm level (data not provided). At the same dose level histomorphologic changes in reproductive organs were reported in the male mice at the 91 day-interval (7 mice with minimal to moderately severe bilateral atrophy/degeneration, 6 mice with moderate to moderately severe decrease in spermatozoa, 9 mice with minimal to moderate increase in abnormal sperm forms) but not in those sacrificed at the earlier intervals. For females of the

300 ppm concentration group bilateral ovarian cysts were reported to have been detected in four mice. Similar lesions were reported to be observed in both sexes also at lower dose levels (data not provided), which by the authors themselves were considered of doubtful biological significance. Because of this estimation of the authors it is assumed that the findings at the lower concentration levels did not represent any significant changes from the controls. The reported findings for mice at the 300 ppm benzene concentration level, however, are difficult to interpret, since testes weight data and numerical incidences on histomorphological changes are not provided from the study. Also, no data on the performance of the control animals are given during the study. For rats no such testicular or ovarian changes were reported from this study.
In a further, however poorly documented study (Wolf et al. 1956) on various laboratory species with intermittent inhalatory benzene exposure (whole chamber exposure; 7 to 8 h/day, 5 d/week) it is reported that groups of 10 to 25 male rats (presumably Wistar) were exposed to 6600 ppm for 93 days, groups of 5 to 10 male guinea pigs (strain not specified) were exposed to 88 ppm for 269 days, and groups of 1 to 2 male rabbits (strain not specified) were exposed to 80 ppm for 243 days. Slight to moderate impairment of testes weight in rats and guinea pigs (date not provided), respectively testes histopathology in rabbits (not further specified) were reported for these conditions which concomitantly led to systemic toxic effects characterised by leucopenia, increase in average weight of the spleen and histopathological changes in the bone marrow (not further specified). No numerical data and no information on the performance of controls are provided from this study. Due to these imponderabilities and due to the very poor documentation the study is not considered valid for hazard assessment purposes.
From an insufficiently documented gavage study on male SHR mice (Feldt et al. 1985; abstract) it was reported that doses of benzene ranging from 0.001 to 0.2 LD50 administered during 5 weeks did not induce dominant lethal mutations.

Human data:
Data on the reproductive effects of occupational exposure to benzene may indicate a potential of benzene to impair fertility in women (Mukhametova and Vozovaya 1972; Vara and Kinnunen 1946; Michon 1965). However, the findings are inconclusive because the studies are limited.

In one study, 30 women with symptoms of benzene toxicity were examined (Vara and Kinnunen 1946). The women worked in an environment containing benzene, however, the levels of benzene in air were not specified, but were assumed to have been much greater than 1 ppm. Twelve of these women had menstrual disorders (profuse or scanty blood flow and dysmenorrhea). Leukopenia was reported in four women, and in the majority of the women the neutrophils and platelets were also reduced. Ten of the 12 women were married. Of these 10 women, 2 had spontaneous abortions, and no births occurred during their employment even though no contraceptive measures had been taken. This led the investigators to suggest that benzene has a detrimental effect on fertility at high levels of exposure. However, the study failed to provide verification that the absence of birth was due to infertility. Gynecological examinations revealed that the scanty menstruations of five of the patients were due to ovarian atrophy. This study is limited in that an appropriate comparison population was not identified. Additionally, little follow-up was conducted on the 30 women with regard to their continued work history and possible symptoms of benzene toxicity.

In another study (Michon 1965), disturbances of the menstrual cycle were found in female workers exposed to aromatic hydrocarbons (benzene, toluene, xylene). The exposure levels of benzene and toluene were below 0.25 ppm. The observed group consisted of 500 women, 20-40 years old. One hundred controls were included in the study. The results showed that 21% of exposed women whose work was involved in sitting or standing had irregular menstrual cycles compared to 12% in the control group. Brief (up to 2), long (6-9), and prolonged (over 9 days) menstrual cycles were present in 26% of women who performed lifting during their work as compared to 13% in the control group. Irregular amounts of menstrual flow and pain were also observed in female workers exposed to aromatic hydrocarbons. The major limitations of this study are that the exposure occurred from a mixture of chemicals, level of exposure were not well defined, duration of exposure was not stated, and activities of the controls were not provided.

Another study examined the reproductive function and incidence of gynecological effects in 360 female gluing operators exposed to petroleum (a major source of benzene) and chlorinated hydrocarbons both dermally and by inhalation (Muhametova and Vozovaya 1972). However, dermal exposure was considered to be negligible. The concentrations of benzene in the air were not well documented. When compared to female workers with no chemical exposure, there was no significant difference in fertility. However, female gluers had developed functional disturbances of the menstrual cycle. Additionally, as chemical exposure time increased, there were increases in the number of premature interruptions of pregnancy, the percentage of cases in which the membranes ruptured late, and the of cases of intrauterine asphyxia of the fetus. The study limitations (including lack of exposure history, simultaneous exposure to other substances, and lack of follow-up) make it difficult to assess the effects of benzene on reproduction.

There are no human data available on the reproductive effects of benzene in males.

Summary for fertility impairment

There are no human data on the reproductive effects of benzene in males. Evidence 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 and to other chemicals in the workplace. Therefore, hazard assessment with respect to fertility will be based on the available data from animal experiments. Aspects related to male and female fertility have been investigated in laboratory animals in studies of different quality and validity and with the inhalatory route of administration only. Available data from guideline according subchronic toxicity studies indicated that the mice species are more sensitive to benzene exposure than the rat species. With respect to possible effects on the organs of the reproductive system no effects for either sex had been observed in these studies with the rat species with concentration levels of up to and including 300 ppm (960 mg/m^3) benzene. Also, no effects on female reproductive capacity and capability were found for rats with concentration levels of up to and including 300 ppm (960 mg/m^3) benzene. In mice, however, the high benzene concentration level of 300 ppm (960 mg/m^3) during the subchronic toxicity study led to clear-cut hematotoxicity (anemia, leucopenia and thrombocytopenia) in both sexes. There were also 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).

From the available studies with repeated inhalatory exposure, the data of the study of Ward et al. (1985) should be used for derivation of a NOAEC for quantitative risk assessment, since

during this study organ weight determinations as well as histopathological evaluations had been performed for both sexes and at periods relevant for reproduction. Based on the effects observed in the mice species at the high benzene concentrations of 300 ppm (960 mg/m^3) benzene a NOAEC/reproductive organ toxicity of 30 ppm (96 mg/m^3) is derived and should be taken forward for quantitative risk assessment.
The available information from the study of Kuna et al. (1992) is not considered adequate for estimations to the overall potential of benzene for fertility impairment with respect to both sexes. Since in the rat female fertility study higher concentration levels (including systemically toxic concentration levels) had not been tested and in addition, since no data on functional testing for male reproductive performance have been generated in mice nor in rats sofar, there is currently no proposal on classification and labelling with respect to fertility.

Developmental toxicity

Animal data:
There are numerous inhalation studies in which animals have been exposed to benzene during pregnancy. None of these studies demonstrated a specific embryotoxic or teratogenic potential even at levels that induced signs of maternal toxicity. However, impairment of fetal development as evidenced by decreased body weights of the offspring and increased skeletal variants as well as delayed ossification were observed at levels often associated with maternal toxicity.

Animal studies with continuous inhalatory exposure

Tatrai et al. (1980) did not find significant skeletal malformations in pups of CFY rats continuously exposed (24 h/day) to benzene air concentrations of 150, 450, 1500, or 3000 mg/m³ (equivalent to about 50, 150, 500, or 1000 ppm) during day 7 to day 14 of gestation. Decreased mean fetal body weights, signs of skeletal retardation (i.e. delayed ossification) and evidence of maternal toxicity (decreased body weight gain, decreased mean placental weight) were observed at all dose levels. At the three higher concentration levels significant postimplantation fetal loss was revealed and an increasing trend in the incidence of skeletal variants.

Another study with continuous inhalatory exposure (24 h/day) to 500 or 1000 mg benzene/m³ (equivalent to about 155 and 310 ppm) to CFLP mice during day 6 to day 15 of gestation resulted in an increase of the ratio of weight retarded and skeletal retarded fetuses as well as in an increased ratio of absorbed or dead fetuses at both concentration levels (Ungvary and Tatrai 1985). Adverse effects on the dams were not indicated. NZ rabbits exposed to the same concentrations during day 7 to day 20 of gestation gave no evidence of developmental toxicity at the lower concentration level of 500 mg/m³. At 1000 mg/m³, there were statistically significant decreases in maternal weight gain, mean fetal body weights and an increase in the number of abortions as well as increased ratios for dead or absorbed fetuses and for minor abnormalities.

Animal studies with intermittent inhalatory exposure

In an experiment conducted by Green et al. (1978) pregnant Sprague-Dawley rats (numbers per group not specified, 15 to 18 litters evaluated) were exposed to 100, 300, and 2200 ppm (~ 325, 974 and 7143 mg/m³) benzene (6 h/day) during day 6 to day 15 of gestation. Three control groups (numbers per group not specified, 14 to 16 litters evaluated) were exposed under identical chamber conditions to filtered air. Maternal body weights were recorded daily. At sacrifice on day 21 of gestation fetuses were examined for externally visible abnormalities, sexed, weighed and crown-rump length determined and further processed for examinations for visceral and skeletal abnormalities. Maternal weight gain was equivalent between controls and the 100 ppm and 300 ppm experimental groups. A significant depression in maternal mean body weight gain was observed in the 2200 ppm exposure group, which was apparent after only two exposures and continued until term. The dams of this group became lethargic but not anaesthetised while in the chamber, whereas the dams exposed to 100 ppm and 300 ppm showed no such effects. Implantation sites/litter, live fetuses/litter, percentage absorptions/implantation sites, percentage of litters with absorptions, and number of litters totally absorbed were comparable between controls and exposed groups even at the high concentration level of 2200 ppm. Mean fetal body weight was similar to controls at concentrations of 100 and 300 ppm, but was statistically significantly reduced (to 4.5 + 0.3 g) at the highest concentration in comparison to the control (5.0 $\pm$ 0.1 g). Mean fetal crown-rump length was similar to controls at concentrations of 100 and 300 ppm, but was statistically significantly reduced at the highest concentration (to 3.8 $\pm$ 0.2 cm) in comparison to the control (4.0 $\pm$ 0.1 cm). Skeletal examination revealed a delay in the ossification of sternebrae, however, with similar litter incidences between the treated groups and their according controls. A statistically significantly increased litter incidence of so-called missing sternebrae (mostly related to the fifth sternebrae, which is the last to be ossified and therefore not yet visible) was reported for the 100 and 2200 ppm exposure groups when compared to their control groups, however not for the intermediate 300 ppm group. Based on the finding of a reduction of maternal weight gain from day 8 until term a LOAEC maternal toxicity of 2200 ppm and a NOAEC maternal toxicity of 300 ppm can be derived from this study. Based on the findings of fetal growth retardation (indicated from fetal body weight/fetal length reduction and ossification delay) a LOAEC developmental toxicity of 2200 ppm and a NOAEC developmental toxicity of 300 ppm can be derived from this study.

In a study conducted by Kuna and Kapp (1981) groups of 18, 20, and 19 inseminated female Sprague-Dawley rats were exposed (whole chamber; 7h/day) to nominal benzene concentrations of 10, 50, and 500 ppm (~ 32.5, 162 and 1624 mg/m³) for 10 consecutive days (day 6 to day 15 of gestation). Animals of the control group (n=17) were similarly exposed to filtered room air. At gestation day 5 and just prior to sacrifice venous blood samples were taken from each female and erythrocyte, total leukocyte, and differential leukocyte counts were determined. At sacrifice on day 20 of gestation the following observations were recorded for each litter: number of ovarian corpora lutea, number of resorption sites, number of live and dead fetuses. Fetuses were examined for externally visible abnormalities, sexed, weighed and crown-rump length determined and further examined for visceral and skeletal abnormalities.

No deaths, observable illness or signs of compound-induced toxicity were observed among females in any of the treatment groups. At necropsy, no abnormalities were observed that could be attributed to benzene exposure. No treatment-related differences were observed in any of the hematology parameters and all control and treatment group values were within normal limits. The pregnancy rates amounted to 64.7, 83.3, 75.0, and 73.7 % in the 0, 10, 50, and 500 ppm groups and were reported to range within the laboratory historical control

values. Mean maternal weight gain during days 0-5 (preexposure period) was similar across groups. Mean maternal body weights at day 15 were statistically significantly different from that of the controls (298 ± 23 g) in the 50 ppm (290 ± 25 g) and 500 ppm (278 ± 19 g) groups and further revealed about 30 % less maternal weight gain during days 5-15 (exposure period) in the 50 ppm (39 ± 13 g) and 500 ppm (37 ± 21 g) groups in comparison to the controls (59 ± 17 g). The implantation efficiencies (number of implantation sites/number of ovarian corpora lutea) were comparable among treated groups and the control. Incidences of absorptions and of fetal viability were comparable to those of controls for all exposure groups. A normal male/female sex distribution was observed in all groups. The mean crown-rump length of fetuses from the 500 ppm exposure level (3.8 ± 0.4 cm) was statistically significantly different from those of controls (4.1 + 0.2 cm). The mean body weights of the live fetuses from the 50 ppm level (3.8 + 0.7 g) and from the 500 ppm level (3.6 ± 0.8 g) were statistically significantly lower than those of the controls (4.4 ± 0.6 g). Fetal weights and lengths were comparable between the 10 ppm level and the control group. Statistically significant increases in the incidences of variant fetuses (mostly delayed ossification) were observed at the50 ppm level (23 out of 125 fetuses) and at the 500 ppm level (30 out of 142 fetuses) in comparison to the incidence in the control group (3 out of 110 fetuses). Based on the finding of a reduction of maternal weight gain during days 5-15 a LOAEC maternal toxicity of 50 ppm and a NOAEC maternal toxicity of 10 ppm can be derived from this study. Based on the findings of fetal growth retardation (indicated from fetal body weight/fetal length reduction and ossification delay) a LOAEC developmental toxicity of 50 ppm and a NOAEC developmental toxicity of 10 ppm can be derived from this study.

A further inhalation teratology study was conducted by Hazelton Laboratories for the American Petroleum Institute, the data of which were published by Coate et al. (1984). In this study groups of 40 inseminated female Sprague-Dawley rats were exposed to 1, 10, 40, and 100 ppm (~ 3.25, 32.5, 130 and 325 mg/m³) benzene by whole chamber exposure during day 6 to day 15 of gestation. During this period animals were exposed to benzene (technical grade) vapors generated in filtered room air for six hrs daily and remained in their chambers 24 hrs a day. Two control groups of 40 animals each were treated similar and exposed to filtered air only. Animals were observed daily on days 0-5 and 16-20. During days 6-15, they were observed prior to, once during, and after daily exposure periods. They were weighed and observed individually on days 0, 5, 8, 10, 16, and 20. At sacrifice on day 20 the following were recorded for each dam: number of corpora lutea per ovary, numbers/placements of uterine implantations, number of resorptions, and numbers of live and dead fetuses. Fetuses were weighed, measured, examined for gross external anomalies and subjected to examination for visceral and skeletal abnormalities.

There were no mortalities and no treatment-related clinical signs or gross pathology abnormalities in the dams. Also no significant changes in maternal body weight gain were observed. Pregnancy rates amounted to 80.0 and 85.0 % in the two control groups and to 92.5, 95.0, 92.5, and 87.5 % in the 1, 10, 40, and 100 ppm exposed groups. No maternal toxicity was noted in any of the groups. The average numbers of implantations, numbers of resorptions and resorption incidence, and the number of live fetuses were similar in all groups. Similarly, the incidence of dams with one or more resorbed implantations was comparable in all groups. As compared to the controls, a slight statistically significant decrease in average male and female fetal body weights was observed in litters of the 100 ppm groups. Also the mean body length of fetuses of this group was slightly smaller, although not statistically significantly different when compared to the controls. External, visceral and skeletal examinations did not reveal any treatment-related malformations. Soft tissue

examination did not reveal significant differences between controls and benzene-exposed litters with respect to average percentage of fetuses per litter with one or more soft tissue variations. Skeletal evaluation revealed a non-significant small delay in the ossification of sternebrae and caudal vertebrae in fetuses of the 100 ppm but not in the 40 ppm group litters. Based on the findings of a statistically significant reduction in mean fetal body weight of about 6 % correlated with a statistically non-significant reduced mean fetal body length and a statistically non-significant delay in skeletal ossification a LOAEC developmental toxicity of 100 ppm (320 mg/m^3) and a NOAEC developmental toxicity of 40 ppm (128 mg/m^3) can be derived. The NOAEL maternal toxicity from this study amounts to 100 ppm (320 mg/m^3).

In a further study (Murray et al. 1979) groups of 35 and 37 CF-1 mice were exposed (whole chamber; 7 h/day, g.d. 6-15) to either a single concentration level of 500 ppm (~ 1624 mg/m³) benzene (technical grade) or to filtered room air and groups of 20 New Zealand white rabbits were similarly exposed from days 6 through 18 of gestation to either filtered room air or to a single concentration level of 500 ppm benzene. The animals were observed daily from day 6 of gestation, and were weighed at several intervals during the experimental period. Food and water consumption were recorded during the experimental period at 3-day intervals for mice and at daily intervals for the rabbits. On days 18 and 29 of gestation, the mice and rabbits, respectively, were sacrificed. At sacrifice blood samples were taken from the rabbit fetuses of the control and benzene-exposed groups and from some additional bred mice and rabbits for hematological determinations (packed cell volume, percent hemoglobin, red blood cell counts, white blood cell counts). Hematological evaluations were not performed on mice fetuses. Further, the number and position of live, dead, and resorbed fetuses were noted. All fetuses were weighed, measured (crown-rump length), sexed, and examined for external alterations and cleft palate. Fetuses were then subjected to examination of visceral and skeletal alterations.
Exposure to 500 ppm benzene was reported to have no significant effects on the appearance of dams or does, their body weight or their body weight gain (data not given). Food and water intake (data not given) was increased for the benzene exposed rabbits but was unaffected in mice. Benzene exposure did not significantly affect the incidence of pregnancies in mice or rabbits. No significant effect on the average number of live fetuses or resorptions per litter was discerned in either species. Mean fetal body weight, but not crown-rump length, was decreased significantly among litters of mice exposed to benzene (0.95 $\pm$ 0.10 g) when compared to their controls (1.01 $\pm$ 0.09 g). In rabbits, fetal body measurements were not altered significantly by exposure to benzene. No malformations were observed in the offspring of mice and rabbits, however, increases in the occurrence of several minor skeletal variants including delayed ossification of sternebrae, skull bones and of unfused occipital bones of the skull were reported to be seen in litters of the benzene-exposed mice (data not given).

Table 4.29 Overview on studies with prenatal exposure to benzene by intermittent inhalation and indications for fetal growth retardation

species	benzene (ppm)	maternal ↓ body weight	fetal growth retardation ↓ body weight	↓ body length	↓ossification	Ref.
CF-1 mouse	500	-	+	-	+	Murray et al., 1979
N. Z. rabbit	500	-	-	-	-	Murray et al., 1979
SD rat	100 300 2200	- - +	- - +	- - +	+ - +	Green et al.; 1978
SD rat	10 50 500	- + +	- + +	- - +	- + +	Kuna and Kapp, 1981
SD rat	1 10 40 100	- - - -	- - - +	- - - (+)	- - - (+)	Coate et al., 1986

In an insufficiently documented gavage study with CD-1 mice (Nawrot and Staples, 1979; abstract) oral administration of 0.5 and 1.0 ml benzene/kg bw on days 6 to 15 of gestation resulted in a significant increase in maternal lethality and in embryonic absorptions; fetal body weight was significantly reduced at all dose levels (0.3, 0.5, and 1.0 ml/kg). Similar findings were obtained after shorter exposure to benzene (gestation days 12 to 15) at the 1.0 ml/kg dose level, but absorptions occurred later in gestation. No statistically significant benzene-related change was observed in the incidence of malformations at any dose level.

Other information

In addition to the animal studies related to investigations on toxic properties of benzene targeted to fertility and/or development, there are also animal studies available on the organtoxic properties of benzene targeted to the hematopoietic system, which, besides existing investigations in the adult animal were extended to investigations of the performance of this substance-specific toxicity in the developing organism. The bulk of available data on the toxicity of benzene to the hematopoietic system is presented in detail in chapter 4.1.2.6 (repeated dose toxicity). In this section, however, we only report data available from investigations on the hematotoxic properties of benzene studied in the developing organism at different stages.

In a study using Swiss-Webster mice (Keller and Snyder, 1988 and 1986) three independent experiments had been performed to collect either fetuses (at 16 days of gestation), neonates (of two days of age), or young offspring (of 6 weeks of age) for the investigation of benzene-

induced hematotoxic effects on either peripheral blood or on hemopoietic progenitor cells in the various hematopoietic organs, the latter either quantified from counts of cell differentials or from functional tests of colony formation. A basic treatment protocol was used for the different progeny produced with the three experiments by exposing pregnant females via inhalation (whole chamber, 6h/day) to benzene concentrations of 5, 10 or 20 ppm (~ 16, 32.5, or 65 mg/m³) for 10 consecutive days (from days 6 through 15 of gestation). Age-matched control progeny was obtained from sham-treated pregnant females exposed to filtered air. It is reported that $\leq$ 5 litters/age group per treatment were obtained. From the first as well as from the second experiment - fetal, respectively neonatal progeny - two male and two female offspring randomly selected from each litter were taken, decapitated and their trunk blood collected for samples of peripheral blood for the determinations of red and white blood cell counts, peripheral cell differentials and for hemoglobin analysis. From these specimen also their livers were taken and further processed for determination of cell differentials and for erythrocytic progenitor cell assays (BFU-E and CFU-E) and granulocytic progenitor cell assay (GM-CFU-C). From the third experiment (6 week old offspring) one male and one female offspring were randomly selected from each litter, samples of peripheral blood obtained from the tail vein and their spleens and bone marrow of the femurs taken and also processed for determination of cell differentials and for erythroid progenitor cell assays and granulocytic progenitor cell assay.

In the dams, however, no hematological investigations had been performed. Also, no data on any gestational parameters are provided from the three experiments, since investigating any embryo-/fetotoxic or teratogenic properties of benzene was not the focus of the study. However, it is reported (data not given) that for all benzene exposure concentrations there was no evidence of toxicity among dams as determined by maternal morbidity, mortality, or weight loss during exposures. Further it is reported for the fetal and neonatal progeny (data not given) that litter sizes, sex ratios, body weights as well as the numbers of dead, resorbed, or malformed fetuses were all within control limits.

Results from the peripheral blood cell indices (red blood cell count, mean corpuscular hemoglobin, nucleated cells/mm^3 and ratio of HbA major to HbA minor) did not reveal any significant differences between benzene-exposed and air-exposed progeny across the different stages of development.

Results from peripheral blood cell differentials (numbers of blasts, dividing/nondividing granulocytes, early/late and primitive nucleated red cells and lymphocytes determined from a total of 100 cells) did not reveal any significant differences between benzene-exposed and air-exposed groups for the early (16-day fetuses) and for the later (6-week old offspring) developmental stages. From the experiment performed on the neonatal stage, the benzene-exposed groups showed significantly less counts of erythroid precursor cells (early nucleated cells), and those neonates exposed *in utero* to benzene concentrations of 20 ppm also exhibited depressed numbers of late nucleated red cells and elevated numbers of granulocytic precursor cells (nondividing granulocytes).

A similar outcome was observed from the results of the cell differentials of the hemopoietic organs (numbers of blasts, dividing/nondividing granulocytes, early/late and primitive nucleated red cells and lymphocytes determined from a total of 500 cells in fetal and neonatal liver, respectively in femural bone marrow and spleen of 6-week old offspring). They did not reveal any significant differences between benzene-exposed and air-exposed groups for the early (16-day fetuses) developmental stages. However, from the experiments performed on

the neonatal stage, again the 20 ppm benzene *in utero* exposed groups showed significantly lower counts of late nucleated red cells and less counts of early nucleated red cells, whereas the numbers of blasts, dividing/nondividing granulocytes and lymphocytes were elevated. In the 6-week old offspring also for the 20 ppm in utero exposed group there were slightly higher numbers of blasts, dividing/nondividing granulocytes and lymphocytes in comparison to their age-matched controls.

The observed lower numbers of erythroid precursor cells (early nucleated cells) from *in utero* benzene-exposed neonatal offspring obviously did not have a negative effect on the circulating red cells in these animals as indicated from their normal cell counts in peripheral blood. Also, no changes in the HBA major/HbA minor ratios, indicative for disturbances of normal maturation of erythroid precursor cells, had been determined in these neonates.

From the functional assays performed on the various precursor cell pools alterations were observed mainly for the more mature erythropoietic colony forming cells. Increases of CFU-E were observed with the cells derived from livers of 16 day old fetuses exposed *in utero* to 5 and 10 ppm benzene, whereas decreases were observed in those exposed to 20 ppm benzene. The observed alterations did not persist (the numbers of CFU-E in the 5 ppm benzene exposed progeny returned to control values in the 2-day old neonates), and all three precursor cell pools were within the normal growth limits at the time the formerly in utero exposed progeny reached six weeks of age.

It is reported from that study that some offspring from the third experiment from the group (those treated in utero with 10 ppm) had been maintained. Of these, five males and five females were directly exposed for two weeks to 10 ppm benzene and three males and five females were similarly exposed to filtered air at of 10 weeks of age. The determinations of numbers of bone marrow and of splenic CFU-E and of GM-CFU-C, which had been performed from the bone marrow and splenic hematopoietic progenitor cells of these animals did not reveal a consistent pattern: while numbers for the females of bone marrow CFU-E were similar between those from the air and the benzene treated group the numbers for the males were decreased in treated groups in comparison to their controls; no changes however were observed for numbers of splenic CFU-E in either sex for the benzene and the air treated groups.

In a further study (Corti and Snyder, 1996) of the same group a similar treatment protocol (exposure to 10 ppm (~ 32.5 mg/m³) benzene via inhalation for 6h/day over 10 consecutive days) and experimental procedure for evaluating benzene induced hematotoxic effects was applied for either adult male, virgin female or pregnant female Swiss Webster mice and aimed at the investigation of interactions of benzene and of ethanol exposure. Besides examinations of the pregnant females, treated for ten consecutive days during gestation days 5 to 16, also their fetuses from day 16 of gestation had been examined. From this experiment a significant reduction in the numbers of CFU-E from (10 ppm benzene exposed) fetal livers in the males is reported, whereas no changes at all were observed for the female fetuses. This latter finding is in contrast to the findings of the study of Keller and Snyder (1988), from which increases in the numbers of hepatic CFU-E in fetal offspring were observed with the identical treatment protocol.

Overall, investigations on the hematotoxic properties of benzene in the developing organism did not reveal signs of clinical hematotoxicity after indirect (in utero) exposure to benzene concentrations of up to 20 ppm. Evidence for some biological effect may be derived from the

changes that had been observed in these studies for hematopoietic progenitor cells, however, there is large variance of the results in the CFU-assays of the studies, both within individual assays, but also when effects on different types of progenitors (CFU-E, BFU-E, CFU-GM) and between different developmental ages and from independent studies applying the same protocol are compared. Also, the reported statistical significance between groups remains doubtful, since the statistical methods applied in the earlier study of 1986 are not considered appropriate and no justification is given. The overall results from these studies are not considered to provide indications for an increased sensitivity of the developing organism to the hematotoxic properties of benzene in comparison to the adult organism.

Human data:
The available data on the developmental effects of benzene in humans are limited and inconclusive. The few studies that do exist are limited by lack of control incidences for end points, problems in identifying exposed populations, a lack of data on exposure levels, and/or concurrent exposure to multiple substances (Budnick et al. 1984; Goldman et al. 1985; Heath 1983; Olsen 1983).

In a study conducted in the Love Canal area (New York, USA) by Heath (1983), the outcome of pregnancy was evaluated in populations living in the proximity of waste sites where within a total of at least 248 chemicals also benzene had been identified. No clear increase in occurrence of spontaneous abortion, birth defects, or low infant birth weight was observed in women living next to the canal. The study limitations of inadequate sample size and lack of exposure history preclude an assessment of significance of these findings.

In another study by Goldman et al. (1985) on the Love canal area, birth weight was assessed in 239 infants exposed during gestation life. There was an association between low birth weight (<2500 gms) and hazardous waste exposure. However, there were inherent problems in the study design and methodology. One of the study groups was comprised of low-income renters and predominantly black individuals. The methods also failed to include 235 families that were evacuated from Love Canal area.

In a further study of Chen et al. (2000) birth weight was investigated in a cohort of Chinese petrochemical workers in a plant that had been exposed to solvents including benzene, toluene, styrol and xylene. The cohort consisted of 354 benzene-exposed and 438 non-exposed participants. As an orientation for benzene during the shift in that plant a time weighted average (TWA) of 0.017 ppm (rubber plant) to 0.191 ppm (chemical plant No.1) was indicated. In this study in the exposed group any exposure to benzene was rated as a concentration detected for any of the 4 measured chemicals (benzene, toluene, styrol and xylene) by personal air sampling, which had been performed for 132 workers only, or by job title or by workshop. By using this definition reduced birth weight was associated with exposure to benzene as well as with perceived work stress. The adjusted mean birth weight was 3445 g (95% CI 3402 to 3489) among those without exposure to benzene and work stress, 3430 g (95% CI 3382 to 3477) for those with only exposure to benzene, 3426 (95% CI 3340 to 3513) for those with only work stress, and 3262 (95% CI 3156 to 3369) for those with exposure to both benzene and work stress. For this study an interaction was observed between exposure to benzene and perceived work stress.

Effects of benzene exposure to menstrual disturbances had been investigated in an exploratory, cross-sectional retrospective study (Thurston et al., 2000). Based on a survey administered to about 3 000 workers of a Chinese petrochemical company, 333 women had been identified with abnormal (>35 days or <21 days) menstrual cycle length (AMCL). Chemical exposure of study participants was assessed by using a questionnaire and coded by years according to the jobs for which exposure to a particular chemical had been reported. Among different variables, that had been explored during the study, longer exposures to benzene (several years) predicted probability of having AMCL. The adjusted odds of AMCL did not change significantly during the first 7 years of benzene exposure, however, the adjusted odds of having AMCL for each additional 5 years of benzene exposure was 1.71 (95% CI 1.27-2.31). Feeling stressed at work was also an important predictor for AMCL.

Finally, no statistically significant clusters of birth defects were found in populations living around the Drake Superfund site (Pennsylvania, USA), an area contaminated with benzene and other carcinogens (Budnick et al. 1984). However, the significance of this finding cannot be determined because of design methodology inadequacies including inadequate sample size and lack of quantification of exposure levels.

One toxicokinetic study showed that benzene crosses the human placenta and is present in the cord blood in amounts equal to or greater than those in maternal blood (Dowty et al. 1976).

In a study of subjects with known benzene exposure Forni et al. (1971) reported the case of a pregnant worker exposed to benzene in the air throughout the entire pregnancy. Although the woman had severe pancytopenia and an increased frequency of chromosomal aberrations, a healthy boy was delivered with no evidence of developmental effects and with no evidence of chromosomal alterations. In the following year a healthy girl was delivered. In another study increased frequencies of chromosome breaks and of sister chromatid exchange were found in lymphocytes from 14 children of female workers exposed by inhalation to benzene and other organic solvents (doses not specified) during pregnancy (Funes-Cravioto et al. 1977). No mention was made for the reasons of this investigation nor of whether the mothers showed signs of toxicity or whether physical abnormalities occurred among their offspring.

Summary for developmental toxicity

Epidemiological studies implicating benzene as a developmental toxicant have many limitations, and thus there is insufficient data to assess the effects of benzene on the human fetus. The studies designed specifically to investigate developmental effects are limited largely because of concomitant exposure to other chemicals, inadequate sample size, and lack of demonstration, respectively quantification of exposure levels. Therefore, hazard assessment with respect to developmental toxicity will be based on the available data from animal experiments.

Most of the animal data are from experiments with inhalatory exposure which is the principal route of concern. The results of inhalation exposure are fairly consistent across species. No specific embryotoxic or teratogenic potential could be demonstrated for benzene, however, it was obvious that benzene may lead to fetal growth retardation as evidenced by decreased fetal body weight, decreased fetal body length and/or skeletal variations including delayed ossification. It has been suggested that benzene fetotoxicity is a function of maternal toxicity because the occurrence of a decrease in fetal weight and an increase in skeletal variants in the various studies often was associated e.g. with a decrease in maternal weight gain. The

mechanisms of this toxicity, however have not been fully elucidated. There are no data on the effects of benzene exposure on maternal food consumption and moreover, hematological effects in maternal animals probably to be expected, respectively blood levels of benzene and its metabolites in the dams and in their fetuses were not assessed in any of these studies. With respect to dose dependency of fetal growth retardation and of maternal toxicity respective investigations are available from the studies with rats only. Benzene exposures for 10 consecutive days during gestation caused maternal toxicity at exposure levels of 50 ppm and higher. None of the clinical findings of fetal growth retardation were observed after exposure levels of 40 ppm and lower. From the available studies with rats the lowest NOAEC developmental toxicity of 10 ppm (32 mg/m^3) is derived from the study of Kuna and Kapp (1981) and should be taken forward for risk characterisation and quantitative risk assessment.

There are no data available on the developmental effects of benzene in humans or in animals following dermal exposure. Oral data are limited to one animal study in which benzene was shown to exhibit embryotoxic and fetotoxic effects associated with signs of severe maternal toxicity.

As to the hematotoxic properties of benzene, studies on indirectly benzene exposed progeny of various developmental ages did not reveal indications for generally different sensitivities of the developing organism to the hematotoxic properties of benzene in comparison to the adult organism. Some changes in hematopoietic progenitor cells had been observed, however, the biological significance of these finding remains unclear.

Conclusion:
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. For quantitative risk assessment with respect to developmental toxicity a NOAEC of 10 ppm (32 mg/m³) is proposed to be used. Data from repeated dose toxicity studies revealed some effects of benzene exposure to the organs of reproduction of both sexes in mice but not in rats, indicating a NOAEC/reproductive organ toxicity of 30 ppm (96 mg/m^3). An available fertility study in rats is recognised, however, this study is not considered sufficient and adequate for overall assessment of an impairment of male/female fertility.

4.1.3 Risk characterisation

4.1.3.1 General aspects

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 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 hematotoxic 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 (conjugative) metabolic pathways. However, at present, it is unclear whether the observed species differences in developing hematotoxicity and leukemia may be explained by species differences in metabolism. As it is poorly understood what metabolite is relevant for toxic effects such as leukemia or hematotoxic effects, the 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. For the most relevant effect, an integrative PKPD modeling approach using animal and human benzene data is confounded by the fact that the type of leukemia in animals is different from the type of leukemia in man. Hence all the results and conclusions from PKPD modeling using animal data are not applicable to man.

There are indications that besides of direct cytotoxic actions on marrow cells, damage may have an immunological basis. Abnormalities of the cell-mediated and humoral immune responses following benzene exposure are presumably related to the defect progenitor cells of the T- and B-lymphocytes. To our present knowledge, benzene effects were attributed to biologically complex mechanisms of action.

In-vitro examinations showed that the differentiation process of myeloid progenitor cell population was altered by benzene metabolites. A pretreatment with hydroquinone enhances the colony-forming response of murine bone marrow cells stimulated with recombinant granulocyte/macrophage colony-stimulating factor (rGM-GSF). Other benzene metabolites, phenol, catechol, and trans-trans-muconaldehyde, did not stimulate this effect. Benzene was not able to induce growth signals for myeloblasts using an in-vitro test on murine IL-3-dependent myeloblastic cell line and human promyeloblastic leukemia cell line, but stimulated their differentiation to promyelocytes and intermediate progenitors. In these tests hydroquinone was found to provide growth and differentiation signals for myeloblasts that increased the numbers of all progenitor forms, but appeared incapable of inducing terminal differentiation.

Acute toxicity

An oral uptake of a tablespoon of benzene (176 mg/kg bw) can cause collapse, bronchitis and pneumonia. The direct aspiration of liquid benzene into the lungs causes immediate pulmonary edema and hemorrhage at the site of contact with the pulmonary tissue. Very high concentrations of benzene vapors produce narcotic effects and can lead to death by respiratory arrest. Fatal effects can occur after inhaling a benzene concentration of 65000 mg/m³ (20020 ppm) for 5-10 minutes. Exposure of 30 minutes to 25000 mg benzene/m³ (7700 ppm) can be dangerous to life threatening. After inhalation of 160-480 mg benzene/m³ (49-178 ppm) for 6 hours headache and lassitude occur while after inhalation of 80 mg benzene/m³ (25 ppm) for 6 hours no acute toxic effects were documented. The odor threshold is 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, hemorrhagic lungs and pulmonary edema were documented. A relationship between chemical burns and death are 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 hyperemic and hemorragic lungs, adrenals and spine. Acute inhalation toxicity is low with a LC50 value of 44500 mg/m³ (13700 ppm) after a 4-hour exposure for 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

Benzene can cause irritation of the mucous membranes (eye, respiratory tract and mouth, esophagus and stomach).

Sensitisation

There are no reports on skin sensitisation or inhalation allergy. Due to the chemical structure of benzene these kinds of immunological events are unlikely to happen.

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 hematopoietic 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, anemia and/or thrombocytopenia, leading to pancytopenia. and aplastic anemia.

The effective vapour concentration inducing hematotoxicity 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 hematotoxicity at 10 ppm (~ 32.5 mg/m³) 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. They found different effects in two mice strains on the colony growth of CFU-E by in-vitro exposure to single or mixtured metabolites 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.
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 hematopoietic multipotential stem cells, early progenitor cells and intermediate stages of differentiation. Morphologically, anemia 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 hemopoietic progenitor cells as quantitated 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 colony 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 [~ 649 mg/m³]).

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 hemopoiesis confirmed that there is an increased demand for erythrocyte production. No morphologic signs of scavenger of degenerated erythrocytes, such as increases of haemosiderin deposits or stainable intracellular iron deposits in the spleen or other organs, 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. In a long-term rat study excess splenic haemosiderosis was found. Anemia is not primarily caused by peripheral loss or destruction of mature erythrocytes, 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 (~ 32.5 mg/m^3) (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. Results from in-vitro immune response were confirmed by host resistance tests.
At present experimental data are lacking allowing firm conclusion on specific influences of different functional immune cell subtypes.

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) of 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 anemia 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 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 above 320 mg/m³ (100 ppm). The LOAEC for red blood depression may be somewhat lower than for white blood depression at 32 mg/m³ (10 ppm). Thus, for blood cell depression an overall LOAEC is suggested to be 32 mg/m³ (10 ppm).

Case control studies presented recently have shown, that the most sensitive reaction in humans to chronic benzene exposure is lymphopenia. The data show that a collective of workers exposed to benzene concentrations in a range between 1.6 and 30.6 ppm had significantly reduced lymphocyte counts as compared to a cohort of non-exposed workers. Taking into consideration information on changes in lymphocyte counts from all studies with benzene exposure a NOAEC for that effect of 3.2 mg/m³ (1 ppm) can be assumed .

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 with mice). Concerning chromosomal effects after inhalation exposure, according to one report a single low dose of 1 ppm (~ 3.25 mg/m³) induced micronuclei in bone marrow cells of rats. However, in investigations on chromosomal aberrations in rats positive effects were obtained only for doses of 100 ppm (~ 325 mg/m ³) and higher (single exposure) or 10 ppm (~ 32.5 mg/m³) and higher (repeated exposure). In mice, the lowest dose with observed effect is reported to be 10 ppm (32.5 mg/m³) (micronuclei after single exposure).

Although only intraperitoneal studies are available, it seems that benzene has the potential for induction of transplacental genetic effects.

There are only few valid data on germ cell mutagenicity in mammals. In mice chromosomal aberrations are induced in spermatogonia by oral doses ranging from 220 to 880 mg/kg bw. Negative results are reported for dominant lethal mutations in mice and rats, but it´s validity cannot be assessed.

Concerning human studies 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 20 ppm (~ 65 mg/m³) induce observable genotoxic effects in man.

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 to the toxicokinetic properties of benzene, it is concluded that it has the potential to reach the gonads and induce germ cell mutations.

Carcinogenicity/Animal data

Benzene induced neoplasm 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 hematopoietic 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 hematopoietic 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 could demonstrate clearly increased lymphatic tumor rates. Additionally, tumor response was not homogeneous in different mouse strains.
In mice, increased rates of malignant lymphomas were seen; however, only few data existed which described the induction of myelogenous leukemias. An increased rate of leukemias without specification of the predominant cell type were found in long-term treated RF/J mice.

Some of the mice studies also demonstrated leukemia of granulocytic cell lineage. However, these studies positive for myelogenous/granulocytic leukemia revealed no significance of tumor response or positive findings were not reproducible. Even, lower rates of myelogenous leukemia were seen after benzene treatment.

In contrast to the benzene induced lymphomas in mice, no clear effect on the rate of lymphomas were observed in long term studies in the rat. In rats, increased frequencies of leukemia 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 may not include a complete registration of different tumor types of the hematopoietic system. Commonly, tumors were simply reported as malignant lymphomas or leukemia without further data on the classification of the predominant cell type or cell lineage affected (diagnosed as not other specified). Classification schemes from early studies rely upon the morphologic appearance of tumor types without characterizing the cell types using cytochemistry studies or cell surface antigens. Also, different classification schemes of murine lymphoid neoplasms have been described. Therefore it can not be expected to confirm the data from human epidemiology by the retrospective analysis of non-comparable animal data. The interpretation of heterogeneous tumor 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 other investigators 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). Peroxidase-dependent metabolism may also contribute to benzene-induced myelotoxicity via the production of highly reactive intermediates that bind to DNA and protein. It was described, that the Zymbal gland, bone marrow, nasal and oral cavities, and mammary gland possess sulfatase activity and, with the exception of nasal cavity, lack sulfotransferase activity. Sulfatases present in extrahepatic tissues may function to shunt phenolic benzene sulfate conjugates, which normally would be excreted and provide a mechanism whereby these polar metabolites can be hydrolyzed and gain access to the target tissue site. The nasal cavity is able to metabolize benzene to phenol, catechol, and hydroquinone. Other target tissues, oral cavity, mammary gland and Zymbal gland, also showed the ability to metabolize benzene to phenol and hydroquinone, but at a lower rate than the nasal cavity did. It was assumed that these tissues have the ability to biotransform benzene and its metabolites to potentially reactive intermediates that may be responsible for benzene-induced toxicities. Additionally, incubation experiments with liver homogenates showed that several benzene metabolites, 1,2,4-benzenetriol, t,t-muconaldehydes, hydroquinone, and catechol caused significant decreases in glutathione levels compared to control. Hydroquinone-mediated reduction in glutathione levels was related to the formation of a reactive intermediate and conjugation with glutathione to form the corresponding glutathione conjugate, 2-(S-glutathionyl)hydroquinone. Whereas phenol and benzene did not deplete liver glutathione level, measurable amounts of the glutathione conjugate were detected. The hepatic glutathione may play an important role in the detoxification of electrophiles and oxidants, its depletion may result in an increased vulnerability or susceptibility of cellular macromolecules to covalent binding by reactive benzene metabolites. It is assumed that these tissue-specific benzene metabolism is likely to contribute to target tissue tumor susceptibility.

Animal models were able to identify the carcinogenic potential of benzene. However, the tumor response differed between animals and humans. Rodents, however differ from humans in that humans have no Zymbal or Harderian gland. Possible explanations not to identify the leukemia of myeloid origin observed in humans may be that mice show differences in their spectrum of hematopoietic tumors spontaneously occurring with respect to the tumor spectrum seen in humans. Tumor spectrum also differs to other animals including the rat. This is an expected observation well known from other tumors or tumor sites.

Human epidemiological data:

From the numerous human epidemiological studies is sufficient scientific evidence 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. 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 <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 leukemia and myelodysplastic syndrom at average benzene-exposure levels of less than 10 ppm (32.5 mg/m^3).

From a theoretical point of view a threshold level might be existing and in this context the data of the meta-analysis of 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 of the 19 different studies. However, the data do not allow to establish such a threshold level. The result of the Wong and Rabe analysis means that the additional risk for acute myeloic leukemia at a mean level of 700 µg/m³ benzene must be lower than 1 cases in 208 000. The study does not allow to exclude an additional risk which is 30 cases in 208 000 with the appropriate certainity. This is an additional risk as high as 1 : 6 933 which cannot be excluded.

Besides Wong and Rabe (1995) various publications have addressed the issue of linearity in the dose-response relation of benzene-induced hematotoxicity and leukemia (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 leukemia 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 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.

Taking all the studies in their results together, it has to be concluded that presently no level of exposure can be determined below which there is no risk to health.

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 inhalatory benzene 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 but not in rats (NOAEC 96 mg/m³, 30 ppm). The significance of these findings in relation to possible impairment of fertility remains unclear, since adequate functional studies are not available. Studies on

indirectly benzene exposed progeny of various developmental ages did not reveal indications for generally different sensitivities of the developing organism to the hematotoxic properties of benzene. Some changes in hematopoietic progenitor cells had been observed in progeny of various developmental stages, however, the biological significance of these finding remains unclear.

4.1.3.2 Workers

4.1.3.2.1 Introductory remarks

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. In industrial chemistry, benzene forms the basis for a great variety of aromatic intermediates and for the group of cycloaliphatic compounds, e.g. in 1994 about 85% of pure benzene was used for the production of ethylbenzene, cumene and cyclohexane. A further source of benzene is gasoline since benzene is not totally extracted in the petrol refinery process. The occupational exposure scenarios have been described and discussed in section 4.1.1.2. Exposure routes to be considered at the workplace are inhalation against benzene vapour and skin contact with the liquid substance. Short-term values and shift averages as listed in tables 4.15 and 4.16 are taken forward to risk characterisation.

The toxicological data have been described and discussed in section 4.1.2. For benzene quantitative human data are available, so it is only rarely necessary to base estimations for risk assessment on animal data. Carcinogenicity, mutagenicity and chronic toxicity are the most prominent effects of benzene according to its toxicity profile. Relevant threshold levels, if identified during hazard assessment, will be taken forward for occupational risk assessment.

Systemic availability for different routes of exposure

A central idea in risk assessment is to identify the maximum internal concentrations of a toxicologically active chemical species which can be endured without effects. Because of lack of knowledge however, for most substances, the ultimative toxicant cannot be identified. This holds true for benzene too. As substitute the socalled “internal NAEL” is used which is expressed as dose equivalent in mg per kg bodyweight or per person. It originates from the NOAEL of the most sensitive study and is calculated as amount of benzene applied externally corrected for absorption as indicator for potential systemic availability. Potency differences at different routes are accounted for by means of route-specific absorption factors. It is recognized, that this default approach does not refer to the specific toxicokinetic and toxicodynamic aspects concerning benzene toxicity.

Benzene seems to be readily absorbed via the dermal, oral and inhalation route (see chap. 4.1.2.1.A). Following oral dosing in animals absorption percentages of almost 100 % were reached. Inhalation studies in rodents suggest an uptake of benzene in a range of 10 % to maximally 50 % which is confirmed by human data. For risk assessment purposes oral and inhalative absorption are assumed to be 100 % and 50 %, respectively.

Major problems arise in the determination of dermal absorption because of the fact that benzene evaporates very fast. Using physicochemical data it can be calculated as a rough estimate that an amount of 1 mg benzene per cm^2 skin applied will be completely evaporated within 10 seconds under normal workplace conditions. Even if it is assumed, that penetration of benzene through human skin might be as high as 0.4 $mg/cm^2/h$ (see Absorption, chap. 4.1.2.1.A) the systemic availability of benzene following skin contact will be essentially limited by the duration of skin contact. With the above given penetration rate in 10 seconds 0.001 mg $benzene/cm^2$ will cross the skin barrier, which is only 0.1 % of the amount originally applied. However, according to the exposure assessment, in scenarios (2), (5), (6), (8) it cannot be excluded that inappropriate use of protective gloves or repeated initial contacts may increase evaporation time and thereby prolong dermal exposure up to a few minutes per day. In these cases internal body burdens after dermal exposure will calculate considerably higher as compared to open conditions.

For risk assessment purposes the amount of benzene absorbed dermally is estimated using a skin penetration rate of 0.4 $mg/cm^2/h$ in combination with the information on the area of contact and contact time. Under conditions of free evaporation generally a contact time of 10 seconds is used for calculations. In doing so internal doses for exposure scenarios (4), (5), (6), (7), (9) and (10) are clearly overestimated because exposure levels of 0.01 mg/cm^2 or lower indicate that complete evaporation will take less than 10 seconds. However, for risk assessment purposes the worst case estimate performed appears to be sufficient because even with this precautionary assumption internal body burdens calculate below the critical levels for concern (see following chapters). An additional calculation using 5 minutes contact time is carried out for scenarios (2), (5), (6) and (8) to reflect situations with prolonged skin contact. Generally it has to be kept in mind, that the total amount of benzene applied on the skin gives an upper limit for possible absorption. In fact, with the outlined calculation procedure for some dermal exposure scenarios the maximum absorption percentage of 100% is reached.

Occupational exposure and internal body burden

In table 4.30 the route specific exposure values are listed and the total human body burdens as result of repeated combined exposure via inhalation and dermal exposure are identified. With a total of 420 mg/person/day, human body burden is highest for scenario (3), production of perfumes.

Skin contact is only a minor source for internal body burdens of benzene under conditions of free evaporation. With a contact time of 10 seconds a maximum value of 0.94 mg/person/day results for scenario (5), distribution of gasoline. However, in scenarios (2), (5a), (5b), (6), (8a) prolonged skin contact may lead to internal body burdens which are significantly higher. For further risk evaluation these body burdens will be taken forward as worst case estimate for dermal exposure.

Internal doses after short term inhalative exposure are not explicitly included in table 4.30 However, the total dose per day as result of short term inhalative exposures should not exceed the level obtained with exposure against shift average concentrations for a whole day. If toxicological effects are evaluated which are thought to depend on total dose, which holds true for most effects under consideration, risk assessment will concentrate on shift average

values. A separate evaluation for short-term scenarios will only be performed if a certain effect appears to be concentration-dependent.

Table 4.30 Occupational exposure levels and total human body burden

		Inhalation		Dermal		Total body burden	Contribution to total body burden in %	
Area of production and use		shift average mg/m³	internal body burden[1] mg/p/d	shift average mg/p/d	internal body burden[2] mg/p/d	mg/p/d	Inhalation	Dermal
1	Production , further processing, refinery	3.5	17.5	420	0.47	18	97	3
2	Recovery of benzene in coking plants by product recovery	15.5	77.5	420	0.47			
					14[3]	91.5	85	15
3	Production of perfumes, use of benzene	84	420	420	0.47	420	100	
4	Production of formulations, use of solvents	0.15	0.75	4.2	0.47	1.2	61	39
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	6.8	34	4.2	0.47			
					4.2[3][4]	38.2	89	11
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	1.26	6.3	4.2	0.47			
					4.2[3][4]	10.5	60	40
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	12.3	8.4	0.94			
					8.4[3][4]	20.7	59	41
7a	Service stations, handling of gasoline (1 % benzene) (without VR)	0.5	2.5	0.4	0.4	2.9	86	14
7b	Service stations, handling of gasoline (1 % benzene) (with VR)	0.1	0.5	0.4	0.4	0.9	56	44
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	67.7	339	1575	0.47			
					14[3]	353	96	4

		Inhalation		Dermal		Total body burden	Contribution to total body burden in %	
Area of production and use		shift average mg/m³	internal body burden[1] mg/p/d	shift average mg/p/d	internal body burden[2] mg/p/d	mg/p/d	Inhalation	Dermal
8b	Cleaning of tanks heating oil tanks (b)	0.44	2.2	negli-gible	negli-gible	2.2	approx 100	
9	Use of formulations with residual benzene, e.g. adhesives paints, containing < 0.1% benzene	1	5	6.5	1.5[5]	6.5	77	23
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	14	0.4	0.4[4][5]	14.4	97	3
11a	Foundries (without LEV)	5.4	27	low	low	27	high	low
11b	Foundries (with LEV)	1.6	8	low	low	8	high	low

[1] shift average x 10 m^3 x 0.5

[2] 0.4 $mg/cm^2/h$ x exposed area x contact time
generally 10 seconds (0.0028 h) is used as contact time under conditions of free evaporation;
internal body burdens calculate for 210 cm^2: 0.4 $mg/cm^2/h$ x 210 cm^2 x 0.0028 h = 0.24 mg/p/d
for 420 cm^2: 0.4 $mg/cm^2/h$ x 420 cm^2 x 0.0028 h = 0.47 mg/p/d
for 840 cm^2: 0.4 $mg/cm^2/h$ x 840 cm^2 x 0.0028 h = 0.94 mg/p/d
for 1300 cm^2: 0.4 $mg/cm^2/h$ x 1300 cm^2 x 0.0028 h = 1.46 mg/p/d

[3] contact time of 5 minutes (0.08 h) used for calculation of prolonged skin contact
internal body burdens calculate for 420 cm^2: 0.4 $mg/cm^2/h$ x 420 cm^2 x 0.08 h = 13.4 mg/p/d
for 840 cm^2: 0.4 $mg/cm^2/h$ x 840 cm^2 x 0.08 h = 26.8 mg/p/d

[4] within the assumed contact time the total amount applied on the skin is absorbed

[5] estimation of contact duration is difficult because evaporation depends on the composition of the formulation. For initial assessment a contact time of 10 seconds is assumed.

Default values for physiological parameters

Body weight, rat	250 g
Body weight, worker	70 kg
Respiratory rate, rat at rest	0.8 l/min/kg
Respiratory rate, worker at rest	0.2 l/min/kg
Respiratory volume of worker during 8 hours at rest	6.7 m³
Respiratory volume of worker during 8 hours of light activity	10 m³

Calculation of MOS values

With the exception of carcinogenicity for toxicological endpoints with quantitative data available, MOS values for benzene are calculated as quotient of relevant NOAEC from human or animal studies and workplace exposure assessments. If the route of application in animal or human studies for a certain endpoint is different from the actual occupational exposure the dose units of the experimental data are adapted previously to MOS calculation. For this procedure the physiological default values from above are used to modify the effects data. As result a socalled "starting point" for risk assessment is identified.

MOS values for inhalative and dermal route are considered separately. The combined MOS-value is calculated as quotient of the internal NAEL and total human body burden. With respect to the possible outcome of an assessment for combined risks, interest focusses on scenarios with conclusion ii at both exposure routes. By theoretical considerations combined exposure will not increase the most critical route-specific risk component more than twice. It is recognized on that background, that combined risks only rarely will decide concern. For matters of completeness however, all combined MOS values are given in this report on benzene.

Risk characterisation concerning carcinogenicity

For excess cancer risks of benzene values reported in the literature concerning a reference exposure of 1 ppm at the workplace span more than two orders of magnitude. According to chap. 4.1.2.8.2 no decision is possible which analysis reveals the most reliable basis for quantitative risk assessment at the workplace. Thus cancer risks at the workplace cannot easily be quantified. On that background as starting point for risk characterisation the reference exposure of 1 ppm or 16 mg/person/day, derived from the envisaged european occupational exposure limit for benzene, is compared to the actual exposure situation as addressed in chapter 4.1.1. As result margins of exposure are determined (MOE) which are further evaluated in a second step.

Evaluation of MOS values

Risk assessment based on MOS values implies the identification of a minimal MOS as decision mark between conclusion ii and iii. To obtain this, assessment factors are identified for benzene, which vary depending on data availability and the specific toxicological endpoint to be evaluated. If necessary scientifically based adjustment factors describe the extrapolation of animal data to the worker population. The uncertainties in the specific calculations are weighed by expert judgement and expressed as an additional "uncertainty factor". The value of the minimal MOS results from the multiplicative combination of the different factors.

If the MOS value for a certain exposure scenario is below the minimal MOS for a specific endpoint, the corresponding risk situation is considered to be of concern. A MOS value higher than the minimal MOS indicates no concern.

In a parallel procedure, which gives identical but more direct results, the toxicological starting point taken forward to risk characterisation is divided by the endpoint-specific assessment factors. As result an exposure level is identified for benzene, which by direct comparison with the occupational exposure levels may serve as trigger for decisions. In the context of this risk

assessment report it will be called “critical exposure level”. Concern will be expressed for scenarios above this trigger value.

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.

Interspecies extrapolation

For reproductive toxicity of benzene risk assessment has to be based on inhalation studies with mice or rats. According to chapter 4.1.2.1 there is reason to assume substance-specific susceptibility differences among species for benzene, however no data are available which allow direct quantitative comparisons. Under certain aspects mice seem to be the most sensitive animal species towards benzene. As default approach interspecies extrapolation concerning reproductive toxicity will rely upon the concept of metabolic rate scaling. For inhalation exposure, the principle of metabolic rate scaling implies that a specific inhalation exposure level (in mg/m^3) is toxicologically equivalent in animals and humans (NO_NL, 1999). However, care has to be taken to rely the extrapolation on directly comparable exposure conditions for both species. For instance in inhalative studies daily exposure time usually is 6 hours. From a metabolically point of view experimental animals are thought to be at rest under study conditions. The according human breathing rate is 0.2 l/min/kg. Together for a human of 70 kg a breathing volume of 5 m^3 would correspond to the cited experimental situation. At the workplace however the breathing volume of workers is assumed to be 10 m^3. This difference has to be corrected for.

Duration adjustment

According to the fact that studies with suitable experimental design are available for benzene there is no need for a specific duration adjustment step in extrapolation. Where adaptation of daily or weekly doses is necessary, e.g. in the calculation of totally administered amounts of benzene, it is assumed that the product of dose multiplied by time is constant for a certain effect.

Intraspecies extrapolation

There are no substance-specific data which allow to quantify possible sensitivity differences among workers. For evaluation of MOS values a specific intraspecies extrapolation factor is not used. To a certain extent the aspect of human variability will be covered by uncertainty considerations.

Uncertainty considerations

The adjustment factors outlined above serve to adapt animal data to humans. They rely mainly upon general knowledge in physiology or toxicity. From a statistical point of view the individual parameters have to be understood as point estimates belonging to probability density functions. It is intended to take each factor from a point near the maximum of its distribution. The multiplicative combination of all factors therefore is supposed to result in a

central tendency point estimate, addressing a situation which is likely to occur. However, the actual risks may either be less or more pronounced than estimated.

In practice for each toxicological endpoint an additional uncertainty factor is defined which is used to modify the initial data in terms of precaution (Delogu, B., 2000). This factor takes into account several aspects, which by their nature are not easy to quantify, as for instance the reliability of the data base, the biological relevance of the observed effects, the slope of the dose response curve or the variability of the human population. Uncertainty factors therefore have to be based on expert judgement. To give some orientation it is proposed to use an uncertainty factor of 5 for the evaluation of repeated dose toxicity based on a subacute oral study (BAU, 1994). Depending on the available database the uncertainty factor may be higher or lower. Small uncertainty factors are used for instance for the assessment of acute and chronic toxicity of benzene because human data are available for these endpoints.

4.1.3.2.2 Occupational risk assessment

Acute toxicity

Local effects (inhalation, dermal):

see Irritation, no further information available

Systemic effects (inhalation, dermal, combined)

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

According to chap.4.1.2.2 benzene concentrations of approximately 6 g/m^3 can cause fatal effects in humans within 10 minutes of exposure, 25 g/m^3 are reported to be endurable but cause serious health damage and even 160 mg/m^3 still lead to symptoms of illness such as headache, lassitude and weariness. No acute toxic clinical symptoms in humans were documented at 80 mg/m^3(25 ppm), inhaled for 6 hours as shift average.

In rabbits and guinea pigs dermal LD_{50} values were reported to lie above 8260 mg/kg (see chap. 4.1.2.2), a dose which did not lead to clinical signs or autopsy findings. There is no data on a dermal NOAEL in humans concerning acute effects.

As starting point for worker risk assessment the inhalative NOAEC in humans of 80 mg/m^3 for exposure duration of 6 hours is chosen, the according internal NAEL calculates to 300 mg/person/day (80 mg/m^3 x 6h / 8h x 10 m^3/person/day x 0.5). For uncertainty considerations a factor of 2 is proposed for all routes on the background that a human NOAEL is available for risk assessment. Evaluation of inhalative exposure scenarios has to account for the difference in exposure duration between human data and usual shift length (6 hours vs 8 hours) whereas the dermal and combined MOS values are already adapted for this aspect. For inhalation the minimal MOS therefore calculates to 2.7 (8h / 6h x 2), for dermal and combined exposure it is simply 2. The critical exposure level is identified as 30

mg/m^3 (80 mg/m^3 / 2.7) for 8 hours inhalation (12.3 ppm) or 150 mg/person/day as internal dose (300 mg/person/day / 2), which is used to assess risks from dermal or combined route.

In table 4.31 MOS values concerning acute risks for exposures during a working day (8 hours) are calculated. For the highest inhalative exposure scenarios concern is indicated. Dermal exposure scenarios, however, do not fall in the concern range. For none of the scenarios additional concern has to be expressed as result of combined inhalative and dermal exposure.

Table 4.31 MOS values for acute toxicity, systemic effects

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		80 mg/m^3			300 mg/p/d (internal dose)			300 mg/p/d (internal dose)		
Minimal MOS		2.7			2			2		
Critical exposure level		30 mg/m^3			150 mg/p/d (internal dose)			150 mg/p/d (internal dose)		
		Exposure mg/m^3	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
1	Production , further processing, refinery	3.5	23		0.47	638		18	17	
2	Recovery of benzene in coking plants by product recovery	15.5	5.2		14	21		91.5	3.3	
3	Production of perfumes, use of benzene	84	0.95	iii	0.47	638		420	0.7	[2]
4	Production of formulations, use of solvents	0.15	533		0.47	638		1.2	250	
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	6.8	12		4.2	71		38.2	7.8	
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	1.26	63		4.2	71		10.5	29	

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		80 mg/m^3			300 mg/p/d (internal dose)			300 mg/p/d (internal dose)		
Minimal MOS		2.7			2			2		
Critical exposure level		30 mg/m^3			150 mg/p/d (internal dose)			150 mg/p/d (internal dose)		
		Exposure mg/m^3	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	36		8.4	36		20.7	14	
7a	Service stations, handling of gasoline (1 % benzene) (without VR)	0.5	160		0.4	750		2.9	103	
7b	Service stations, handling of gasoline (1 % benzene) (with VR)	0.1	800		0.4	750		0.9	333	
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	67.7	1.2	iii	14	21		353	0.9	[2]
8b	Cleaning of tanks heating oil tanks (b)	0.44	182		negli-gible	high		2.2	136	
9	Use of formulations with residual benzene, e.g. adhesives paints, containing < 0.1% benzene	1	80		1.5	200		6.5	46	
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	30		0.4	750		14.4	21	
11a	Foundries (without LEV)	5.4	15		low	high		27	11	
11b	Foundries (with LEV)	1.6	50		low	high		8	38	

(1) blank fields: conclusion ii
(2) conclusion iii already results from the inhalation exposure, therefore no specific concern for combined exposure scenarios is indicated

Irritation/Corrosivity

Dermal

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

In humans acute lethal poisoning with very high concentrated benzene vapours led to second degree chemical burns at the exposed skin areas. Liquid benzene on direct contact with the skin may cause erythema and blistering. In rabbits benzene is irritatant to the skin. No data are available on the effects of dilutions. For risk assessment purposes 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.

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. In most cases skin contact critically depends on the proper use of protective gloves. Even though suitable personal protective equipment (PPE) usually should be available at the working places in question unintended contact by non-proper use is considered to represent an incident which may occur frequently in different exposure situations. Therefore a risk from skin irritation has to be considered.

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 damage.

Eyes

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

After instillation of benzene in the eyes of rabbits inflammation, swelling of the eyelids and slight corneal reactions have been observed. If the pure substance reaches the eyes of humans similar effects as in laboratory animals have to be expected. No data are available concerning the effects of dilutions. In accordance with the concentration limits for classification and labelling in the Preparations Directive it is assumed for risk assessment purposes, that preparations containing ≥ 20 % benzene will most probably be irritant to 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. Eye contact critically depends on proper handling of the fluid and the proper use of eye glasses. Even though suitable personal protective equipment (PPE) usually should be available at the working places in question unintended contact by non-proper use is considered to represent an incident which may occur in different exposure situations. Therefore a risk from eye irritation has to be considered.

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

Inhalation

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

In humans direct aspiration of liquid benzene into the lungs causes immediate pulmonary edema and hemorrhage at the site of contact. High concentrations of benzene vapours are irritating to the mucous membranes of the eyes, nose and respiratory tract of humans. Airborne concentrations up to 300 ppm (972 mg/m^3), as used in different inhalation studies, did not reveal local effects in the respiratory tract of mice.

The airborne concentration of 972 mg/m^3 is used as starting point for risk assessment. No special aspects concerning data extrapolation have to be accounted for during MOS evaluation. An uncertainty factor does not seem necessary because of the limited severity of the nature of the effect. The minimal MOS is 1, the critical airborne concentration is 972 mg/m^3.

The highest inhalative exposure against benzene vapour is expected during production of perfumes, scenario (3), with a shift average value of 84 mg/m^3 (26 ppm). In the case of local effects in the respiratory tract, short-term exposure scenarios are of interest too, because it cannot be excluded that local effects are a concentration dependent rather than dose dependent effect. The highest short-term exposure reported is 64 mg/m^3 (20 ppm) during production, further processing and refinery, scenario (1).

All inhalative exposures at the workplace are below the critical airborne concentration. The MOS values for scenario (3) and short-term scenario (1) calculate to 11 and 15, respectively. In summary irritating effects of benzene by inhalation are not of concern for workers.

Sensitisation

Dermal

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

There is no data on animal sensitisation. Benzene is not suspected to be a potent skin sensitizer in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern that workers might develop a contact allergy against benzene.

Inhalation

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

No information on respiratory sensitisation is available. Benzene is not suspected to be a potent respiratory sensitizer in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern that workers might get inhalatively sensitized against benzene.

Repeated dose toxicity

Local effects (inhalation, dermal):

see Irritation, no further information available

Systemic effects (inhalation, dermal, combined)

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

Quantitative information on benzene toxicity following repeated administration is available from inhalation studies with laboratory animals and from human data. The main targets of toxicity in animals and humans after repeated application are the hematopoietic system and the cells of the bone marrow. Also benzene may be suppressive on the cellular and humoral immunity.

In repeated dose studies in mice benzene dose-dependently caused lymphocytopenia, anaemia and pancytopenia characterized by a decrease in all peripheral blood cell types and a marked reduction in marrow progenitor cells. Marrow progenitor cells seem to be a more sensitive parameter of benzene effects than the bone marrow cellularity. Repeated inhalation exposure in mice was effective from 10 ppm benzene.

In humans chronic benzene exposure leads to depression of white and red blood cells. Case control studies in chinese workers have shown decreased lymphocyte counts for a group of persons exposed to 1-20 ppm (see chap. 4.1.2.6.2). From these studies the NOAEC for chronic effects of benzene in humans is assumed to be 1 ppm (3.2 mg/m^3).

For risk assessment purposes the human NOAEC of 1 ppm (3.2 mg/m^3) will be used as starting point. The corresponding internal NAEL calculates to 16 mg/person/d (3.2 mg/m^3 x 10 m^3/person/d x 0.5). No further factors need to be introduced for evaluation of the MOS

values with respect to risks at the workplace because the NOAEC of 1 ppm is directly derived from the population of interest namely workers. In addition, exposure conditions of the case control studies are judged to be of direct relevance for occupational risk assessment. Therefore the minimal MOS simply is 1. The critical exposure level is 3.2 mg/m^3 (1 ppm) for inhalation or 16 mg/person/day as internal dose, which is used to assess risks from dermal or combined exposure.

In table 4.32 MOS values concerning risks of benzene at the workplace by repeated dose toxicity are calculated. The resulting MOS values fall in a range between 0.04 (scenario 3, inhalation) and 40 (scenarios 7, 10, dermal contact), indicating quite different levels of concern. Whereas dermal MOS values generally are above the minimal MOS, for six inhalative scenarios concern has to be expressed. In addition concern is derived from combined inhalative and dermal exposure in scenario (6). It is recognized, that for some scenarios MOS values close to 1 identify borderline risk situations. There is, however, no substantial argument in these cases which would help to trigger the decision on concern. Thus the minimal MOS of 1 is applied rather strictly.

Table 4.32 MOS values concerning repeated dose toxicity, systemic effects

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		3.2 mg/m^3			16 mg/p/d (internal dose)			16 mg/p/d (internel dose)		
Minimal MOS		1			1			1		
Critical exposure level		3.2 mg/m^3			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
		Exposure mg/m^3	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
1	Production , further processing, refinery	3.5	0.9	iii	0.47	34		18	0.9	[2]
2	Recovery of benzene in coking plants by product recovery	15.5	0.2	iii	14	1.1		91.5	0.2	[2]
3	Production of perfumes, use of benzene	84	0.04	iii	0.47	34		420	0.04	[2]
4	Production of formulations, use of solvents	0.15	21		0.47	34		1.2	13	

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		3.2 mg/m^3			16 mg/p/d (internal dose)			16 mg/p/d (internel dose)		
Minimal MOS		1			1			1		
Critical exposure level		3.2 mg/m^3			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
		Exposure mg/m^3	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	6.8	0.5	[3]	4.2	3.8		38.2	0.4	[3]
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	1.26	2.5		4.2	3.8		10.5	1.5	
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	1.4		8.4	1.9		20.7	0.8	[3]
7a	Service stations, handling of gasoline (1 % benzene) (without VR)	0.5	6.4		0.4	40		2.9	5.5	
7b	Service stations, handling of gasoline (1 % benzene) (with VR)	0.1	32		0.4	40		0.9	18	
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	67.7	0.05	iii	14	1.1		353	0.05	[2]
8b	Cleaning of tanks heating oil tanks (b)	0.44	7.3		negli-gible	high		2.2	7.2	
9	Use of formulations with residual benzene, e.g. adhesives paints, containing < 0.1% benzene	1	3.2		1.5	11		6.5	2.5	

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		3.2 mg/m³			16 mg/p/d (internal dose)			16 mg/p/d (internel dose)		
Minimal MOS		1			1			1		
Critical exposure level		3.2 mg/m³			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
		Exposure mg/m³	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	1.2		0.4	40		14.4	1.1	
11a	Foundries (without LEV)	5.4	0.6	iii	low	high		27	0.6	[2]
11b	Foundries (with LEV)	1.6	2.0		low	high		8	2.0	

[1] blank fields: conclusion ii
[2] conclusion iii already results from the inhalation exposure, therefore no specific concern for combined exposure scenarios is indicated
[3] A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

Mutagenicity

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

Benzene has been widely studied regarding its mutagenicity. In studies in vivo it induced mutagenic effects in mammals, especially chromosomal aberrations and micronuclei. Based on intraperitoneal studies, there is some indication that benzene may have the potential to induce transplacental genetic effects. Only few valid data on germ cell mutagenicity in mammals are available which, however, gave no consistent results. Weighing all evidences it is concluded, that benzene has the potential to reach the gonads and induce germ cell mutations (chap. 4.1.2.7). A dose-response relationship cannot be derived. According to one report from a rat inhalation study a single exposure at 1 ppm induced micronuclei in bone marrow cells. In mice the lowest airborne concentration with observed effects is reported to be 10 ppm.

In summary there is some evidence that benzene exposure might lead to heritable damage. A threshold dose for a possible onset of effects cannot be derived. In addition it has to be assumed that the mutagenic properties of benzene essentially contribute to cancer risks since a genotoxic mechanism seems to be involved in tumour formation. As consequence 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

(Inhalation, dermal, combined)

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

From several animal studies with inhalative and oral exposure there is clear indication that benzene is carcinogenic. Target organs include the hematopoietic system and a spectrum of tissues with epithelial origin indicating that benzene is a multipotent animal carcinogen. The predominant tumours induced in the inhalation studies concerned the hemopoietic system, particularly lymphomas have been found. According to chap. 4.1.2.1 the animal model by several reasons cannot be used to evaluate the situation in humans, thus risk assessment concerning leukaemia has to be based on human data.

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. The most relevant human data for quantitative risk assessment were obtained from the so called "Pliofilm cohort" (employees in the rubber industry in Ohio).

In the past years several attempts were made to quantitatively analyse the data of this study using different mathematical models. In more recent evaluations follow-ups until 1987 are included and individual cumulative exposures are reassessed. Quantitative risk estimates are expressed as additional benzene-attributable leukaemia mortality for an average exposure of 1 ppm over a working lifetime, which usually is assumed to be 45 years. The different attempts to quantify the excess cancer risks of benzene resulted in estimations which span several orders of magnitude. Rinski (1987), for instance, estimates the additional benzene mortality to 1.6 – 3.1 cases per thousand exposed individuals whereas the analysis by Crump (1994) reveals a range of 0.02 – 0.036 cases per thousand (see chap 4.1.2.8.2). In the Recommendations of the Scientific Expert Group (CEC 1994) the different data given in the literature is combined to a total estimation of an excess risk for leukaemia of 0.5 - 6.6 cases per 1000 workers, exposed to 1 ppm over a working lifetime.

From the publication of Paxton et al. (1994a) a hypothesis might be derived, suggesting a certain level of benzene exposure above which the risk of leukaemia significantly increases (see chapter 4.1.3.0). However, with the current scientific knowledge, a level of exposure below which there is no risk to health cannot be established. Thus for the time being a threshold mechanism cannot be discussed further for risk assessment purposes.

According to the information in chap. 4.1.2.8.2 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. In the following for risk evaluation the inhalative exposure to 1 ppm which is equivalent to an internal body

burden of 16 mg per person per day (1 ppm x 3.24 mg/m^3/ppm x 10 m^3/person/day x 0.5) is used as reference exposure to calculate a MOE.

In table 4.33 for the different exposure scenarios the according MOE values are given. The question is, if it is possible to identify a minimal MOE which may indicate occupational risks that could be considered as being low. 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. It therefore has to be concluded that a MOE of 1 is a clear indication for concern. A minimal MOE identifying low risk situations should at least be one order of magnitude higher. For preliminary considerations a minimal MOE of 10 is used, which would correspond to a critical airborne concentration of 0.1 ppm or an internal body burden of 1.6 mg/person/day.

Table 4.33 shows that for the majority of the inhalative exposure scenarios MOE values are smaller than 10 thereby clearly indicating concern. Whether the MOE values of scenarios (4) and (7b) (20 and 33, respectively) are sufficient to substantiate a different level of concern might be discussed on the background of the uncertainties associated with in the minimal MOE used for these preliminary considerations. For skin contact, however, with the minimal MOE of 10 two clearly distinct risk situations are identified. MOE values below 10 are unequivocally associated with the assumption of hindered evaporation. Clearly higher MOE values result, if free evaporation is anticipated. Taking additionally into account, that the internal body burdens after dermal contact for scenarios (4), (7), (9), (10) are calculated too high because 10 seconds are assumed for free evaporation (see chap. 4.1.3.2), dermal cancer risks in these cases might be considered as low.

Overall, conclusion iii is applied to all scenarios because an exposure level without cancer risk cannot be identified for benzene. The above outlined differentiation of the various situations according to their risk level might however be helpful for discussion of risk reduction measures at the workplace.

Table 4.33 MOE values concerning cancer risks by benzene

		Inhalation			Dermal			Combined		
Starting point for MOE calculation		1 ppm			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
preliminary minimal MOE		10			10			10		
preliminary critical exposure level		0.1 ppm			1.6 mg/p/d (internal dose)			1.6 mg/p/d (internal dose)		
		Exposure[1] ppm	MOE	Conclusion	Exposure (internal dose) mg/p/d	MOE	Conclusion	Exposure (internal dose) mg/p/d	MOE	Conclusion
1	Production , further processing, refinery	1.1	0.9	iii	0.47	34	iii[2]	18	0.9	[3]
2	Recovery of benzene in coking plants by product recovery	4.8	0.2	iii	14[4]	1.1	iii	91.5	0.2	[3]
3	Production of perfumes, use of benzene	26	0.04	iii	0.47	34	iii[2]	420	0.04	[3]
4	Production of formulations, use of solvents	0.05	20	iii[2]	0.47	34	iii[2]	1.2	13	
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	2.1	0.5	[5]	4.2[4]	3.8	[5]	38.2	0.4	[5]
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	0.39	2.6	[5]	4.2[4]	3.8	[5]	10.5	1.5	[5]
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	0.70	1.4	[5]	8.4[4]	1.9	[5]	20.7	0.8	[5]
7a	Service stations, handling of gasoline (1 % benzene) (without VR)	0.15	6.7	[5]	0.4	40	[5]	2.9	5.5	[5]

		Inhalation			Dermal			Combined		
Starting point for MOE calculation		1 ppm			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
preliminary minimal MOE		10			10			10		
preliminary critical exposure level		0.1 ppm			1.6 mg/p/d (internal dose)			1.6 mg/p/d (internal dose)		
		Exposure[(1)] ppm	MOE	Conclusion	Exposure (internal dose) mg/p/d	MOE	Conclusion	Exposure (internal dose) mg/p/d	MOE	Conclusion
7b	Service stations, handling of gasoline (1 % benzene) (with VR)	0.03	33	[(5)]	0.4	40	[(5)]	0.9	18	
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	21	0.05	iii	14[(4)]	1.1	iii	353	0.05	[(3)]
8b	Cleaning of tanks heating oil tanks (b)	0.14	7.1	iii	negli-gible	high	iii[(2)]	2.2	7.2	[(3)]
9	Use of formulations with resudual benzene, e.g. adhesives paints, containing < 0.1% benzene	0.31	3.2	iii	1.5	11	iii[(2)]	6.5	2.5	[(3)]
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	0.8	1.3	iii	0.4	40	iii[(2)]	14.4	1.1	[(3)]
11a	Foundries (without LEV)	1.7	0.6	iii	low	high	iii[(2)]	27	0.6	[(3)]
11b	Foundries (with LEV)	0.49	2.0	iii	low	high	iii[(2)]	8	2.0	[(3)]

(1) 1 mg/m^3 = 0.309 ppm
(2) MOE values are greater than 10; for discussion of the according risk levels see text
(3) Conclusion iii already results from inhalation or dermal exposure, therefore no specific concern for combined exposure scenarios is indicated
(4) internal body burdens estimated under the assumption of hindered evaporation
(5) A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

Reproductive toxicity

Fertility impairment (inhalation, dermal, combined)

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

Reliable human data concerning fertility effects of benzene are not available. Therefore hazard assessment has to be based on animal experiments. Aspects related to fertility have been investigated in studies of different quality and validity. From chronic toxicity studies mice appear to be the most sensitive animal species. 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 (971 mg/m^3). The NOAEC in this study was 30 ppm (97 mg/m^3). From the hazard assessment no preference for an additional fertility study can be derived (chap. 4.1.2.9).

As starting point for MOS calculation the NOAEC in mice of 97 mg/m^3 (30 ppm) will be used. The corresponding internal NAEL calculates to 485 mg/person/day (97 mg/m^3 x 10 m^3/person/day x 0.5). Evaluation of the MOS values has to account for the following aspects: (i) adaptation of exposure conditions from experimental animals to workers reveals a factor of 2, no further interspecies extrapolation is necessary (see chap. 4.1.3.2.1) (ii) for uncertainty considerations an additional factor of 5 is proposed, taking into account that effects have been obtained at high airborne concentrations only. Together the minimal MOS calculates to 10 (2 x 5). The critical exposure level is identified as 9.7 mg/m^3 (97 mg/m^3 / 10) for inhalation, or 49 mg/person/day as internal dose (485 mg/person/day / 10), which is used to assess risks by dermal or combined exposure.

As can be derived from the data in table 4.34 some inhalative MOS values are below the minimal acceptable MOS, but none of the dermal scenarios is in the concern range. As result of combined inhalative and dermal exposure no additional concern has to be expressed.

Table 4.34 MOS values concerning risks of fertility impairment by benzene

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		97 mg/m³			485 mg/p/d (internal dose)			485 mg/p/d (internal dose)		
Minimal MOS		10			10			10		
Critical exposure level		9.7 mg/m³			49 mg/p/d (internal dose)			49 mg/p/d (internal dose)		
		Exposure mg/m³	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
1	Production , further processing, refinery	3.5	28		0.47	> 1000		18	27	
2	Recovery of benzene in coking plants by product recovery	15.5	6.3	iii	14	35		91.5	5.3	[2]
3	Production of perfumes, use of benzene	84	1.2	iii	0.47	> 1000		420	1.2	[2]
4	Production of formulations, use of solvents	0.15	647		0.47	> 1000		1.2	404	
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	6.8	14		4.2	115		38.2	13	
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	1.26	77		4.2	115		10.5	46	
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	43		8.4	58		20.7	23	
7a	Service stations, handling of gasoline (1 % benzene) (without VR)	0.5	194		0.4	> 1000		2.9	167	

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		97 mg/m^3			485 mg/p/d (internal dose)			485 mg/p/d (internal dose)		
Minimal MOS		10			10			10		
Critical exposure level		9.7 mg/m^3			49 mg/p/d (internal dose)			49 mg/p/d (internal dose)		
		Exposure mg/m^3	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
7b	Service stations, handling of gasoline (1 % benzene) (with VR)	0.1	970		0.4	>1000		0.9	539	
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	67.7	1.4	iii	14	35		353	1.4	[2]
8b	Cleaning of tanks heating oil tanks (b)	0.44	220		negli-gible	high		2.2	220	
9	Use of formulations with resudual benzene, e.g. adhesives paints, containing < 0.1% benzene	1	97		1.5	323		6.5	75	
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	36		0.4	>1000		14.4	34	
11a	Foundries (without LEV)	5.4	18		low	high		27	18	
11b	Foundries (with LEV)	1.6	61		low	high		8	61	

[1] blank fields: conclusion ii

[2] conclusion iii already results from the inhalation exposure, therefore no specific concern for combined exposure scenarios is indicated

Developmental toxicity (inhalation, dermal, combined)

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

Reliable human data concerning developmental effects of benzene are not available. Therefore hazard assessment has to be based on animal studies. From the results of inhalation experiments no specific embryotoxic or teratogenic potential could be demonstrated for benzene, however it was 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. Only studies with rats are available concerning this endpoint. Overall the lowest NOAEC observed is 10 ppm (32 mg/m^3).

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 (32 mg/m^3 x 10 m^3/person/day x 0.5). Evaluation of the MOS values has to account for the following aspects: (i) adaptation of exposure conditions from experimental animals to workers reveals a factor of 2, no further interspecies extrapolation is necessary (see chap. 4.1.3.2.1) (ii) for uncertainty considerations a factor of 5 is proposed taking into account that at the LOAEC of 50 ppm fetal growth retardation, but no teratogenic effects have been observed. Together the minimal MOS calculates to 10 (2 x 5). The critical exposure level is identified as 3.2 mg/m^3 (32 mg/m^3 / 10) for inhalation (1 ppm), or 16 mg/person/day as internal dose (160 mg/person/day / 10) which is used to assess risks by dermal or combined exposure.

It is realized that the critical exposure levels identified for developmental toxicity are identical to those for repeated dose toxicity although considerations are based on different starting points. As a consequence the scenarios of concern for the developing organism and adults are similar. This overall result is supported by additional toxicological information relevant for the unborn: as stated in chap. 4.1.2.9 inhalative studies on indirectly exposed progeny did not reveal indications for generally different sensitivities of the developing organism to the hematotoxic properties of benzene in comparison to the adult organism. It is therefore believed to be highly justified to base the risk assessment for the mother and the unborn child on the same critical exposure levels. In table 4.35 the MOS values for the different exposure scenarios are listed in detail.

Table 4.35 MOS values concerning risks of developmental toxicity by benzene

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		32 mg/m^3			160 mg/p/d (internal dose)			160 mg/p/d (internal dose)		
Minimal MOS		10			10			10		
Critical exposure level		3.2 mg/m^3			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
		Exposure mg/m^3	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
1	Production , further processing, refinery	3.5	9.1		0.47	340		18	8.9	
2	Recovery of benzene in coking plants by product recovery	15.5	2.1	iii	14	11		91.5	1.7	[2]
3	Production of perfumes, use of benzene	84	0.4		0.47	340		420	0.4	
4	Production of formulations, use of solvents	0.15	213		0.47	340		1.2	133	
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	6.8	4.7	[3]	4.2	38		38.2	4.2	[3]
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	1.26	25		4.2	38		10.5	15	
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	14		8.4	19		20.7	7.7	[3]
7a	Service stations, handling of gasoline (1 % benzene) (without VR)	0.5	64		0.4	400		2.9	55	

		Inhalation			Dermal			Combined		
Starting point for MOS calculation		32 mg/m³			160 mg/p/d (internal dose)			160 mg/p/d (internal dose)		
Minimal MOS		10			10			10		
Critical exposure level		3.2 mg/m³			16 mg/p/d (internal dose)			16 mg/p/d (internal dose)		
		Exposure mg/m³	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]	Exposure (internal dose) mg/p/d	MOS	Conclusion[1]
7b	Service stations, handling of gasoline (1 % benzene) (with VR)	0.1	320		0.4	400		0.9	178	
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	67.7	0.5	iii	14	11		353	0.5	[2]
8b	Cleaning of tanks heating oil tanks (b)	0.44	73		negli-gible	high		2.2	73	
9	Use of formulations with resudual benzene, e.g. adhesives paints, containing < 0.1% benzene	1	32		1.5	107		6.5	25	
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	12		0.4	400		14.4	11	
11a	Foundries (without LEV)	5.4	5.9	iii	low	high		27	5.9	[2]
11b	Foundries (with LEV)	1.6	20		low	high		8	20	

[1] blank fields: conclusion ii
[2] conclusion iii already results from the inhalation exposure, therefore no specific concern for combined exposure scenarios is indicated
[3] A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

4.1.3.2.3 Summary evaluation

Several different exposure scenarios at the workplace have been identified which lead to inhalative or dermal contact with benzene. Benzene will be easily absorbed after inhalation and skin contact. Internal body burdens after dermal exposure critically depend on the question of contact duration. Risks from open dermal contact with benzene can generally be addressed as low because of rapid evaporation. If however, skin contact is prolonged either by inappropriate use of protective gloves or by repeated initial contacts with fluids containing benzene significant risks may result.

The effect spectrum of benzene is broad, main areas of concern are mutagenicity, carcinogenicity, repeated dose toxicity and, with reservation, developmental toxicity. For a summary of the most critical exposure scenarios in the order of risk see table 4.36 with respect to inhalation and table 4.37 with respect to dermal exposure. Mutagenicity has not been included in these tables because a ranking is not meaningful on the background that concern applies for all scenarios.

The highest risks by inhalative exposure are obtained for production of perfumes, scenario (3), whereas the top candidates for dermal risks are recovery of benzene in coking plants and cleaning of crude benzene tanks, scenarios (2), (8a). For all scenarios concern is expressed in the first place because of inhalative exposure, inhalation being simply the major exposure route in quantitative terms. Concerning dermal risk assessment two clearly different situations are identified: in case of free evaporation dermal risks generally are low, if, however, evaporation is hindered, cancer risks by skin contact cannot be excluded. If both exposure pathways are considered in combination the ranking of scenarios according to the inhalative risks does not change significantly which indicates the predominant role of inhalation.

Several measures to reduce benzene exposure at the workplace are already applied or envisaged, as for instance the OEL of 1 ppm or the limit of 1% concerning the benzene content of gasoline. As result of the actual occupational risk assessment however, concern still has to be expressed for several workplaces with benzene exposure even if this conditions are implemented. Further risk reduction measures therefore appear to be strongly indicated. On the background of cancer risks inhalative exposure against airborne concentrations of 3.2 mg/m^3 (1 ppm) cannot be addressed as low risk scenarios and should be further reduced. Additional emphasis should be given to prevent prolonged dermal contact with benzene which might considerably contribute to total risk. In that context it should be realized, that a main problem may arise by hindered evaporation because of non proper use of suitable gloves. In these cases free evaporation would significantly reduce the risks, which could mean that risks would be lower if PPE would not be used.

Table 4.36 Ranking of the most critical inhalative exposure scenarios for benzene and associated health risks[1]

Scenario		Exposure level in mg/m³	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)
3	Production of perfumes, use of benzene	84	iii	iii	iii	iii
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	67.7	iii	iii	iii	iii
2	Recovery of benzene in coking plants by product recovery	15.5	iii	iii	iii	
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	6.8	[4]	[4]		
11a	Foundries (without LEV)	5.4	iii	iii		
1	Production , further processing, refinery	3.5	iii	iii		
10	Tire retreading, plastics, inter alia using adhesives, content of benzene limited to 0.1%	2.7	iii			
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	2.25	[4]			
11b	Foundries (with LEV)	1.6	iii			
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	1.26	[4]			
9	Use of formulations with resudual benzene, e.g. adhesives paints, containing < 0.1% benzene	1	iii			

Scenario		Exposure level in mg/m³	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)
7a	Service stations, handling of gasoline (1% benzene) (without VR)	0.5	[4]			
8b	Cleaning of tanks heating oil tanks	0.44	iii			
4	Production of formulations, use of solvents	0.15	iii[3]			
7b	Service stations, handling of gasoline (1% benzene) (with VR)	0.1	[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
(4) A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

Table 4.37 Ranking of the most critical dermal exposure scenarios for benzene and associated health risks[1]

Scenario		Exposure level (internal dose) 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	14[3]	iii			
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	14[3]	iii			

Scenario		Exposure level (internal dose) 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
6	Automobile industry, mechanic engineering, car repair, car recycling (1 % benzene)	8.4[3]	[5]			
5a	Distribution of gasoline (marine road, rail), 1% benzene (without VR)	4.2[3]	[5]			
5b	Distribution of gasoline (marine road, rail), 1% benzene (with VR)	4.2[3]	[5]			
9	Use of formulations with resudual benzene, e.g. adhesives paints, containing < 0.1% benzene	1.5	iii[4]			
other scenarios		< 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
(5) A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

In table 4.38 occupational exposure scenarios are listed in the order of scenario numbers to give an overview for all situations with concern. All toxicological endpoints are listed which at least in one case give reason for conclusion iii. Concern results mainly from inhalative exposure. For risks concerning carcinogenicity dermal exposure is relevant too. For repeated dose toxicity and developmental toxicity combination of both exposure routes identifies additional concern for scenario (6). For that reason an extra column for combined exposure is included in table 4.38 Irritation, respiratory sensitisation and local effects after acute or repeated exposure are not included in table 4.38 because these endpoints do not lead to conclusion iii. For skin and eye irritation concern is not expressed although risks at the workplace cannot be excluded. However, control measures available because of classification and labelling are judged to be sufficient for risk reduction if complied with.

Table 4.38 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					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]	

Scenario		Acute tox.	Repeated dose tox. / Developmental tox.			Muta-genicity	Carcino-genicity		Ferti-lity
		Inhalation	Inhalation	Dermal	Combined	Inhalation / Dermal	Inhalation	Dermal	Inhalation
8a	Cleaning of tanks crude benzene tanks, gasoline tanks	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)	
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 chapter 4.1.3.2.2/Carcinogenicity
(4) A formal conclusion is not drawn because this exposure scenario refers to non-isolated benzene in gasoline

4.1.3.3 Consumers

There is contrarily information concerning benzene as a constituent in consumer products (see Table 2.4 and 4.1.1.3). There are data that benzene may be a contaminant in consumer products. 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.

Exposure

Inhalation is the dominant pathway for benzene exposure in humans, whereas oral and dermal exposure can be neglected. The following concentrations of benzene which have been estimated for the different exposure scenarios are considered to be relevant for the risk characterisation:

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. Moreover, during smoking humans are exposed to a variety of other toxic chemicals originating from combustion of tobacco.

Effects

Acute Toxicity

Following the exposure assessment (scenario 2 + 4), consumers are not expected to be exposed to benzene in the range of doses which can be derived from acute oral toxicity figures based on different animal LD50 values (oral, rats: > 5000 mg/kg bw). In experiments with rabbits and guinea pigs, the substance has demonstrated low dermal toxicity (LD50 >8000 mg/kg bw), in experiments with rats the acute inhalation toxicity was also low (LC50 ~ 44 g/m³, 13.700 ppm).

In humans no acute toxic clinical symptoms were documented at 80 mg/m³ (25 ppm), inhaled for 6 hours while a one-hour exposure to 1600 mg/m³ caused only some symptoms of illness. Therefore, the substance is considered to be of no concern for the consumer in relation to acute oral , inhalation or dermal toxicity.

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

Scenario 3

Filling of gasoline lasting only for some minutes is considered as an acute inhalation exposure. The margin of safety of 62 between the human no effect level of 80 mg/m³ and the short term exposure of 1.3 mg/m³ is considered to be sufficient with respect to the exposure scenario.

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

Irritation /Corrosivity

High concentrations of benzene vapours are irritating to the mucous membranes of the eyes, nose, and respiratory tract. Liquid benzene on direct contact with the skin may cause erythema and blistering. 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 and for risk reduction measures beyond those which are being applied already.

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 handling benzene.

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

Repeated dose toxicity / Non-neoplastic lesions

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. Rats seem to be less sensitive than mice. 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). At that concentration a depression in the numbers of circulating red cells and lymphocytes and the number of splenic nucleated cells were observed.

The LOAEC of 32 mg/m³ (10 ppm) in mice characterised the most sensitive adverse effect of benzene after repeated exposure to animals.

In humans, hematological effects of varying severity have occurred in workers occupational exposed to high levels of benzene. The prevalence of leucopenia correlates with the 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 above 320 mg/m³ (100 ppm). The LOAEC for red blood cell depression may be somewhat lower than for white blood cell depression and would be 32 mg/m³ (10 ppm). Thus, for blood cell depression an overall LOAEC is suggested to be 32 mg/m³ (10 ppm). For depression of lymphocytes, a NOAEC of 3.2 mg/m³ (1 ppm) has been derived (cf. 4.1.2.6.2). This value will be used for quantitative risk assessment procedures for subchronic and chronic inhalation exposure scenarios.

Margin of safety (MOS)

For the decision on the appropriateness of MOS, the following aspects regarding the critical effects as well as exposure have been considered and taken into account:

- Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. The data were published in peer reviewed journals or submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognized guidelines and to GLP.

The findings of all studies are not contradictory so that the judgement can be based on the database (cf. 4.1.2.6).

There are no reasons to assume limited confidence.

Intra- and interspecies variation (for humans see below)

The myelotoxicity of benzene seems to be the result of relatively high concentrations of metabolites in the bone marrow of animals species and in the toxicological properties of these metabolites (cf. 4.1.2.1). The ability of bone marrow cells to metabolise benzene (CYP2E1) is in the focus of recent investigations in different species and humans. Data have shown, that intraspecies/intrastrain variability of CYP2E1 activity in bone marrow of rodents is small, but the CYP2E1 activity between the bone marrow of rodents and non-rodents species varied.

Rats seem to be less sensitive than mice (LOAEC 32 mg/m³ in mice). In humans, haematological effects have occurred at the same level of benzene of 32 mg/m³ (10 ppm). As the most sensitive reaction in humans exposed occupationally to different benzene concentrations a depression of lymphocytes occurred. A NOAEC for that effect of 3.2 mg/m³ (1 ppm) will be used for quantitative risk assessment.

Some evidence for subclinical haematopoietic changes in neonates of animals intermittently exposed to benzene at about 20 ppm during gestation had been reported from studies with mice, however, the significance of these changes is not known.

Dose-response relationship

A steep dose-response relationship is observed in mice (LOAEC 10 ppm; severe effects at 100 ppm in laboratory animals). The effects in humans are observed at the same concentration range.

The nature and severity of the effect

The effect observed in animals and humans are adverse haematological effects, these effects are considered to be severe. The effects are not limited to the species tested, there is also high relevance for humans. The depression of lymphocytes observed in occupationally exposed humans (at low benzene concentrations) may be regarded as an early indicator of intoxication, which precedes the appearance of other disturbances in cellular immunity reactions.

Differences in exposure (route, duration, frequency and pattern)

The measured benzene concentration in air (worst case scenario) is compared with a human NOAEC.

There are no reasons to assume that special concern can be derived from this procedure.

The human population to which the quantitative and/or qualitative information on exposure applies

Variability in kinetics: As pointed out CYP2E1 activity plays an important role for benzene induced haematotoxicity in man (Rothman et al., 1997). Hence, the intrahuman variability of CYP2E1 has to be taken into consideration. Variability of CYP2E1 activity in the liver is reported to vary between 4-30 fold from in vitro and in vivo studies (Diener et al., 1998). In human white blood cells, representing bone marrow activity, CYP2E1 activity varied 3-fold (Bernauer et al., 2000).

Variability in dynamics: Patients with impaired bone marrow function, e.g. cancer patients under treatment with cytostatic drugs might constitute a population under particular risk.

Children seem not to be at special risk according to the study with pregnant animals.

Other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for the different inhalation exposure scenario

Table 4.39 Summary of Margins of Safety for Repeated dose toxicity of benzene (non-neoplastic effects), Fertility, and Developmental toxicity for different inhalation exposure scenarios

Scenario	Benzene concentration (mg/m³)	Margin of safety (MOS)		
		RDT (NOAEC 3.2 mg/m³)	Fertility (NOAEC 96 mg/m³)	Devel. Toxicity (NOAEC 31.9 mg/m³)
1) Passive smokers	0.007	460	13700	4560
2) Painting (user)	0.017	190	5650	1880
4) Exposure from car interior accessories	0.012	270	8000	2660

Repeated dose toxicity

For the scenarios painting, and exposure from car interior accessories the margins of safety regarding non-neoplastic effects are judged to be sufficient.

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

Mutagenicity

Benzene is an in vivo mutagen in mammals, especially chromosomal aberrations and micronuclei are induced.

Benzene 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.

There is a need for limiting the risks; 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). From the numerous human epidemiological studies is sufficient scientific evidence to assume a causal relationship between benzene exposure and acute non-lymphatic leukaemia.

Benzene is carcinogenic to human 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.

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

Toxicity for reproduction

Fertility

From the available studies with repeated inhalation exposure to rats and mice, the data of the study of Ward et al. (1985) will be used for derivation of a NOAEC fertility for quantitative risk assessment, since during this study organ weight determinations as well as histopathological evaluations had been performed for both sexes and at periods relevant for reproduction. No effects for either sex had been observed in these studies with rats at concentrations of up to and including 960 mg/m^3 benzene. Also, no effects on female reproductive capacity and capability were found for rats at this concentration levels. In mice, however, the high benzene concentration of 960 mg/m^3 during the chronic toxicity study led to clear-cut hematotoxicity 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). Based on the effects in mice at high benzene concentrations of 960 mg/m^3 (300 ppm) a NOAEC/reproductive organ toxicity of 96 mg/m^3 (30 ppm) is derived.

An available fertility study in rats (Kuna et al., 1992) is recognised, however, this study is not considered sufficient and adequate for an overall assessment of an impairment of male/female fertility.

Developmental toxicity

Whereas no specific embryotoxic and teratogenic potential 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 after exposure levels of 40 ppm or lower. From the available studies with rats the lowest NOAEC developmental toxicity of 32 mg/m³ (10 ppm) is derived from the study of Kuna and Kapp (1981) and will be used for quantitative risk assessment.

Margin of safety (MOS)

For the decision on the appropriateness of MOS, the following aspects regarding the critical effects as well as exposure have been considered and taken into account:

Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. The data were published in peer reviewed journals or submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognized guidelines and to GLP.

The overall findings of all studies are not contradictory so that the judgement can be based on the database (cf. 4.1.2.9).

Intra- and interspecies variation

The results after inhalatory exposure are fairly consistent across animal species. There is no reason to assume that human susceptibility differs from the situation in animals.

Dose response relationship

None of the clinical fetotoxic findings were observed after exposure to relatively low levels of benzene of 10 ppm (32 mg/m³). At higher inhalatory exposures (between 50 and 500 ppm, 160 and 1600 mg/m³) decreases in maternal weight gain (about 35%), lower mean fetal body weights (about 6 to 13%) and increases in the percentage of fetuses with delayed skeletal ossification (17-23%) were observed. Hence is no indication for a step dose-response relationship.

The human population to which the quantitative and/or qualitative information on exposure applies

Variability in kinetics: As pointed out CYP2E1 activity plays an important role for benzene induced haematotoxicity in man (Rothmann et al., 1997). Hence, the intrahuman variability of CYP2E1 has to be taken into consideration. Variability of CYP2E1 activity in the liver is reported to vary between 4-30 fold from in vitro and in vivo studies (Diener et al., 1998). In human white blood cells, representing bone marrow activity, CYP2E1 activity varied 3-fold (Bernauer et al., 2000).

The nature and severity of the effect

No specific embryotoxic and teratogenic potential could be demonstrated for benzene. Fetal growth retardation was observed at concentration levels which induced also maternally toxic effects. It is questionable whether the observed effect of growth retardation can be considered as severe effects since they may be reversible.

The mechanisms of this toxicity have not been fully elucidated, and there are scarce data on the effects of benzene on maternal food consumption and none on blood levels of benzene and its metabolites in the dams and in their fetuses.

Differences in exposure (route, duration, frequency and pattern)

The measured benzene concentration in air (worst case scenario) is compared with the NOAEC from studies in rats.

There are no reasons to assume that special concern can be derived from this procedure.

Other factors

There are no other factors known requiring a peculiar margin of safety.

Special subpopulations do not apply.

MOS for inhalation exposure scenarios

Fertility

For the scenarios painting, as well as exposure from car interior accessories cars the margin of safety regarding reproductive organ effects (cf. Table 4.39) is judged to be sufficient.

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

Developmental toxicity

For the scenarios painting as well as for exposure from car interior accessories the margin of safety regarding reproductive organ effects (cf. Table 4.39) is judged to be sufficient.

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

Scenario 3

For the scenario filling gasoline the margin of safety for developmental effects of 25 is also considered to be sufficient taking into account that the fetal growth retardation effects observed in experimental animals may be reversible and were predominantly observed at concentrations that turned out to be maternally toxic. Furthermore, this decision seems to be justified with respect to the exposure scenario (short duration time and frequency of exposure).

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

4.1.3.4 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 (cf. Table 4.18). 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 (see Appendix A II, table No. 7 and table 3.4.1). The air concentration of 20 µg/m³ as realistic worst case is used for the risk assessment of unintentional benzene releases from road traffic.

Repeated dose toxicity / Non-neoplastic lesions

The main exposure source via breathing air is considered here for MOS.

For details regarding the NOAEC used for the risk assessment discussion see 4.1.2.6.2 and 4.1.3.3.

MOS for local inhalation exposure scenario (point source)

The concentration of benzene in the air at a point source is 890 µg/m^3.

The margin of safety for non-neoplastic effects between the

calculated exposure level of 890 µg/m^3

and the

NOAEC of 3.2 mg/m^3

is judged to be not sufficient (MOS 3.6).

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

MOS for regional inhalation exposure scenario (regional scenario)

The concentration of benzene in the air at a regional source is 1.54 µg/m^3.

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 (MOS 2080).

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

MOS for inhalation exposure from road traffic

The concentration of benzene from road traffic is assumed to be 20 µg/m^3.

The margin of safety for non-neoplastic effects between the

assumed exposure level of 20 µg/m^3

and the

NOAEC of 3.2 mg/m^3

is judged to be not sufficient taking into consideration the upper range of monitoring data (275 µg/m^3) as well as the the severity of the effects, the high variability in the human population of the metabolic enzyme CYP2E1 and the possible specific human sub population with higher risk (MOS 160).

No formal risk characterisation 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.

Mutagenicity

Benzene 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 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.

Toxicity for reproduction

For details regarding the NOAECs for fertility and developmental toxicity used for the risk assessment see 4.1.3.3.

Fertility

MOS for local exposure scenario (point source)

The highest air concentration of benzene at a point source is 890 µg/m^3.

The margin of safety for reproductive effects between the

calculated exposure level of 890 µg/m^3

and the

NOAEC of 96 mg/m^3

is judged to be sufficient (MOS 108).

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

MOS for regional exposure scenario

The regional concentration of benzene in the air was calculated to be 1.5 µg/m^3.

The margin of safety for reproductive effects between the

calculated regional exposure level of 1.5 µg/m^3

and the

NOAEC of 96 mg/m^3

is judged to be sufficient (MOS 64000).

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

MOS for inhalation exposure from road traffic

The air concentration of benzene from road traffic is assumed to be 20 µg/m³.

The margin of safety for reproductive effects between the

assumed exposure level of 20 µg/m³

and the

NOAEC of 96 mg/m³

is judged to be sufficient (MOS 4800).

No formal risk characterisation 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.

Developmental toxicity

MOS for local inhalation exposure scenario (point source)

The concentration of benzene in the air at a point source is 890 µg/m^3.

The margin of safety for developmental effects between the

calculated exposure level of 890 µg/m^3

and the

NOAEC of 31.9 mg/m^3

is judged to be sufficient taking into consideration that the effect of growth retardation in experimental animals are considered to be reversible, and were predominantly observed at concentrations that turned out to be maternally toxic (MOS 36).

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

MOS for regional inhalation exposure scenario

The concentration of benzene in the air at a regional source is 1.54 µg/m^3.

The margin of safety for developmental effects between the

calculated regional exposure level of 1.54 µg/m^3

and the

NOAEC of 32 mg/m^3

is judged to be sufficient (MOS 20700).

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

MOS for inhalation exposure from road traffic

The air concentration of benzene is assumed to be 20 µg/m^3.

The margin of safety for developmental effects between the

assumed exposure level of 20 µg/m^3

and the

NOAEC of 32 mg/m^3

is judged to be sufficient (MOS 1600).

No formal risk characterisation 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.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Occupational exposure

Refer to chapter 4.1.1.1.

4.2.1.2 Consumer exposure

4.2.1.3 Indirect exposure via the environment

4.2.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.2.2.1 Explosivity

Benzene is not explosive.

4.2.2.2 Flammability

Benzene is highly flammable.

4.2.2.3 Oxidising potential

Due to its chemical structure, benzene is not expected to possess any oxidizing properties.

4.2.3 Risk characterisation

4.2.3.1 Workers

Benzene is highly flammable. Adequate worker protection measures must be observed. Risk reduction measures beyond those which are being applied already are not considered necessary.

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

4.2.3.2 Consumers

4.2.3.3 Man exposed indirectly via the environment

5 CONCLUSIONS / RESULTS

5.1 GENERAL

Benzene occurs naturally as a component of petroleum and to a lesser extent, as a component of condensate from natural gas production. Benzene is produced 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 in the risk assessment report there are 48 companies producing and/or processing pure benzene (CAS-No. 71-43-2) in the EU. Total production is estimated to be 7 247 kt/a and 590 kt/a are imported into the EU. 130 kt/a are exported from the EU.

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.

5.2 ENVIRONMENTAL RISKS

Releases of benzene to the environment from production and processing occur mainly to the atmosphere. Releases to water and soil have been measured and have been estimated using the Technical Guidance Document and site specific information. The major release of benzene is to the atmosphere from vehicle emissions. At the local level, the stripping of benzene in WWTPs may also constitute a significant release. Benzene releases can also occur through other fuel sources and during combustion of fossil fuels. Benzene is volatilized from water and is removed from the atmosphere by reaction with hydroxyl radicals, other reactive species and mainly by advection. Benzene will not adsorb to soil and sediment. Considering all available test results it seems appropriate to classify benzene as readily biodegradable. Benzene is expected to show a low to moderate bioaccumulation potential. Measured levels of benzene are available for all major environmental compartments because huge amounts are released to the environment. Data for contaminated sites are also available.

For the aquatic compartment, benzene is not expected to cause adverse effects in a WWTP, or in surface water at background levels. However, high levels of benzene have been measured or calculated in WWTP's and surface water at contaminated sites. These levels may be expected to cause adverse effects on aquatic organisms. For 23 sites of all 48 sites a risk to the microorganism population of industrial waste water treatment plants can be expected. Based on PECs calculated for the local environment at 2 of 48 sites where benzene is produced and/or used as an intermediate, benzene is likely to cause adverse effects in surface water.

Based on the available toxicity data for plants exposed via the atmosphere and the predicted and measured air concentration of benzene in the risk assessment, benzene is unlikely to cause adverse effects in the atmosphere near to sites where benzene is produced and/or prosessed and in ambient city air.

However, it is known that benzene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone. 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.

Based on the available toxicity data and the predicted soil concentration of benzene in the risk assessment, benzene is unlikely to cause adverse effects in the terrestrial compartment near to sites where benzene is produced and/or prosessed.

The following conclusions are drawn from the risk characterization of benzene:

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 production and/or processing sites of the substance. 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 and for risk reduction measures beyond those which are being applied already

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 of the substance, the PEClocal/PNECaqua ratio is > 1. It has to be noted that the PEC calculations for these sites are partly based on default values.

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

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 and for risk reduction measures beyond those which are being applied already

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 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.

Terrestrial compartment

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

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 and for risk reduction measures beyond those which are being applied already

5.3 HUMAN HEALTH

5.3.1 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.

5.3.2 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.
For exposure to benzene arising from exposures to gasoline at filling stations no formal risk characterisation has been performed since benzene exposures arising from handling gasoline are not formally a part of this risk assessment. Any conclusions regarding risk reduction measures for gasoline have to wait for the risk assessment of gasoline.

5.3.3 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.

For exposure to benzene from road traffic no formal risk characterisation has been performed since benzene exposures arising from gasoline are not formally a part of this risk assessment.

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The report provides 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.

Appendix A I

of the Risk Assessment Report

Benzene CAS-No.: 71-43-2

Distribution and fate

May 2001

Distribution and Fate

$d := Tag$

Substance: Benzene CAS.Nr.: 71-43-2

melting point:	$MP := 278.65 \cdot K$
vapour pressure:	$VP := 9970 \cdot Pa$
water solubility:	$SOL := 1800 \cdot mg \cdot l^{-1}$
part. coefficient octanol/water:	$LOGP_{OW} := 2.13$
moleculare weight:	$MOLW := 0.07811 \cdot kg \cdot mol^{-1}$
gas constant:	$R := 8.3143 \cdot J \cdot (mol \cdot (K))^{-1}$
temperature:	$T := 293.15 \cdot K$
conc. of suspended matter in the river:	$SUSP_{water} := 15 \cdot mg \cdot l^{-1}$
density of the solid phase:	$RHO_{solid} := 2500 \cdot kg \cdot m^{-3}$
volume fraction water in susp. matter:	$Fwater_{susp} := 0.9$
volume fraction solids in susp.matter:	$Fsolid_{susp} := 0.1$
volume fraction of water in sediment:	$Fwater_{sed} := 0.8$
volume fraction of solids in sediment:	$Fsolid_{sed} := 0.2$
volume fraction of air in soil:	$Fair_{soil} := 0.2$
volume fraction of water in soil:	$Fwater_{soil} := 0.2$
volume fraction of solids in soil:	$Fsolid_{soil} := 0.6$
aerobic fraction of the sediment comp.:	$Faer_{sed} := 0.1$
product of CONjunge and $SURF_{air}$:	$product := 10^{-4} \cdot Pa$

distribution air/water: Henry-constant

$$HENRY := \frac{VP \cdot MOLW}{SOL} \qquad HENRY = 432.643 \cdot Pa \cdot m^3 \cdot mol^{-1}$$

$$\log\left(\frac{HENRY}{Pa \cdot m^3 \cdot mol^{-1}}\right) = 2.636$$

$$K_{air\_water} := \frac{HENRY}{R \cdot T} \qquad K_{air\_water} = 0.178$$

solid/water-partition ceefficient Kp_{comp} and total compartment/water-partition coefficient K_{comp_water}

$a := 0.52$ (a,b from chapter 4.3, table 1)

$b := 1.02$ $K_{OC} := 10^{a \cdot LOGP_{OW} + b} \cdot l \cdot kg^{-1}$ $K_{OC} = 134.153 \cdot l \cdot kg^{-1}$

Suspended matter

$Kp_{susp} := 0.1 \cdot K_{OC}$ $Kp_{susp} = 13.415 \cdot l \cdot kg^{-1}$

$K_{susp\_water} := Fwater_{susp} + Fsolid_{susp} \cdot Kp_{susp} \cdot RHO_{solid}$ $K_{susp\_water} = 4.254$

factor for the calculation of $Clocal_{water}$:

$faktor := 1 + Kp_{susp} \cdot SUSP_{water}$ $faktor = 1$

Sediment

$Kp_{sed} := 0.1 \cdot K_{OC}$ $Kp_{sed} = 13.415 \cdot l \cdot kg^{-1}$

$K_{sed\_water} := Fwater_{sed} + Fsolid_{sed} \cdot Kp_{sed} \cdot RHO_{solid}$ $K_{sed\_water} = 7.508$

Soil

$Kp_{soil} := 0.02 \cdot K_{OC}$ $Kp_{soil} = 2.683 \cdot l \cdot kg^{-1}$

$K_{soil\_water} := Fair_{soil} \cdot K_{air\_water} + Fwater_{soil} + Fsolid_{soil} \cdot Kp_{soil} \cdot RHO_{solid}$

$K_{soil\_water} = 4.26$

Sludge

$K_{p\_sludge} := 0.37 \cdot K_{OC}$ $K_{p\_sludge} = 49.637 \cdot l \cdot kg^{-1}$

Elimination in STPs

rate constant in STP: k =1 h^{-1}

elimination P = f (k, logpow, logH) = 93.9 %

fraction directed to surface water $Fstp_{water}$ =6.1 %

biodegradation in different compartments

surface water

$kbio_{water} := 4.7 \cdot 10^{-2} \cdot d^{-1}$ (cTGD, table 5)

soil

$DT50bio_{soil} := 30 \cdot d$ (cTGD, table 6)

$kbio_{soil} := \frac{\ln(2)}{DT50bio_{soil}}$ $kbio_{soil} = 0.023 \cdot d^{-1}$

sediment

$kbio_{sed} := \frac{\ln(2)}{DT50bio_{soil}} \cdot Faer_{sed}$ $kbio_{sed} = 2.31 \cdot 10^{-3} \cdot d^{-1}$

degradation in surface waters

$khydr_{water} := 6.93 \cdot 10^{-7} \cdot d^{-1}$

$kphoto_{water} := 6.93 \cdot 10^{-7} \cdot d^{-1}$

$kdeg_{water} := khydr_{water} + kphoto_{water} + kbio_{water}$

$kdeg_{water} = 0.047 \cdot d^{-1}$

Atmosphere

calculation of CONjunge * SURFaer for the OPS-model

$VPL := \frac{VP}{\exp\left[6.79 \cdot \left(1 - \frac{MP}{285 \cdot K}\right)\right]}$ $VP := wenn(MP > 285 \cdot K, VPL, VP)$ $VP = 9.97 \cdot 10^{3} \cdot Pa$

$Fass_{aer} := \frac{product}{VP + product}$

$Fass_{aer} = 1.003 \cdot 10^{-8}$

degradation in the atmosphere

$kdeg_{air}$ =0.0517 d^{-1} (see RAR benzene, Chapter 3.1.1.3.1)

Appendix II

of the Risk Assessment Report

Benzene CAS-No.: 71-43-2

Summary of monitoring data

September 2002

Appendix II

Water

Air

Biota

Soil and Sediment

Food

Table 1: Benzene in Fresh Surface Water

Location	Concentration [µg/l]	Period	Remark	Reference
Germany • Rhein and tributaries	not detected < 0.1 – 0.2	1990 – 1991 monit. Programme 1994	detection limit: 5µg/l 0.1 µg/l	Landesamt für Wasser und Abfall Nordrhein-Westfalen 1991, 92
Germany • Lausitzer Neisse, Große Röder, Elbe, Zwickauer Mulde, Schwarze Elster	not detected	1994 monitoring programme	detection limit: 0.16µg/l	Sächsisches Landesamt für Umwelt and Geologie 1995 b
Germany • Rhein km 163.9	<0.5	1995 monitoring programme		AWBR 1995
Germany: Elbe • Schmilka • Zehren • Torgau • Madgeburg • Schnackeburg • Boizenburg • Zollenspieker • Seemanshöft • Grauerort • Cuxhaven	 <0.1 <0.1 <0.1 <1 <0.5 <1 <5 <5 <0.5 <0.5	1994 monitoring programme	detection limit: 0.1µg/l weekly samples	ARGE Elbe 1996
Germany • rivers of Hessia	0.2 - 0.5	1994/95	all BTX aromatics	Hessische Landesanstalt für Umwelt 1997

cont. of Table 1

Location	Concentration [µg/l]	Period	Remark	Reference
Germany • Elbe, Schwarze Elster, Mulde, Saale, Unstrut, Weisse Elster, Havel, Aland	not detected	1994 monitoring programme	quantification limit: 2µg/l	Landesamt für Umweltschutz Sachsen Anhalt 1995
Germany: Elbe tributaries • Schwarze Elster at Gorsdorf • Mulde at Dessau • Saale at Rosenburg	 <2 - <5 <2 - <5 <1	1994 monitoring programme	detection limit: 0.1 µg/l weekly samples	ARGE Elbe 1996
Germany/Netherlands • Rhine at Lobith • • • Ijsselmeer at Andiik • Haringvlietwassers at Stellendam	 min: 0 mean: 0.1 max.: 0.5 not detected max: 0.1	1994 monitoring programme	detection limit: 0.1 µg/l	RIWA 1994
Germany/Switzerland/ • Rhine at Basel/Weil am Rhein	1994: benzene was measured often at 0.5 1995: <0.5 1996: <0.5, max. 1.7	1995/6 monitoring programme since 1993	detection limit: 0.5 µg/l; two weekly samples no value greater than 0.5 µg/l	Gewässerschutzamt Basel-Stadt 1994, 1995, 1996
Netherlands • rivers and lakes • Rhine • North Sea coastal water	 generally: <0.1 median: 0.026 <0.005 - 0.02	1980s		RIVM 1988

cont. of Table 1

Location	Concentration [µg/l]	Period	Remark	Reference
Netherlands • Voorste Stroom • Mark-Dintel	relative occurence in both rivers: 11-30% of all samples	prior to 1991	both rivers discharge into the North Sea, 75000 samples taken throughout the whole year.	Pols et al. 1991
Spain • Llobregat river	mean: 0.76 median: 0.64 range: 0.05 - 1.80	September 1989 - March 1990		Guardiola et al. 1991
United Kingdom • 80 rivers and estuaries	average: 7.05 maximum: 89.4	December 1988 to February 1989	detection limit: 0.1 µg/l 93 out of 154 samples were below detection limit, remaining 61 samples with conc. above detection limit.	SAC scientific Ltd 1989 cited in Nielsen et al. 1991
United Kingdom • Tyne • Wear • Tees	<0.1 - 31.7	1990 - 1994	detection limit: 0.1 – 0.6 µg/l 45 of 40 samples less than detection limit	CEFIC 1996

Table 2: Benzene in Sea Water

Location	Concentration [µg/l]	Period	Remark	Reference
United Kingdom • Humber estuary • Tees estuary • Tyne estuary • Thames estaury	 2 - 12 <1 - 18 1 - 3 <1 - 9	1984		Minsitry of Agriculture, Fisheries and Food`s Fisheries Laboratory at Burnham-on Crouch cited in Nielsen et al. 1991
Netherlands • North Sea coastal water • North Sea central part	 <0.005 - 0.02 average: 0.005	1980s		RIVM 1988

Table 3: Benzene in Groundwater

Location	Concentration [µg/l]	Period	Remark	Reference
Croatia • wells near Zagreb	0.033 - 0.040	prior 1991	infiltration of Sava river into the groundwater	Ahel 1991
Denmark • no site specified	mean: 0.20 average: 0.41 maximum: 5.10	Danish groundwater monitoring programme 1989 - 1995	delection limit: >0.05 number of analysis: 1 874 number of drillings: 558 number of detections: 126	Danmarks og Gronlnads Geologiske Undersogelser 1996
Netherlands	0.005 - 0.03	early 1980s	unpolluted areas	RIVM 1988; cited in Nielsen et al. 1991 under the name of Slooff 1988
Switzerland • Zürich	0.045	1974		Grob and Grob 1974; cited in Nielsen et al. 1991
United Kindgom • East Anglia	210 m from facility: 1-10 120 m from facility: 250 10 m from facility: 1 250	1981	contaminated chalk aquifier near petrol storage facility	Tester and Harker 1981; cited in Nielsen et al. 1991

cont. of Table 3

Location	Concentration [µg/l]	Period	Remark	Reference
United Kingdom	arithm. mean: 0.027 (11 bore holes) average: 0.009 (32 bore holes) maximum: 0.07	summer 1983	32 public and private supply boreholes: 11 were found to contain benzene	Kenrick et al. 1985; cited in Nielsen et al. 1991
United Kindgom • Birmingham	maximum: 0.6	1986-1988	59 industrial supply boreholes in Birmingham aquifier	Rivett et al. 1991; cited in Nielsen et al. 1991

Table 4: Benzene in Drinking Water

Location	Concentration [µg/l]	Period	Remarks	Reference
EU	<0.1 – 1		range value literature compilation	Neumeier 1991; cited in CONCAWE 1994a
Germany	0.1 – 1		range value literature compilation	Reynolds & Harrison, 1982, cited in IPCS 1993 and CONCAWE 1994a
Germany	0.018 - 0.045		range value literature compilation	Eikman et al. 1992; cited in CONCAWE 1994a
Netherlands	<0.005		detection limit: 0.005 µg/l	Kool et al. 1979; as reported in RIVM 1988
Spain • Barcelona	<0.05	September 1989 -March 1990: weekly sample	All tap water samples were less than the detection level (<0.05 µg/l). The raw water from the Llobregat river had benzene levels of 0.05 - 1.80 µg/l, mean of 0.76 µg/l, and median of 0.64 µg/l	Guardiola et al. 1991

Table 5: Benzene in Rainwater

Location	Concentration [µg/l]	Period	Remark	Reference
The Netherlands	Average: 0.03	prior 1985		RIVM 1988
Germany • Berlin	residential area: 0.13 sites near the airport: 0.20 - 0.23 site at a busy traffic intersection: 0.10 - 0.46	1974 - 1975		Lahmann et al. 1977; cited in Nielsen et al. 1991

Table 6: Benzene in Waste Water Treatment Plant Influents and Effluents

Location	Concentration [µg/l]	Period	Remark	Reference
Belgium • industrial WWTP	effluent: 800	1994	detection limit: 0.1 µg/l, 702 out of 730 measurements were below the detection limit of 0.1 µg/l	APA 1995
Finland • industrial WWTP	influent: <10 000 effluent: <100	1994	detection limit: 100 µg/l	APA 1995
France • industrial WWTP	influent: 1 500			APA 1995
France • industrial WWTP	influent: min: <100 max.:8 000			APA 1995
France • industrial WWTP	influent: 2 000 – 82 000	1999		APA 1999
Germany	car-wash: 1.4 - 5.5 garage: 70.65 petrol depots: 0.05 – 1 267	November 1983 - May 1984	monthly sampling at eight petrol service stations and two petrol depots	Baumung et al. 1985

cont. of Table 6

Location	Concentration [µg/l]	Period	Remark	Reference
Germany • industrial WWTP	effluent: min: < 5 max. 8	1999		APA 1999
Germany - Hessia • municipal STP • industrial WWTP	 effluent: 0.2 - 2 effluent: 0.1 - 10 (different BTX)	 1994/95 1995	 detection limit: 0.02; n=7 n=4	Fooken C et al, Hessische Landesanstalt für Umwelt 1997
Germany • industrial WWTP	effluent: average: <0.7	1994	detection limit: <1 µg/l	APA 1995
Germany • industrial WWTP	influent: 40 - 160 effluent: <1	1999		Emschergenossenschaft 2000
Italy • industrial WWTP	effluent: below detection limit	1994	detection limit: 5 µg/l	APA 1995
Netherlands • industrial WWTP	effluent min.: <0.2 max.: 1 260 average: 169	1995		APA 1995
Netherlands • industrial WWTP	effluent: 0.79 - 1.6	1993 - 1994		APA 1995
Sweden • Goeteborg: municipal WWTP	influent: 0.1 - 5 average: 3.9 (1989) average: 3.5 (1990) average: 0.3 (1991) effluent: <0.5	1989 - 1991		Paxeus et al. 1992

cont. of Table 6

Location	Concentration [µg/l]	Period	Remark	Reference
United Kingdom • industrial WWTP	in site effluent: 78 000 50 yards downstream: 100	1995		APA 1995
United Kingdom • industrial WWTP	effluent: 63 200	1995		APA 1995
U.S.A • WWTP of two refineries	influent: 15 600 effluent: < 6	prior 1981	detection limit: 6 µg/l	API 1981

Table 7: Benzene in City Air

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Austria • Vienna city, 52m top of building street canyon residential local background	arithmetic average 10.1 26.9 7.1 3.7	October 1986 – February 1987		Lanzerstorfer and Puxbaum 1990
Austria • Vienna: low traffic density • Vienna: high traffic density • Vienna: service station	 annual average: 2.0 - 3.2 annual average: 8.8 - 15.5 annual average: 16.0	1992-1993		Hanus-Illnar and Hrabcik 1994
Austria • Vienna: high traffic • rural site	14-days-mean range: 5 – 20, max.: 28 about 2, winter: < 5	1992/93	exposure time: 14 days sampling 1.5 m above ground	Hanus-Illnar and Hrabcik 1995

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Austria • Lobau/petrol depot	annual average: 12.7 - 17.0	1992-1993	dependent on distance, detection limit 0.8 µg/m^3.	Hanus-Illnar and Hrabcik 1994
Belgium • Antwerpen	annual average level: 4.4	September 1997 – September 1998		MACBETH
Denmark • Copenhagen: Jagtwej	mean weekday street/background February 1994: 31.4 / 5.1 May 1994: 26.6 / 4.9 August 1994: 16.2 / 2.6 December 1994: 14.3 / 3.6 March 1995: 12.3 / 4.5	February 1994 - March 1995	measured at street level in central Copenhagen (street) background measured on top of 20 m high building (roof)	Hansen and Palmgren 1996
Denmark • Copenhagen	weekly average: 18	one week in February 1996		Mowrer et al. 1996
Denmark • Copenhagen	annual average level: 3.1	September 1997 – September 1998		MACBETH
Finland • Helsinki	arithmetic mean: 1.66 winter: mean: 1.7, max: 2.9 spring: mean: 1.4, max: 2.6 summer: mean: 1.8, max: 7.7 fall: mean: 1.9, max: 7.0	1996/1997		Edwards, Jantunen 2001
France • Angers: city street • Angers: background level of city air	maximum 34 +/- 15 5 +/- 3	June 1994	sampled at crossroad during peak hours of traffic (8-9 h and 17-18 h)	Davy et al. 1995

France • Grenoble	winter average: 10.4, max: 42.9 summer average: 9.5, max. 44.6 whole year average: 15.2, max: 44.6	1987		Foster et al. 1991
France • Grenoble	1,62 – 9,72	04. May – 11. May 1995	samples were recorded for two hour-periods continuosly for one week	Ferrari et al. 1998

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
France, Paris • street maximum • intersection maximum • street minimum • intersection minimum • street average • intersection average • underground parking	minimum - maximum 41 64 2 15 14 32.5 240	September - December 1993	24-h sampling detection limit: 2 µg/m^3	Coursimault et al. 1995
France • Rouen	annual average level: 4.7	September 1997 – September 1998		MACBETH
France • Rouen	Average : 4 Rush hour mean: 15.3	1997 - 1998	Background sites; mean of 6 monitoring campaigns excluding all values > 90th percentile	Gonzales-Flesca et al. 2000
France • 8 locations in Strasbourg. Border between France and Germany: Oberhausbergen and Willstätt	annual average: 1.5 - 21 all averages in 5-8 range with one exception, Blvd Wilson: 21 98% value 5-30 with one exception, Blvd. Wilson: 50	April 1993 to March 1994	detection limit 0.4 µg/m^3 30 min – 1 h sampling	UMEG and ASPA; November 1994
France • near three coal-fired power stations	3.1 - 20	prior 1992		Garcia et al. 1992
Near coal coke oven • different coal coke producing companies	inside plant: 40 - 31000 outside plant: 6 - 63, varied upon distance	prior 1991		Thomas 1991
Germany • Hamburg	annual antithetic mean: 6. 9 - 19.3	April 1986 - April 1987	12 sites in residential, industrial, downtown, near street with dense traffic areas	Bruckmann et al. 1988

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • Former Federal Republic of Germany	range: 0.4 – 348 (max. value = Northrhine-Westfalia 1981-83) average values: 7.5 – 142 (max value = residential area close to a coke oven)	1974 - 1986	literature compilation	GDCh 1992
Germany • Hamburg Elbtunnel	24-h average: 80.5 - 95.3	1989	tunnel	Dannecker et al. 1990
Germany • Bremen: heavy traffic street	annual mean 16 - 27	1993		Wieben et al. 1994
Germany Lower Saxony • Braunschweig • Hannover	monthly average • 3 – 6.5 • 7 - 14	January to December 1991 January to December 1992	city air in streets with heavy traffic	LUEN 1993
Germany • Cities in Nordrhein-Westfalen	• Range of average near cookers: 6.9 – 17.8 • Range of 1987-88 average for 62 town and city locations: 10.2 – 10.2 • Range of average near various industries: 6.2 - 17.8, Aromatics plant average 7.9, range 4.4-15.5. • Range during smog period 20.9-85.6 (17 – 19 January 1985)	1980-1988 monitoring programme	30 Min/10 L samples. GC/FID, detection limit 0.5 µg/m^3.	LIS 1988

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany North Rhine-Westfalia • Ruhr area (regional) • Eggegebierge (pristine) • Eifel (pristine) • Rothhaargebirge (pristine) • Nettetal (rural) • Krefeld-Ostwall (city) • Essen-Ost (city) • Düsseldorf-Mörsenbroich (city)	annual average 3.5 0.96 0.82 0.88 2.0 11.1 12.7 22.8	1990	The Northrheine-Westfalia State Centre for Air Quality Control and Noise Abatement (LIS) operates TEMES, the telemetric air pollution monitoring network with 76 stationary and 8 mobile monitoring stations.	Pfeffer 1994
Germany • Nordrhein-Westfalen Polluted areas situated along Rhine and Ruhr rivers	• Rhein-Ruhr: 1989 annual mean 4.8 min 1.8, max 9.7. • Ruhrgebiet 1989: Regional means: East 4.9, Middle 5.2, West 4.0. • Rhein: Middle 5.3, South 5.0 • Düsseldorf-Mörsenbroich max. half hour mean: 63.3	1989 monitoring programme		LIS 1991

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • Nordrhein-Westfalen Polluted areas situated along Rhine and Ruhr rivers	• Rhein-Ruhr: 1990 annual mean 3.5, min 1.3, max 9.9 • Ruhrgebiet 1990: Regional means: East 3.28, Middle 3.71, West 3.01. • Rhein: Mid 3.78, South 3.91 • Düsseldorf-Mörsenbroich max. half hour mean: 38.8 • Berlin average 5.1, range of averages 3.3-8.8	1990 monitoring programme		LIS 1992
Germany • Nordrhein-Westfalen Polluted areas situated along Rhine and Ruhr rivers	• Rhein-Ruhr 1992 mean 3.01 min 1.51, max 5.59. • Ruhrgebiet 1992: Regional means: East 2.44, Middle 3.15, West 2.84. • Rhein Middle: 3.3, South 3.56	1992 monitoring programme		LIS 1994a
Germany • Nordrhein-Westfalen Polluted areas situated along Rhine and Ruhr rivers	• Rhein-Ruhr 1993 mean 2.75 min 1.2, max 5.06 • Ruhrgebiet 1993: regional means: East 2.6, Middle 3.05, West 2.25. • Region Düsseldorf 3.0, region Köln 2.92; region Bonn 2.92	1993 monitoring programme		Landesumweltamt Nordrhein-Westfalen 1994
Germany • Düsseldorf, Cornelius Street • Essen, Hindenburg Street	annual average: 13.5, min.: 1.7, max.: 35.5; N = 96 annual average: 11.6, Min.: 3.3, max.: 29.7; N = 87	1993	sampled at 1.5 m height Düsseldorf: 55000 vehicles./d Essen: 35 000 vehicles /d	Pfeffer et al. 1995

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • West-Berlin: 11 sites	annual average: 5.4 range : 2.6 - 10.3	1989	highest values in winter, decrease in values from previous years, 60 l/30 min samplers. 0.7 µg/m^3 limit of detection.	BIFAU 1990
Germany • West-Berlin: 11 sites	annual average: 5.1 range: 3.3 - 8.8	1990	40 l samplers/20 min. 0.55 µg/m^3 limit of detection.	BIFAU 1991
Germany • East-Berlin and Brandenburg 12 sampling locations	annual average: 1.6 – 14.5 (range), 6.9 (mean) Averages: 1988-6.1, 1989-5.4, 1990-5.1, 1991-6.9	1991	detection limit: 0.5 µg/m^3 note: 1991 was the first year that the former East Berlin was included in measurements. 30 l/15 min samplers	TÜV Berlin Brandenburg 1992
Germany • Berlin, Lahnstrasse • Karl-Marx-Strasse • Schildhornstrasse	annual mean 15 16 21	1991	The benzene concentrations in cities are proportional to street geometry (height of buildings) and numbers of cars/day.	UBA 1994
Germany • Berlin: 18 city locations	Annual average: 1.8 – 14 / 7.47 (range/average for active sampling) Annual average 1.7 – 11.8 / 7.47(range/average for passive badges)	October 1993 to September 1994	good correlation between passive badges and 30 minute active samples shown: passive badges 6 – 8 days/sample; 30 min active limit of determination 1.4 µg/m^3 Samples collected at 3.5-4 m height, 30 minute-60 l samples.	BIFAU 1994
Germany, Brandenburg • Nauen • Cottbus	mean: 12.6, Range: 3 – 30 50%: 11.2, 98%: 29.8 mean: 11.1, range: 1 – 38 50%: 9.3, 98 %: 34	1994	24 h sampling near roads with high traffic Adsorption on acierated carbon, GC	Landesumweltamt Brandenburg 1995

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • 3 cities in Hessia: Hanau, Kassel, Wetzlar-Giessen	average: 3.1 - 8.8 98% value 10.4-45.7, Hanau (Jan - Dec 1993). Average: 1.6 – 6.6 98% value 6.7-31.8, Kassel (July 1989 – June 1990). Average; 1.5 – 4.0 98% value 5.9-29.7, Wetzlar-Giessen (July 1987 – June 1988).	1987 – 1993	no time specified, no indication of continuous or spot sampling.	HLFU 1995 a
Germany • Untermain-West, Hessia (between Raunheim (near Frankfurt airport) and Frankfurt-Niederrad)	average value per km^2: 4.8 range: 2.6-8.2 98% value-max: 41.5 min: 8.3	Jan-Dec 1991	no information on method of sampling	HLFU; December 1992
Germany • Untermain-Ost, Hessia (between Frankfurt-Niederrad and Mühlheim am Main)	average value per km^2: 5.5 range: 2.5-13.1 98% value-max: 69 min: 7.5	Jan-Dec 1992	no information on method of sampling	HLFU; October 1993
Germany • Frankfurt-Griesheim	annual average: 5.3 max. daily mean: 25 max half hour value: 70 98% value: 19	Jan-Dec 1994	30 min average values were measured and from these the longer term average values were calculated	HLFU 1995 b

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • Frankfurt-Griesheim	annual mean: 4.6 max monthly mean: 8 max. half-hour mean: 72	Jan.- Dec. 1995		HLfU 1997
Germany • Mainz-Parcusstrasse site	3 month period - average 10.85 98%=34.05, 75%=14.45, 50%=8.95. January – March Max for monthly average 11.97 max daily average 22.5 max 30 min average 96.11 Values for March 1995 average 9.28 max daily 16.76 max 30 min 42.89	Jan-March 1995	30 min average values were measured and from these the longer term average values were calculated	LFUG; March 1995
Germany • 6 Sites in former East Germany	• Weissenfels: average 3.3, range 2.1-5.9, 98% value 15 • Naumburg: average 2.1, range 1.3-5.2, 98% value 10 • Zeitz: average 3.4, range 2.1-7.0, 98% value 17 • Hohenmölsen: average 2.2, range 1.7-4.3, 98% value 10 • Theissen-Bornitz-Profen: average 2.8, range 2.0-4.1, 98% value 13 • Lützen: average 2.1, range 1.7-2.5, 98% value 12	1993 monitoring programme	30 Min samples	Landesamt für Umweltschutz Sachsen-Anhalt 1994 b

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • 4 Sites in former East Germany	• Weissenfels: average 3.3, range 2.1-5.9, 98% value 15 • Naumburg: average 2.1, range 1.3-5.2, 98% value 10 • Zeitz: average 3.4, range 2.1-7.0, 98% value 17 • Hohenmölsen: average 2.2 range 1.7-4.3, 98% value 10 • Theissen-Bornitz-Profen: average 2.8, range 2.0-4.1, 98% value 13 • Lützen: average 2.1, range 1.7-2.5, 98% value 12	October 1992 - September 1993 monitoring programme		Landesamt für Umweltschutz Sachsen-Anhalt 1994 a
Germany Sachsen • Freiberg • Borna (heavy industry area) • 14 sites	Annual average / annual 98% • 6.0 / 19 • 5 7 15 • 2-5 7 / 7- 15	Februa-ry 1995	30 Minute sample.	Sächsisches Landesamt für Umwelt und Geologie 1995 a
Germany, Sachsen • Chemnitz (city) • Aue –Schneeberg (mountain area)	Range of averages over the whole monitoring period per km^2): 2-6 2-5	August 1993 – August 1994	sampling by adsorption on active carbon, GC-FID limit of detection: 1 µg/m^3	Sächsisches Landesamt für Umwelt und Geologie 1995 c

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Sachsen • Aue • Bautzen • Borna • Dresden • Freiberg • Glauchau • Görlitz • Leipzig • Zwickau	month.av./98%/30 min max. • 6.7 / 23.6 / 37.1 • 5.7 / 23.8 / 43.7 • 6.8 / 26.6 / 72.3 • 7.1 / 20.1 / 37.5 • 7.3 / 27.2 / 73.2 • 5.0 / 21.7 / 51.1 • 6.3 / 20.8 / 32.2 • 6.1 / 20.1 / 38.9 • 5.5 / 23.1 / 64.8	October 1994 – May 1995	30min sampling by adsorption, GC-FID limit of detection: < 1µg/m^3	Sächsisches Amt für Umwelt und Geologie 1995 c
Germany, Sachsen • Melpitz	mean value: • 2,17 – 11,83	July – December 1993	modified commercial GC system (Chrompack, model CP 9000)	Gnauck T., Rolle W. 1998
Germany • Baden-Württemberg 6 regions heavily polluted areas	reg. mean, range, and 98% value • Mannheim/Ladenburg: 3.6, 2.0-6.4, 15.5 • Weinheim/Schriesheim: 3.1, 2.2-4.9, 12.9 • Dossenheim/Heidelberg: 3.5, 2.3-5.9, 16.7 • Sandhausen/Leimen/Wiesloch: 3.2, 2.3-4.6, 13.7 • Offenburg: 3.2, 2.3-4.2, 13.6 • Kehl 2.8, 2.2-4.8, 13.7.	January 1992 – January 1993	30 min samples every 2 weeks, Monday – Sunday, 6:00 – 21:00. Sampling on active carbon, GC of CS_2 eluates limit of detection: 0.4 g/m^3	UMEG 1993 a UMEG 1994 c

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany • Mannheim/Heidelberg	Regional mean, range and 98% value • Mannheim/Ladenburg: mean: 3.6, range: 2.0-6.4, 98%: 15.5 • Weinheim/Schriesheim: mean: 3.1, range: 2.2-4.9, 98%: 12.9 • Dossenheim/Heidelberg: mean: 3.5, range: 2.3-5.9, 98%: 16.7 • Sandhausen/Leimen/Weis-loch mean 3.2, range 2.3-4.6, 98%:13.7	January 1992 - February 1993 monitoring programme	30 min samples every 2 weeks, Monday – Sunday, 6:00 – 21:00. Sampling on active carbon, GC of CS_2 eluates limit of detection: 0.4 g/m^3	UMEG 1994 c
Germany, Baden-Württemberg • Pforzheim • Mühlacker	• Pforzeim: range of annual average 1.7 to 5.5, 98% value 6-24 • Mühlacker: range of annual values: 1.6-3.4, 98% value 6-14	April 1990 - März 1991 monitoring programme	30 min samples every 2 weeks, Monday – Sunday, 6:00 – 21:00. Sampling on active carbon, GC of CS_2 eluates limit of detection: 0.4 g/m^3	UMEG 1992 c
Germany, Baden-Württemberg • Heilbronn/Neckarsulm	• Heilbornn: range of annual averages 1.77 to 5.56, 98% value 6.32-18.98 • Neckarsulm: range of annual averages 1.66-3.27, 98% value 6.87-18.05	October 1990 - October 1991 monitoring programme		UMEG 1992 a

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Baden-Württemberg • Reutlingen/Tübingen	• Reutlingen range of annual averages 1.32 to 3.5, 98% value 4.37-16.23. • Tübingen: range of annual averages 1.25-3.95, 98% value 4.16-15.36	Octobert 1990 - October 1991 monitoring programme		UMEG 1992 b
Germany, Baden-Württemberg • Kehl • Offenburg	Average (mean) / 98% (mean) • 2.2- 4.8 (2.8)/ 6.8 – 23.3 (13.7) • 2.3 – 4.2 (3.2) / 8.2 – 21.5 (13.6)	July 1991 - July 1992 monitorng programme		UMEG 1993 b
Germany, Baden-Württemberg • Rhein, Lörrach, Grenzach-Wyhlen, Rheinfelden	Regional mean, range and 98% value • Weil am Rhein/Lörrach: mean: 3.2, range: 2.2-4.9, 98%: 13 • Grenzach-Wyhlen/Rheinfelden mean: 2.9, range: 2.0-4.4, 98%: 10 Street Measurements annual mean, 98% value, and range of 30 minute samples • Grenzach-Wyhlen: mean: 8.7, range: 0 - 36.2, 98%: 34 • Rheinfelden: mean 6.5, range: 0.1 – 20.9, 98%: 17	October 1992 - September 1993 monitoring programme		UMEG 1994 d

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Baden-Württemberg 65 stations, divided into 4 categories A: smog areas with high density of population and industry B. other smog areas C: densely populated overall rural D: two background stations	Ranges A: 1.1 – 8.4 B: 1.1 – 5.0 C: 0.8 – 5.3 D: 0.7 – 1.0	1993	30 min samples every 2 weeks, Monday – Sunday, 6:00 – 21:00. Sampling on active carbon, GC of CS_2 eluates limit of detection: 0.4 g/m^3	UMEG 1994 a
Germany, Baden-Württemberg 62 stations, divided into 4 categories A: smog areas with high density of population and industry B. other smog areas C: densely populated overall rural D: two background stations	Ranges A: 1.3 – 5.0 B: 1.3 – 4.7 C: 0.6 – 4.7 D: 0.8 – 1.0	1994	30 min samples every 2 weeks, Monday – Sunday, 6:00 – 21:00. Sampling on active carbon, GC of CS_2 eluates limit of detection: 0.4 g/m^3	UMEG 1994 b
Germany, Baden-Württemberg • Ulm, Neu-Ulm, and surrounding areas	annual average - parking lot: 3.1 range 0-14.6, 98% = 8.0 annual average - traffic: 8.4 - 12 range 0.1-51.5 Ulm, Neu-Ulm, Umgebung: average: 3.0 range of average values: 2.0-5.8 98% value: 12 range 6-28	Apr 1993 - Mar 1994	30 Minute samples.	UMEG and BSLU 1995

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Baden-Württemberg • Measurements on street borders (90 sites with 1043 data)	Monthly averages 14- 28 overall average : 20	September 1992 – August 1993		UMEG 1994 e
Germany, Bavaria • Industrial areas • Areas with heavy traffic • City area with small scale traffic • Residential areas • Recreation areas	• 9.0 – 22.4 • 21.8 – 47.3 • 9.4 18.7 • 8.8. – 14.8 • 6.8 – 8.5	February 1990 – February 1991	sampling Mondays to Fridays from 9:00 to 18:00 into a kryotrap, GC-FID sampling 20 min, but comparable to 30 min	BLFU; January 1992
Germany, Bavaria • 16 cities in Bavaria	Hof: 2.65 (lowest) Ansbach: 3.72 (lowest) Munich: 18.32 (highest) Regensburg: 13.8 (highest) Augsburg: 2.9 (lowest) Ingolstadt (lowest)	1992/1993	street measurements range of average for 4-6-day samples, GC	BLFU; October 1994

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Bavaria • 15 Cities in Bavaria (some duplication with TUEV 1987/1988 reported data in HEDSET)	München:1987/1988;1990-1993: 9.3 – 14.4 Nürnberg:1988-1989;1991-1992 9.8 Neuburg/Donau 1991-1992: 3.5 – 4.4 Ingolstadt 1993: 5.8 Neu-Ulm 1993-1994: 3.5 Gröbenzell 1993: 3.3 Burghausen 1998-1989: 2.5 Nürnberg 1991-1992: 9.8	1988-19934	samples represent varied sampling: continuous and stationary.	BLFU; April 1995
Germany, Bavaria • one site Northwest centre of Munich, front of BLFU	Average: 8.1 <0.1 - 136.3 range of continuous measurements	October 1990-July 1991	continuous monitoring with 10 minutes sampling per measurement; adsorption on Tenax and active carbon; GC-FID with cry focussing limit of detection: 0.1 µg/m^3	BLFU; November 1991
Germany, Bavaria • Munich: Aubinger Lohe (subburban) • Munich: Rosenheimer Strasse	daily mean 0.72 - 1.55 12.9 - 36.57 max: 275	24 – 31 January 1994 31 January - 7 February 1994	Aubinger Aue: residential area at western city rim Rosenheimer Strasse: 26000 vehicles/d	TÜV Umwelttechnik 1994
Germany, Bavaria • Munich, Neuherbergstrasse	2-9	21 – 25 March 1994	residential area in northern city boundary	DEKRA Umwelt GmbH 1994

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Bavarai • Munich, highway (Mittlerer Ring): 7 sites (TÜV); 6 sites (DEKRA)	Daily average concentrations TÜV: 7 – 34 DEKRA: 4 - 58	TÜV: July 1991 DECRA: February – March 1992	high traffic area	BLFU; March 1994
Germany; Bavaria • Munich, recreation area • Munich, centre • Munich: high traffic area in suburb	Average/10 minutes max. values • 3.3 / 11.1 • 9.3 / 147.0 • 13.3 / 152.0	June – July 1993 October 1990 – March 1992 March 1992 – March 1993	10 minutes sampling into kryotrap, GC-FID limit o f detection: 0.1 µg/m^3	BLFU; May 1994
Germany, Bavaria • Neuburg/Donau • Berchtesgarden • Oberstdorf • Furt im Wald	Average 30 min- / max. • 4 / 48 • 7 / 24 • 2 / 8 • 1 / 2	Dec. 1991 – Dec. 1992 Oct. 1992 – Febr. 1993 July 1993 – Sept. 1993 April 1994	30 min. sampling into kryotrap, GC-FID limit of detection: 0.1µg/m^3	BLFU; May 1994
Germany, Bavaria • urban/suburban/rual within the Greater Munich Area (GMA)	• median: 9,72 • mean value: 11,67 • maximum: 48,28 • median: 9,07 • mean value: 10,04 • maximum: 44,71	12.August - 26.August1993 08.April - 02.May 1994	on-line gaschromatographic (GC) technique, non detection limit	Rappenglück B., Fabian P. 1999

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Germany, Bavaria • Burghausen (Western residential area) • Burghausen (Eastern industrial area)	Average / 98% / max. • 3.1 – 7.6 / 9.9 – 35.8 / 14.4 – 158.8 • 2.7 – 81 / 13.7 – 101.5 / 14.7 – 104.9	November 1988 – August 1989	detection limit 0.6 µg/m^3. max values in 30 minute samples.	BLFU; April 1991
Greece • central Athens: Ancient Agora	annual average: 16.2 range: 2.6 - 60.6	June 1993 - July 1994	sampling periods: 7:00 - 8:00 hr sampling site: Ancient Agora 4 m above ground, uninfluenced by surrounding buildings	Moschonas and Glavas, 1996
Greece • Athens	annual average level: 20.7	September 1997 – September 1998		MACBETH
Italy • Padua	annual average level: 8	September 1997 – September 1998		MACBETH
Italy • Rome: intense traffic street	min.: 6.9 (August) annual mean: 18.6 max.: 36 (November)	May 1992 - April 1993		Fuselli et al. 1995
Italy • Rome	annual mean: 47	1992 - 1993		Brocco et al. 1997
Italy • Rome	Mean: 13.1 Range: 6.2 – 24.8	December 1998 – June 1999	Mean of hourly averages measured at four urban monitoring stations for 60 d during 7 a.m. to 2 p.m.	Crebelli et al. 2001
Italy • Turin	mean: 45.0 median: 25.2 standard deviation: 81.1	1991	sampling on 10 consecutive days/month; 24 h each day	Gilli et al., 1994
Italy	annual mean: 22,19	1991	number of samples: 20	Gilli et al., December 1996

• Turin	summer: 14,26 winter: 31,88 annual mean: 21,45 summer: 20,96 winter: 23,55	1994		

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Italy • Rome • Milan • Taranto	 39.0 39.1 43.9	prior 1992	no details on monitoring period given concentrations refer to high emission periods: 9 - 11 a.m.	Ciccioli et al. 1992
Italy • Bologna	54 sites: 0,8 – 5,8 54 sites: 1,4 – 9,9	29.April – 28. May 1997 02. March – 31. March 1998	Perkin Elmer ATD-400 attached to a HP-6890 Series GC System gas chromatograph with a flame ionisation detector	Perez Ballesta et al. 1998
The Netherlands • cities • winter • largescale level • Bilthoven	average 1.6 - 9.0 5.3 - 59.4 ca. 2 2.8 (mean) / 10.4 (max.)	1982 - 9183	literature compilation.	RIVM 1988, cites in IPCS 1993
The Netherlands (Southern Netherlands) • Huijbergen • Moerdijk • Vredepeel	 average: 1,9 st.dev.: 2,0 average: 2,1 st.dev.: 2,6 average: 1,6 st.dev.: 1,5	March 1991 – February 1997	st.dev.: standard deviation of the daily averaged concentrations; the number of samples was limited to approximately 90 daily samples per year	Thijsse et al. 1999
Spain • Murcia	annual average level: 11.7	September 1997 – September 1998		MACBETH
Sweden • Stockholm: city centre	4 sites: 44.3 - 147.7 (average) 3.2 – 609.3 (1 hour samples)	1982 - 1983	eight 1 h samples	Jonson et al. 1985 cited in Nielsen et al. 1991

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
Sweden • Goeteborg Tingstad tunnel	61 and 450 (summer: 2 measurements) 104 and 301 (winter: 3 measurements)	Summer 1991 Winter 1992	sampling time: 30-50 minutes no averaging time indicated high value in summer occurred on day of slow traffic. benzene was 7% of total non-methane volatile hydrocarbons	Barrefors and Petersson, 1992
Sweden, Goeteborg • Tingstad tunnel • Gnistäng tunnel • smoky café (Junggrens) • car coupé • rural air	 360 194 38 55 0.9	 19.2.1992 8.10 - 8.40 hr 5.3.1992 8.00 - 8.20 hr 15.4.1992 13.25 - 13.55 hr 24.9.1992 7.50 - 8.10 hr	 3200 vehicles/h, 0-70 km/h, 10% heavy duty trucks	Barrefors 1996
Sweden 30 Swedish cities	annual mean: 2.4 - 6.2	October 1994 - March 1995	a steady decrease is observed compared to values of 1992-1994; detection limit: 0.16 µg/m^3	Mowrer et al. 1996
Switzerland • Basle (urban/residential) • Geneva (urban/residential) • Zürich (urban/transit road) • Lugano (urban) • Arau (small town) • forest (rural near village) • Payerne (rural near village) • Montana (alpine, remote) • Davos (alpine near town)	mean +/- standard deviation 1.8 +/- 0.9 3.9 +/- 1.2 6.0 +/- 1.4 3.1 +/- 0.9 2.0 +/- 1.0 1.1 +/- 0.7 1.4 +/- 1.2 0.9 +/- 0.5 0.8 +/- 0.5	June - December 1993	13 14-day-double samples	Monn and Hangartner, 1996

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
United Kingdom • Birmingham	Mean: 49.6 +/- 22.4	November 1999 – February 200	trafficked roadsides, 4 roads, sampling 3 times per day	Kim et al. 2001
United Kingdom • London • Kingston-upon-Thames	Average 1 h / range 1 h • 10 – 28.1 / 2.0 – 84.3 • 181.8 (short sample)	 1982, 1985 – 1987 not reported	literature compilation sampling time : 1 h sampling time not reported	Nielsen et al. 1991
United Kingdom • Central London	annual average: 13 monthly mean: 3.25 - 45.5	1991-1992	smog episode in winter	UK Department of the Environment 1994
United Kingdom • Central London: Exhibition Road, South Kensigton	mean quarterly weekday concentrations 3rd quarter 1991: 11 4th quarter 1991: 25.9 1st quarter 1992: 13.3 2nd quarter 1992: 9.7	July 1991 - June 1992	samples 5 m from kerbside of a moderately busy road (1500 - 1700 vehicles/h during daytime peak) enclosed on each side by buildings of 15 m smog episode during December 1991 winter means are typically about 1.8-1.9 times higher than summer means.	Derwent et al., 1995
United Kingdom • Central London: Exhibition Road • Central London: Marylebone Road	monthly average: ExbR/MarR March: 11.0 / 23.0 April: 11.3 / 18.4 May: 10.7 / 18.4 June: 6.2 / 22.3 September: 11.7 / 15.6	March - September 1992		Field et al., 1994

cont. of Table 7

Location	Concentration [µg/m^3]	Period	Remarks	Reference
United Kingdom • Edinburg Centre • Belfast South • Middlesbrough • Birmingham East • London Bloomsbury • Cardiff East • London Eltham	annual mean / max. hourly conc. 4.5 / 23.3 6.2 / 47.0 3.6 / 131.2 4.9 / 40.2 7.1 / 96.9 9.4 / 87.8 3.9 / 46.3	1993	manage med by National Environmental Technology Centre for the Department of the Environment	National Environmental Technology Centre for the Department of the Environment 1997
USA • Southern California	average (and range) 12,9 (3,2-37,2)	08. – 09. September1993	canister sampler, GC-MS-system	Fraser et al. 1998

Tabelle 8: Benzene in Rural and Pristine Areas

Location	Concentration [µg/m^3]	Period	Remark	Reference
Austria • rural (mountain 5 km northwest of Vienna)	3.7 /standard dev. 3.1 0.9 (no influence from Vienna) 4.9 (influence from Vienna) annual average: 1.0 – 1.8	October 1986 – February 1987	20 min sampling on sorbants, thermal desorption, kryofocussing, GC-FID	Lanzendorfer and Puxbaum 1990
Atlantic ocean	0.03 – 1.85	prior to 1984		Rudolph et al 1984 cited in RIVM 1988

cont. of Table 8

Location	Concentration [µg/m^3]	Period	Remark	Reference
France Porsoder, Brittany (at Atlantic) • continental air masses • North Sea air masses • England air masses • stagnant oceanic air masses • oceanic air masses	monthly averages ranges 0.582 – 1.879 0.324 – 1.620 0.091 – 1.296 0.123 – 0.842 0.026 – 0.518	February 1992 – February 1993	12 sample/day four-day air parcels originating from five trajectories were analysed	Boudries at el. 1994
Northern hemisphere • Barrow, Arkansa, 71^o N • Cape Meares, Oregon, 45^o N • Niwot Ridge,Colorado,42^o N • Whiteface Mtn, NY, 44^o N • Mauna Loa, Hawai, 20^o N Southern hemisphere • Samoa, 14^o S • Cape Pt. South Africa, 35^o S • Cape Grim, Tasmania, 42^o S • South Pole, 90^o S	average concentration • 0.544 +/- 0.062 • 0.750 +/- 0.117 • 0.398 +/- 0.085 • 0.854 +/- 0.150 • 0.404 +/- 0.140 • 0.244 +/- 0.049 • 0.202 +/- 0.104 • 0.179 +/- 0.117 • 0	1980 – 1983	detection limit: 16 ng/m^3	Rasmussen and Khalil 1983
Germany • Storkow, former GDR (forest)	one measurement: 0.54	18 July 1991: 3 am	pine forest southeast of Berlin	Ciccioli et al. 1993
Germany • Pennewitt in Mecklemburg-Vorpommern – rural area	0,0324 – 4,47	05.-16. August 1994		Koppmann et al. 1998

cont. of Table 8

Location	Concentration [µg/m^3]	Period	Remark	Reference
Germany, Northrhine-Wetsfalia	Annual average	1992		LIS 1994 a
• Bielefeld	• 7.81		• town northeast of Ruhr area	
• Borken	• 2.37 – 3.71		• town north of Ruhr area	
• Nettal	• 2.36		• town	
• Soest	• 1.72		• town east of Ruhr area	
• Stolberg	• 2.51 – 8.04		• town southwest of Ruhr area	
• Eggegebirge	• 1.42		• mountain area	
• Eifel	• 0.96		• mountain area	
• Rothaargebirge	• 0.91		• mountain area	
Germany, Northrhine-Wetsfalia	Annual average	1993		Landesumweltamt Nordrhein-Westfalen 1994
• Bielefeld	• 5.42		• town northeast of Ruhr area	
• Borken	• 2.96		• town north of Ruhr area	
• Nettal	• 2.05		• town	
• Soest	• 1.83		• town east of Ruhr area	
• Stolberg	• 1.74 – 8.37		• town southwest of Ruhr area	
• Eggegebirge	• 0.75		• mountain area	
• Eifel	• 0.89		• mountain area	
• Rothaargebirge	• 0.91		• mountain area	
Germany	3	prior to 1991		Müller J, 1991
• Schauinsland/Black Forest (mountain area: 1200 m)				

cont. of Table 8

Location	Concentration [µg/m^3]	Period	Remark	Reference
Italy • Montelibretti subarban cite near Rome • Monti Cimini: forest site	1.84 4.39	prior 1992	corresponds high emission periods at 9 – 11 a.m.	Ciccioli et al. 1992
Italy • Castel Porziano: Mediterrean macchia area, 25 km west of Rome; one measurement	one measurement: 3.08	27 February 1992, noon		Ciccioli et al. 1993
Nepal • 5 050 m height at the foot of Mount Everest.	1 measurement 1.99 3 measurements: 0.27 – 0.5	18 September 1991 3 and 4 October 1991		Ciccioli et al. 1993
Nepal • Katmandu, Himalaya	6.48	December 1982 – January 1983	indoor biomass combustion affects ambient air quality in the high altitude villages	Davidson et al. 1986
The Netherlands • country-wide scale	annual average: ca. 2	early 80s	cities are estimated to be a factor of 2 to 10 higher.	RIVM 1988
The Netherlands	annual mean: 1,1	1994		RIVM 1996
Sweden • 12 km WNW of city centre	range: 0.3 – 13.7 average: 3	1983		Petersson et al 1982, cited in Nielsen et al. 1991
United Kindgom • Harwell, Oxfordshire	three month running mean: 1.3 – 5.5	1986-1990	minima occurred in June – September. Maximal occurred in November – February.	UK Department of Environment (DoE), 1994

cont. of Table 8

Location	Concentration [µg/m^3]	Period	Remark	Reference
USA • New York City	average landfill gas composition 3,01		GC/MD system	Eklund et al. 1998
Canada • Southern Ontario	background concentration: 1700 observed: 1900	1993-1994	non detection limits	Mac Leod M.; Mackay D. 1999

Table 9: Benzene near Fuel Service Stations and in Vehicles

Location	Concentration [µg/m^3]	Period	Remarks	References
European countries • 13 countries: self-service fuelling	non detected – 13130	1984 - 1985	short sampling times (1 – 8 minutes, average: 2 minutes) no analytical details reported.	CONCAWE; June 1987
European countries • 12 petrol self- service stations • 4 petrol distribution station	Range /arithmetic mean • backgropund:1.6 – 38.1 / 7.9 and 8.5 (2 sites) • boundary of station: 1.8 – 119.0 / 16.2 and 14.5 (2 sites) • downwind boundary of station: 7.3 – 91.1 /20.6 • background: 1.1 – 93.3 /11 and 16.5 (2 sites) • boundary of station: 1.3 – 35.2 / 7.7 and 16.7 (2sites)	September 1990 – March 1992	12 h sampling into Chromosorb, thermal desorption, GC-FID	CONCAWE; August 1994
France • Paris: inside automobile, urban and suburban travel while driving	38 - 46	October 1991 - September 1992	highest value in central Paris average 1.5 h trip	Dor et al. 1995

cont. of Table 9

Location	Concentration [µg/m^3]	Period	Remarks	References
France • Paris: inside automobile, diesel engine while driving	3.2 - 3.5	1991 - 1992	measurements with engine cold, running, and warm (after running).	Dor et al. 1995
France • Paris: inside automobile, petrol engine while driving	12 - 33	1991 - 1992	highest value (33) during engine running, low values with engine cold (12) and warm (18).	Dor et al. 1995
Germany • inside/outside passenger car • inside passenger car, under extreme conditions: parking in the sun, windows closed	inside / outside of car 79 - 139 / 62 - 174 car parking in sunshine: 2 700	25 October 1983	three measurements 9 - 10 degree C temperature	Mücke et al. 1984
Germany, Bavaria • two petrol stations at highway near Munich	(a) 348 – 1288 (a) 462 – 1701 (b) 2940 – 27170 (mean: 14620)	• Winter 1985 • Winter 1985 • Summer 1986	a) long-term measurements 4 – 8 h (related to persons) b) short-term measurements 1/2 min (related to refuelling points)	Roemmelt et al. 1989
Germany; Hessen • 3 petrol stations • 1 m from petrol filling point during refuelling (2-3 min)	• 2 – 56 (mean 10 – 26) • 1020 – 5615 (mean 2720)	Aug 1988, Jan. 1989, and June 1989	short-term measurements during daytime in summer and winter 8:00 – 15:00 h • 10 samples • 7 samples	Hessischen Minister für Umwelt, Energie und Bundesangelegenheiten 1991
Sweden • at service stations	min: 10 geometric mean: 760 max: 27300	prior to 1992	Small differences between summer and winter. The position in relation to wind direction had the greatest influence on exposure.	Nordlinder and Ljungkvist 1992

cont. of Table 9

Location	Concentration [µg/m^3]	Period	Remarks	References
Italy • Milan: gasoline stores, during loading • Milan: measured at filling station	• tanks with gas recycle spring: 597-1701 summer: 332-639 winter: 2160-5818 • tanks without gas recycle summer. 2426-3600 winter: 1545 - 3530 • filling station winter: 1545-3530 summer: 289-802 winter: 166-734 tanker unloading: 2137	1992		Guerra et al., 1995
Not Reported: inside taxi, highway drive	3 - 8		literature compilation, diesel cars - 3 mg/m^3, Petrol cars - 8 mg/m^3.	Holmberg and Lundberg 1985, also cited in CEFIC 1996
Not Reported: inside taxi, city rush hour driving	40 - 110		literature compilation, diesel cars only. Highest value occurs with 35% queuing and stops.	Holmberg and Lundberg 1985, also cites in CEFIC 1996
United Kingdom • inside passenger cars	Mean: 203.7 +/- 152.3	November 1999 – February 2000	12 cars, measurements 3 times per car and day, in 50 % of the cars smoking occurred, all cars were older than 10 years	Kim et al. 2001
USA	averaged 2,9mg/m³ (SD = 5,8 mg/m³; median duration = 3 min) with a range of < 0,076-36 mg/m³, and postexposure breath levels averaged 160 µg/m³ (SD =		measured benzene exposure and uptake (via benzene in exhaled breath) among 39 self-service costumers using self-administered monitoring	Egeghy et al.; December 2000

	260 µg/m³) with a range of < 3,2-1,400 µg/m³			

Table 10: Benzene in Indoor Air

Location	Concentration [µg/m^3]	Period	Remark	Reference
Germany • Munich	in classroom: 9 in school yard: 10 outside near street: 14 (3 day average - August 1993). Mobile measurements ranged from 10-32 (Nov-Dec 1993).	25 – 27 May 1993	measurements inside (school and classroom), moving, ambient (continuous and non-continuous).	BLFU; March 1994
Germany • Frankfurt city	indoor: 15 outdoor 19 Indoor/outdoor ratio=0.8 Frankfurt city 19 Frankfurt residential area 11	prior to 1991	Samples were collected at 2.5 m height in front of houses, sampling Friday morning to Monday evening. Indoor air was samples in rooms sealed with double glass windows and closed inner doors. weekdays: 20 000 vehicle/day weekend: < 10 000 vehicles/weekend	Müller 1991
Germany • Berlin	• distance: 8-12 m min: 2; 50 percentil: 12.1; max. 21.6; N = 28 • distance: 10-40 m min: 4, 50 percentil: 7, max: 13; N = 37 • distance >200 m min: 1; 50 percentil 3, max: 10; N = 106	1992/93	indoor air in close vicinity of service stations: 8 - 200 m Indoor air benzene concentrations in homes next to service stations are about twice as high as in other homes. These differences are statistically significant.	Laue et al. 1994

cont. of Table 10

Location	Concentration [µg/m^3]	Period	Remark	Reference
Germany • Frankfurt/Main: 32 flats in neighbourhood of 12 petrol filling stations	indoor: flat near filling station • mean: 10.2 +/- 4.0 • max: 22.4 indoor: control flat • mean: 5.6 +/- 1.5 • max: 8 outdoor of flat near filling station • 9.3 +/- 3.4 • max: 20.3 outdoor: conrol • mean: 4.8 +/- 1.3 • max: 7.1	November 1993	Indoor benzene concentrations were independent of distance to the filling stations (10 - 40 m), height of flat in building and traffic situation in street next to flat. outdoor measurements: out of windows	Heudorf and Hentschel 1995
Nepal • Katmandu, Himalaya	907.2	December 1982 - January 1983	measured in residences in the Himalayas of Nepal where biomass fules are used for cooking and heating	Davidson et al. 1986
Switzerland	10 percentil: <5 50 percentil: 7 0090 percentil: 14 max: 20	prior to 1992	benzene indoor air concentrations in new and recently renovated buildings	Rothweiler et al. 1992

cont. of Table 10

Location	Concentration [µg/m^3]	Period	Remark	Reference
Brazil • Rio de Janeiro	average of indoor and outdoor in the office 1st floor: indoor: 18.4 outdoor: 11.6 indoor/outdoor: 1.6 9th floor: indoor: 31.1 outdoor: 9.9 indoor/outdoor: 3.1 13th floor: indoor: 34.5 outdoor: 12.2 indoor/outdoor: 2.8 25th floor: indoor: 15.9 outdoor: 3.3 indoor/outdoor: 4.8	one week in December 1995	samplings were made for 6 h during daytime, with the office normally occupied	Brikus et al. 1998

Table 11: Survey of Benzene in Indoor Air of German Homes [Krause et al. 1987]

	Benzene in Room Air [µg/m^3]										
	N	10%	50%	90%	95%	98%	Max	GM[1]	SGM[2]	AM[3]	SAM[4]
ALL MEASUREMENTS	479	1.5	7.2	17.3	22.3	31.2	90.0	6.18	2.59	9.0	8.09
Number of Smokers											
No smokers in household	238	1.4	6.1	14.2	17.2	30.0	90.0	5.06	2.45	7.26	7.40
1 smoker in household	159	0.7	8.7	17.3	19.0	25.7	63.9	6.68	2.66	9.49	7.48
2 smokers in household	67	2.5	12.0	25.8	36.4	41.2	50.7	9.86	2.42	13.35	9.60
3 or more smokers in household	15	1.9	8.6	24.9	26.9	30.4	30.4	8.05	2.81	11.01	9.32
Ambient Temperature											
To 5.9°C	82	5.8	10.0	22.6	28.2	31.6	50.7	10.88	1.70	12.63	7.81
6 - 10.9°C	141	4.0	10.6	19.8	25.8	41.2	90.0	9.05	2.31	11.95	9.98
11 - 15.9°C	65	1.7	6.9	17.3	18.5	23.4	26.3	6.46	2.34	8.50	5.66
16 - 19.9°C	110	0.7	4.1	11.1	15.6	16.7	30.0	3.68	2.55	5.41	4.98
20°C and more	81	0.7	3.8	12.0	15.4	19.0	36.4	3.54	2.57	5.48	6.09
Population Size											
<20,000 population	184	0.7	4.8	16.7	22.0	30.0	63.9	4.26	2.94	7.19	8.10
20,000 to 10,000 population	127	3.1	8.6	16.4	20.0	27.4	35.4	8.00	1.93	9.71	5.98
100,000 population	167	2.4	8.3	18.9	24.9	34.3	90.0	7.69	2.36	10.45	9.08
Region Type											
Urban (dense)	270	1.9	8.0	17.6	22.0	30.5	90.0	6.96	2.44	9.56	7.73
Suburban (transitional)	118	1.6	8.5	19.0	28.2	41.2	63.9	7.24	2.64	10.61	9.65
Rural	91	0.7	3.7	12.0	16.1	21.8	30.0	3.49	2.48	5.23	5.40

[1]Geometric Mean [2]Standard Deviation of Geometric Mean
[3]Arithmetic Mean [4]Standard Deviation of Arithmetic Mean

Table 12: Summary of Active and Passive Smoking-related Benzene Exposure

Data Description	Result	Comments	Reference
Indoor Air			
- U.S. homes - smokers - U.S. homes - no smokers	10.5 μg/m^3 7 μg/m^3	Median for 300 homes Median for 200 homes	Wallace 1989
- German homes - smokers - German homes - no smokers	10 to 12 μg/m^3 6.5 μg/m^3	Possibly refers to Krause et al., 1987 data	German Enquete Kommission 1994
- German homes - smokers - German homes - no smokers	11 μg/m^3 6.5 μg/m^3	Further details not provided in HEDSET	Krause et al. 1987
- German school	9 μg/m^3	3 day average in classroom	BLFU; October 1994
- Smoky U.S. tavern Outside at same location	21 and 27 μg/m^3 8 and 6 μg/m^3	2 samples at each site 2-hour samples	Loefroth 1989
Smoker Exposure			
- direct smoking related exposure	10 to 100 μg/cigarette, estimated average 30 μg/cigarette	Mainstream and sidestream smoke	CONCAWE (1994a)
- sidestream smoke	345 to 653 μg/cigarette	Multiple studies cited in reference, estimated quantities to smoker	CONCAWE (1994a) (Brunneman et al. 1990)
- passive smoking	3.5 μg/cigarette	14-hour exposure assumed	CONCAWE (1994a) (Wallace 1989)
- sidestream smoke	500 μg/cigarette	From smoking machine data	Loefroth 1989
Breath Samples			
- Smoker exhaled air	15 μg/m^3	In exhaled breath	Wallace 1989
- Nonsmoker exhaled air	1.5 to 2 μg/m^3	In exhaled breath	Wallace 1989
- Nonsmoker exhaled air (living with smoker)	3.6 to 4.2 μg/m^3	In exhaled breath	Wallace et al. 1987; 1989

Table 13: Benzene in Biota

Location/biota	Concentration	Period	Remark	Reference
Germany • North Rhine-Westfalia: human blood	Geometric means: large city/rural area woman: 0.072 / 0.048 µg/L children: 0.143 / 0.128 µg/L 3 of 269 children: >0.5 µg/L, max. 0.97 µg/L	1991	55 year old women 6 year old children not occupationally exposed	Ministerium für Umwelt, Raumordnung and Landwirtschaft des Landes Nordrhein-Westfalen 1993
Japan • fish (grey mallets)	Toluene and benzene were found in fish tainted by waste water from oil refineries.	prior 1991		Ogata M et al. 1991
USA • Massachusetts, Woods Hole (Oceanographic Institute)	20 µg/kg by dry weight	prior 1982	headspace GC/MS of homogenised algae *Ulva lactuca, Hypnea musciformis* (seaweeds) grown in tanks using circulating seawater	Whelan et al 1982
USA • California Pacific Ocean, close to the outlet of the Los Angeles waste water treatment plant	µg/kg wet weight / number of samples • Pacific sand crab liver: <1 / 1 • Scorpion fish liver: 16 / 1 • Dover sole liver: 52 / 1 • White croakers liver: 15 / 1 • Shrimp muscle: <1 / 1 • Invertebrates whole: 8 / 1	June 1981	grab samples of fish, crabs and other sea-dwelling animals headspace GC/MS of homogenised samples	Gossett et al. 1983

Table 14: Benzene in Soil and Sediment

Location	Concentration	Period	Remark	Reference
Germany • Hamburg: eight petrol service stations: next to petrol pump	station/soil depth [cm]/concentration [mg/kg] 1. 0 - 5: 18 20 - 30: 1.5 50 - 60: not found 2. 0 - 5: not found 3. 0.5: not found 20 - 30: 0.6 50 - 60: 1.0 4. 0 - 5: not found 5. 0 - 5: 0.1 20 - 30: not found 50 - 60: not found 6. 0 - 5: not found 20 - 30: not found 50 - 60: not found 7. 0 - 5: 0.4 20 - 30: 0.1 50 - 60: not found 8. 20 - 30: not found 9. 30 - 40: not found		samples were taken in 1 - 2 m distance to the petrol pump; samples were drilled to a depth of 60 cm; detection limit: 0.1 mg/kg	Stachel 1993
Germany, Elbe Hamburg • above the harbour • harbour • minor surface waters in Hamburg	Min / max / median µg/kg dry matter • 122 / 192 / 166 • 42 / 12100 / 142 • 0 / 184 / 84	1992 – 1993 • 4 samples • 10 samples • 28 samples	no experimental details on sampling and analytical procedures were reported	Freie und Hansestadt Hamburg, Umweltbehörde, August 1994
Germany Hamburg • Georgswerder (leachate from landfill)	Range of values from 4 different sampling sites (oily liquid) µg/L • < limit of detection (LOD) • <LOD – 7.1 • <LOD – 28 • 60 - 96	1981 - 1982	no experimental details on sampling and analysis were reported	Götz 1984

cont. of Table 14

Location	Concentration	Period	Remark	Reference
USA • California Pacific Ocean, close to the outlet of the Los Angeles waste water treatment plant	µg/kg/wet weight / number of samples • Sediment: < 1/2	June 1981	grab samples of sediment headspace GC/MS of homogenised samples	Gossett et al. 1983
Netherlands • soil of two gas works stations	1 - 2 mg/kg	prior 1987		Friman and Marose 1987
United Kingdom • Sediment in Tees Estuary	1.3 - 3.9 µg/kg	prior 1982	The authors expect these values to be as little as a third of the true concentration.	Whitby et al 1982 cited in Nielsen et al. 1991

Table 15: Benzene in Food

Food	Concentration [ng/g]	Period	Remark	Reference
Food with no added benzoates				
Apple juice Strained apple juice Strained apple-cherry juice Cranberry juice cocktail Cranberry juice concentrate fresh cranberries raspberry drink grape drink fruit punch orange soda cola soda	<1 0 <1 1 0 <1 0 <1 <1 <1 0	foods were collected and analysed from 1991 to early 1992 in the United States	Purge-and-trap headspace concentration/capillary gas chromatography with flame ionization detection (GC/FID). Findings were confirmed by static headspace concentration/capillary gas chromatography with mass selective detection (GC/MS)	McNeal et al. 1993

cont. of Table 15

Food	Concentration [ng/g]	Period	Remark	Reference
Food with no added benzoates				
brewed instant coffee	0			McNeal et al. 1993
red raspberry preserves	1			
black currant preserves	2			
strawberry preserves	0			
grape jelly	0			
liquid smoke brand A	121			
liquid smoke brand B	21			
liquid beef bouillon	0			
raw potato	0			
baked potato	0			
ground nutmeg	0			
fried egg	0			
hard-boiled egg	<1			
fresh tomato	0			
smoked fish	<1			
roasted peanuts	<1			
foods containing added benzoates				
bloody marry mix. liquid	3			McNeal et al. 1993
fruit punch	<1			
diet cola	<1			
diet orange soda A	<1			
diet orange soda B	0			
diet white grape soda	<1			
imitation grape jelly	5			
duck sauce	7			
all purpose sauce	1			
barbeque sauce	5			
soy sauce	0			
pickled vegetables	<1			
citrus salad	<1			

cont. of Table 15

Food	Concentration [ng/g]	Period	Remark	Reference
foods containing added benzoates				
Margarita mix. liquid	2			McNeal et al. 1993
iced tea	0			
diet raspberry soda	<1			
diet cherry berry soda	2			
diet grapefruit soda	1			
litre strawberry preserves	<1			
imitation strawberry preserves	38			
litre orange marmelade	1			
litre grape jelly	1			
taco sauce brand A	9			
taco sauce brand B	22			
sweet relish	<1			
salad peppers	<1			
litre syrtes product	<1			
Fish, meat, pies, waffles, etc	Migration of benzene from susceptors into food during heating in a microwave over 8 of 11 susceptors resulted in migration of <1.6 – 34 ng/cm^2 into the food in contact with the susceptors	Prior to 1992	heating of the food on an metalised polyethylene terephthalate (PET) film in a microwave oven, headspace GC-FID detector or MS	McNeal and Hollifield 1993 cf. IUCLID data set
Chicken, ham, pork, codfish	Concentration [µg/kg] without / with radiation (dose of radiation in kGy) • Chicken: - / 12 (45 – 68) • Ham: - / 5 (36 – 54) • Pork: - / 7 (45 – 68) • Codfish: <1 / 2 (30)	Prior to 1992	experimental details on sampling and analysis were not reported	Singh 1992

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Appendix A III

of the Risk Assessment Report

Benzene CAS-No.: 71-43-2

Continental and regional exposure

April 2002

SimpleBox2.0a - calculation of continental and regional PEC's

- adaptation to TGD (1996) / EUSES 1.00

INPUT - Benzene

Parameter names acc. SimpleBox20	Unit	Input	Parameter names according Euses
Physicochemical properties			
COMPOUND NAME	[-]	Benzene	Substance
MOL WEIGHT	[g.mol^{-1}]	78,11	Molecular weight
MELTING POINT	[° C]	5.5	Melting Point
VAPOR PRESSURE(20)	[Pa]	9970	Vapour pressure at 20°C
log Kow	[log10]	2.13	Octanol-water partition coefficient
SOLUBILITY(25)	[mg.l^{-1}]	1800	Water solubility
Distribution - Partition coefficients			
- Solids water partitioning (derived from K_{oc})			
Kp(soil)	[l.kg$_d^{-1}$]	2.683	Solids-water partitioning in soil
Kp(sed)	[l.kg$_d^{-1}$]	13.415	Solids-water partitioning in sediment
Kp(susp)	[l.kg$_d^{-1}$]	13.415	Solids-water partitioning in sudpended matter
- Biota-water			
BCF(fish)	[l.kg$_w^{-1}$]	13	Biocentration factor for aquatic biota
Degradation and Transfromation rates			
- Characterisation and STP			
PASSreadytest	[y / n]	y	Characterization of biodegradability
- Environmental Total Degradation			
kdeg(air)	[d^{-1}]	5.17E-02	Rate constant for degradation in air
kdeg(water)	[d^{-1}]	4.62E-02	Rate constant for degradation in bulk surface water
kdeg(soil)	[d^{-1}]	2.31E-02	Rate constant for degradation in bulk soil
kdeg(sed)	[d^{-1}]	2.31E-03	Rate constant for degradation in bulk sediment
Sewage treatment (e.g. calculated by SimpleTreat)			
- Continental			
FR(volatstp) [C]	[-]	4.26E-01	Fraction of emission directed to air (STPcont)
FR(effstp) [C]	[-]	6.10E-02	Fraction of emission directed to water (STPcont)
FR(sludgestp) [C]	[-]	0.00E+00	(1) Fraction of emission directed to sludge (STPcont)
- Regional			
FR(volatstp) [R]	[-]	4.26E-01	Fraction of emission directed to air (STPreg)
FR(effstp) [R]	[-]	6.10E-02	Fraction of emission directed to water (STPreg)
FR(sludgestp) [R]	[-]	0.00E+00	(1) Fraction of emission directed to sludge (STPreg)
Release estimation			
- Continental			
Edirect(air) [C]	[t.y^{-1}]	164618	Total continental emission to air
STPload [C]	[t.y^{-1}]	23262	Total continental emission to wastewater
Edirect(water1) [C]	[t.y^{-1}]	0	Total continental emission to surface water
Edirect(soil3) [C]	[t.y^{-1}]	590	Total continental emission to industrial soil
Edirect(soil2) [C]	[t.y^{-1}]	0	Total continental emission to agricultural soil
- Regional			
Edirect(air) [R]	[t.y^{-1}]	18291	Total regional emission to air
STPload [R]	[t.y^{-1}]	2585	Total regional emission to wastewater
Edirect(water1) [R]	[t.y^{-1}]	0	Total regional emission to surface water
Edirect(soil3) [R]	[t.y^{-1}]	65.6	Total regional emission to industrial soil
Edirect(soil2) [R]	[t.y^{-1}]	0	Total regional emission to agricultural soil

(1) As the sewage sludge arising from the production and/or processing of benzene in the chemical industry is for the most part disposed of by incineration, release into the soil as a result of the spreading of sewage sludge on farmland is not assumed.

OUTPUT - Benzene

Parameter names acc. SimpleBox20	Unit	Output	Parameter names according Euses
Output			
- Continental			
PECsurfacewater (total)	[mg.l^{-1}]	3.20E-05	Continental PEC in surface water (total)
PECsurfacewater (dissolved)	[mg.l^{-1}]	3.20E-05	Continental PEC in surface water (dissolved)
PECair	[mg.m^{-3}]	7.26E-04	Continental PEC in air (total)
PECagr.soil	[mg.kg$_{wwt}^{-1}$]	8.18E-06	Continental PEC in agricultural soil (total)
PECporewater agr.soil	[mg.l^{-1}]	3.29E-06	Continental PEC in pore water of agricultural soils
PECnat.soil	[mg.kg$_{wwt}^{-1}$]	9.47E-06	Continental PEC in natural soil (total)
PECind.soil	[mg.kg$_{wwt}^{-1}$]	1.32E-04	Continental PEC in industrial soil (total)
PECsediment	[mg.kg$_{wwt}^{-1}$]	1.55E-04	Continental PEC in sediment (total)
- Regional			
PECsurfacewater (total)	[mg.l^{-1}]	2.75E-04	Regional PEC in surface water (total)
PECsurfacewater (dissolved)	[mg.l^{-1}]	2.75E-04	Regional PEC in surface water (dissolved)
PECair	[mg.m^{-3}]	1.54E-03	Regional PEC in air (total)
PECagr.soil	[mg.kg$_{wwt}^{-1}$]	1.74E-05	Regional PEC in agricultural soil (total)
PECporewater agr.soil	[mg.l^{-1}]	7.00E-06	Regional PEC in pore water of agricultural soils
PECnat.soil	[mg.kg$_{wwt}^{-1}$]	2.01E-05	Regional PEC in natural soil (total)
PECind.soil	[mg.kg$_{wwt}^{-1}$]	1.22E-03	Regional PEC in industrial soil (total)
PECsediment	[mg.kg$_{wwt}^{-1}$]	1.33E-03	Regional PEC in sediment (total)

Appendix A IV

of the Risk Assessment Report

Benzene CAS-No.: 71-43-2

Indirect exposure via the environment

April 2002

INDIRECT EXPOSURE VIA THE ENVIRONMENT

(TGD On New and Existing Chemicals, chapter 2)

Parameter [Unit]	*Symbol*
Definitions (for the use in this document)	
definition of the unit 'kg$_{bw}$' for body weight	$kg_{bw} := 1 \cdot kg$
definition of the unit 'd' for day	$d := 1 \cdot Tag$
	$scenario := 1..2$
	$local := 1$
	$regional := 2$
Constants	
gas - constant R	$R := 8.314 \cdot J \cdot K^{-1} \cdot mol^{-1}$
Defaults	
volumefraction air in plant tissue [-]	$Fair_{plant} := 0.3$
volumefraction water in plant tissue [-]	$Fwater_{plant} := 0.65$
volumefraction lipids in plant tissue [-]	$Flipid_{plant} := 0.01$
bulk density of plant tissue [$kg_{wet\ plant} * m_{plant}^{-3}$]	$RHO_{plant} := 700 \cdot kg \cdot m^{-3}$
leaf surface area [m^2]	$AREA_{plant} := 5 \cdot m^2$
conductance (0.001 $m*s^{-1}$) [$m*d^{-1}$]	$g_{plant} := 0.001 \cdot m \cdot s^{-1}$
shoot volume [m^3]	$V_{leaf} := 0.002 \cdot m^3$
transpiration stream [m^3*d^{-1}]	$Q_{transp} := 1 \cdot 10^{-3} \cdot m^3 \cdot d^{-1}$
correction exponent for differences between plant lipids and octanol [-]	$b := 0.95$
growth rate constant for dilution by growth [d^{-1}]	$kgrowth_{plant} := 0.035 \cdot d^{-1}$
pseudo-first order rate constant for metabolism in plants [d^{-1}]	$kmetab_{plant} := 0 \cdot d^{-1}$
pseudo-first order rate constant for photolysis in plants [d^{-1}]	$kphoto_{plant} := 0 \cdot d^{-1}$

concentration in meat and milk

daily intake of grass [$kg_{wetgrass}*d^{-1}$]	$IC_{grass} := 67.6 \cdot kg \cdot d^{-1}$
daily intake of soil [$kg_{wet\ soil}*d^{-1}$]	$IC_{soil} := 0.46 \cdot kg \cdot d^{-1}$
daily intake of air [$m_{air}^3*d^{-1}$]	$IC_{air} := 122 \cdot m^3 \cdot d^{-1}$
daily intake of drinkingwater [$l*d^{-1}$]	$IC_{drw} := 55 \cdot l \cdot d^{-1}$

daily intake for human

daily intake for the several pathways [$kg_{chem}*d^{-1}$] or [$m^{3*}d^{-1}$]	$IH_{drw} := 2 \cdot l \cdot d^{-1}$
	$IH_{fish} := 0.115 \cdot kg \cdot d^{-1}$
	$IH_{stem} := 1.2 \cdot kg \cdot d^{-1}$
	$IH_{root} := 0.384 \cdot kg \cdot d^{-1}$
	$IH_{meat} := 0.301 \cdot kg \cdot d^{-1}$
	$IH_{milk} := 0.561 \cdot kg \cdot d^{-1}$
	$IH_{air} := 20 \cdot m^3 \cdot d^{-1}$
bioavailability through route of intake [-]	$BIO_{inh} := 0.75$
	$BIO_{oral} := 1.0$
average body weight of human [kg]	$BW := 70 \cdot kg_{bw}$

Default emission to air, direct, mean value and regional PEC

Name: Benzene CAS - No.:71-43-2

Input

chemical properties

octanol-water partitioning coefficient [-]	$\log K_{OW} := 2.13$ $K_{OW} := 10^{\log K_{OW}}$
Henry - partitioning coefficient [Pa*m^3*mol^{-1}]	$HENRY := 433 \cdot Pa \cdot m^3 \cdot mol^{-1}$
air-water partitioning coefficient [-]	$K_{air\_water} := 0.178$
fraction of the chemical associated with aerosol particles [-]	$F_{ass\_aer} := 1.0 \cdot 10^{-8}$
half-life for biodegration in surface water [d]	$DT_{50\_bio\_water} := 15 \cdot d$

environmental concentrations

annual average local PEC in surface water (dissolved) [$mg_{chem} * l_{water}^{-1}$]	$PEClocal_{water\_ann} := 0.040 \cdot mg \cdot l^{-1}$
annual average local PEC in air (total) [$mg_{chem} * m_{air}^{-3}$]	$PEClocal_{air\_ann} := 0.890 \cdot mg \cdot m^{-3}$
local PEC in grassland (total), averaged over 180 days [$mg_{chem} * kg_{soil}^{-1}$]	$PEClocal_{grassland} := 0.0132 \cdot mg \cdot kg^{-1}$
local PEC in porewater of agriculture soil [$mg_{chem} * l_{porewater}^{-1}$]	$PEClocal_{agr\_soil\_porew} := 0.0048 \cdot mg \cdot l^{-1}$
local PEC in porewater of grassland [$mg_{chem} * l_{porewater}^{-1}$]	$PEClocal_{grassland\_porew} := 0.0052 \cdot mg \cdot l^{-1}$
local PEC in groundwater under agriculture soil [$mg_{chem} * l_{water}^{-1}$]	$PEClocal_{grw} := 0.0048 \cdot mg \cdot l^{-1}$
regional PEC in surface water (dissolved) [$mg_{chem} * l_{water}^{-1}$]	$PECregional_{water} := 2.75 \cdot 10^{-4} \cdot mg \cdot l^{-1}$
regional PEC in air (total) [$mg_{chem} * m_{air}^{-3}$]	$PECregional_{air} := 1.54 \cdot 10^{-3} \cdot mg \cdot m^{-3}$
regional PEC in agriculture soil (total) [mg_{chem}*kg_{soil}^{-1}	$PECregional_{agr\_soil} := 1.74 \cdot 10^{-5} \cdot mg \cdot kg^{-1}$
regional PEC in porewater of agriculture soils [mg_{chem}*l_{water}^{-1}	$PECregional_{agr\_soil\_porew} := 7.00 \cdot 10^{-6} \cdot mg \cdot l^{-1}$

Definition of the concentrations used for indirect exposure

$C_{water_{local}} := PEClocal_{water\_ann}$ $C_{water_{regional}} := PECregional_{water}$

$C_{air_{local}} := PEClocal_{air\_ann}$ $C_{air_{regional}} := PECregional_{air}$

$C_{grassland_{local}} := PEClocal_{grassland}$ $C_{grassland_{regional}} := PECregional_{agr\_soil}$

$C_{agr\_porew_{local}} := PEClocal_{agr\_soil\_porew}$ $C_{agr\_porew_{regional}} := PECregional_{agr\_soil\_porew}$

$C_{grass\_porew_{local}} := PEClocal_{grassland\_porew}$ $C_{grass\_porew_{regional}} := PECregional_{agr\_soil\_porew}$

$C_{grw_{local}} := PEClocal_{grw}$ $C_{grw_{regional}} := PECregional_{agr\_soil\_porew}$

<u>bioconcentration in fish</u>

bioconcentration factor for fish
[$m_{water}^3 * kg_{chem}^{-1}$]

$$BCF_{fish} := 10^{0.85 \cdot \log K_{OW} - 0.7} \cdot l \cdot kg^{-1}$$

modified equation for logKow > 6

$$BCF_{fish} := wenn\left[\log K_{OW} > 6, \left[-0.278 \cdot \left(\log K_{OW}\right)^2 + 3.38 \cdot \log K_{OW} - 5.94\right] \cdot l \cdot kg^{-1}, BCF_{fish}\right]$$

$$C_{fish_{scenario}} := BCF_{fish} \cdot C_{water_{scenario}}$$

<u>bioconcentration in plants</u>

$$K_{plant\_water} := Fwater_{plant} + Flipid_{plant} \cdot K_{OW}^{b}$$

$$Croot_{agr\_plant_{scenario}} := \frac{K_{plant\_water} \cdot C_{agr\_porew_{scenario}}}{RHO_{plant}}$$

$$TSCF := 0.784 \cdot e^{\frac{-\left(\log K_{OW} - 1.78\right)^2}{2.44}}$$

remark: for $\log K_{OW}$ out of the range from -0.5 to 4.5
the TSCF is limited by the values for $\log K_{OW}$ = -0.5 resp. 4.5

$$TSCF := wenn\left(\log K_{OW} < -0.5, 0.903, TSCF\right)$$
$$TSCF := wenn\left(\log K_{OW} > 4.5, 0.832, TSCF\right)$$

$$K_{leaf\_air} := Fair_{plant} + \frac{K_{plant\_water}}{K_{air\_water}}$$

$$kelim_{plant} := kmetab_{plant} + kphoto_{plant}$$

$$\alpha := \frac{AREA_{plant} \cdot g_{plant}}{K_{leaf\_air} \cdot V_{leaf}} + kelim_{plant} + kgrowth_{plant}$$

$$\beta_{agr\_plant_{scenario}} := C_{agr\_porew_{scenario}} \cdot TSCF \cdot \frac{Q_{transp}}{V_{leaf}} + \left(1 - F_{ass\_aer}\right) \cdot C_{air_{scenario}} \cdot g_{plant} \cdot \frac{AREA_{plant}}{V_{leaf}}$$

$$C_{leaf\_crops_{scenario}} := \frac{\beta_{agr\_plant_{scenario}}}{\alpha \cdot RHO_{plant}}$$

$$\beta_{grass\_plant_{scenario}} := C_{grass\_porew_{scenario}} \cdot TSCF \cdot \frac{Q_{transp}}{V_{leaf}} + \left(1 - F_{ass\_aer}\right) \cdot C_{air_{scenario}} \cdot g_{plant} \cdot \frac{AREA_{plant}}{V_{leaf}}$$

$$C_{leaf\_grass_{scenario}} := \frac{\beta_{grass\_plant_{scenario}}}{\alpha \cdot RHO_{plant}}$$

purification of drinking water

system may defined dependent from the aerobic biodegradation

$$system := wenn\left(DT_{50\_bio\_water} < 10 \cdot d, 0, 1\right)$$

select a column on dependence from log K_{OW}

$$FIndex := wenn\left(logK_{OW} < 4, 0, wenn\left(logK_{OW} > 5, 2, 1\right)\right)$$

$$Fpur_{logKow} := \begin{bmatrix} 1 & \frac{1}{4} & \frac{1}{16} \\ 1 & \frac{1}{2} & \frac{1}{4} \end{bmatrix}$$

$$Fpur := \frac{Fpur_{logKow_{system, FIndex}}}{wenn\left(HENRY > 100 \cdot Pa \cdot m^3 \cdot mol^{-1}, 2, 1\right)}$$

$$C_{drw_{scenario}} := wenn\left[C_{grw_{scenario}} > \left(C_{water_{scenario}} \cdot Fpur\right), C_{grw_{scenario}}, C_{water_{scenario}} \cdot Fpur\right]$$

Biotransfer to meat and milk

$$BTF_{meat} := 10^{-7.6 + logK_{OW}} \cdot kg^{-1} \cdot d$$

remark: for $logK_{OW}$ out of the range from 1.5 to 6.5
the BTF_{meat} is limited by the values for $logK_{OW}$ = 1.5 resp. 6.5

$$BTF_{meat} := wenn\left(logK_{OW} < 1.5, 7.943 \cdot 10^{-7} \cdot kg^{-1} \cdot d, BTF_{meat}\right)$$

$$BTF_{meat} := wenn\left(logK_{OW} > 6.5, 0.07943 kg^{-1} \cdot d, BTF_{meat}\right)$$

$$C_{meat_{scenario}} := BTF_{meat} \cdot \left(\begin{matrix} C_{leaf\_grass_{scenario}} \cdot IC_{grass} + C_{grassland_{scenario}} \cdot IC_{soil} \cdots \\ + C_{air_{scenario}} \cdot IC_{air} + C_{drw_{scenario}} \cdot IC_{drw} \end{matrix}\right)$$

$$BTF_{milk} := 10^{-8.1 + logK_{OW}} \cdot kg^{-1} \cdot d$$

remark: for $logK_{OW}$ out of the range from 3 to 6.5
the BTF_{milk} is limited by the values for $logK_{OW}$ = 1.5 resp. 6.5

$$BTF_{milk} := wenn\left(logK_{OW} < 3, 7.943 \cdot 10^{-6} \cdot kg^{-1} \cdot d, BTF_{milk}\right)$$

$$BTF_{milk} := wenn\left(logK_{OW} > 6.5, 0.02512 kg^{-1} \cdot d, BTF_{milk}\right)$$

$$C_{milk_{scenario}} := BTF_{milk} \cdot \left(\begin{array}{l} C_{leaf\_grass_{scenario}} \cdot IC_{grass} + C_{grassland_{scenario}} \cdot IC_{soil} \cdots \\ + C_{air_{scenario}} \cdot IC_{air} + C_{drw_{scenario}} \cdot IC_{drw} \end{array} \right)$$

total daily intake for human

daily dose through intake of several pathways
[$kg_{chem}*kg_{bw}^{-1}*d^{-1}$]

$$DOSE_{drw_{scenario}} := \frac{C_{drw_{scenario}} \cdot IH_{drw}}{BW} \qquad DOSE_{air_{scenario}} := \frac{C_{air_{scenario}} \cdot IH_{air} \cdot BIO_{inh}}{BW \cdot BIO_{oral}}$$

$$DOSE_{stem_{scenario}} := \frac{C_{leaf\_crops_{scenario}} \cdot IH_{stem}}{BW} \qquad DOSE_{root_{scenario}} := \frac{Croot_{agr\_plant_{scenario}} \cdot IH_{root}}{BW}$$

$$DOSE_{meat_{scenario}} := \frac{C_{meat_{scenario}} \cdot IH_{meat}}{BW} \qquad DOSE_{milk_{scenario}} := \frac{C_{milk_{scenario}} \cdot IH_{milk}}{BW}$$

$$DOSE_{fish_{scenario}} := \frac{C_{fish_{scenario}} \cdot IH_{fish}}{BW}$$

total daily intake for human

total daily intake for human as sum of each pathway
[$kg_{chem}*kg_{bw}^{-1}*d^{-1}$]

$$DOSE_{tot_{scenario}} := DOSE_{drw_{scenario}} + DOSE_{fish_{scenario}} + DOSE_{stem_{scenario}} + DOSE_{root_{scenario}} \ldots + DOSE_{meat_{scenario}} + DOSE_{milk_{scenario}} + DOSE_{air_{scenario}}$$

relative doses of specific different pathway (%)

$$RDOSE_{drw_{scenario}} := \frac{DOSE_{drw_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{air_{scenario}} := \frac{DOSE_{air_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{stem_{scenario}} := \frac{DOSE_{stem_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{root_{scenario}} := \frac{DOSE_{root_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{meat_{scenario}} := \frac{DOSE_{meat_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{milk_{scenario}} := \frac{DOSE_{milk_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{fish_{scenario}} := \frac{DOSE_{fish_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

Result of calculation

$DOSE_{tot_{local}} = 0.192421 \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{tot_{regional}} = 3.402371 \times 10^{-4} \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{drw_{local}} = 0.296967\ \%$

$DOSE_{drw_{regional}} = 1.154657\ \%$

$DOSE_{air_{local}} = 99.1128\ \%$

$DOSE_{air_{regional}} = 96.991195\ \%$

$DOSE_{stem_{local}} = 0.111936\%$

$DOSE_{stem_{regional}} = 0.10954\ \%$

$DOSE_{root_{local}} = 0.033343\ \%$

$DOSE_{root_{regional}} = 0.0275\ \%$

$DOSE_{meat_{local}} = 8.369827 \times 10^{-4}\ \%$

$DOSE_{meat_{regional}} = 8.432901 \times 10^{-4}\ \%$

$DOSE_{milk_{local}} = 3.656768 \times 10^{-3}\ \%$

$DOSE_{milk_{regional}} = 3.684325 \times 10^{-3}\ \%$

$DOSE_{fish_{local}} = 0.44046\ \%$

$DOSE_{fish_{regional}} = 1.71258\ \%$

Default emission to air via wwtp, mean value

environmental concentrations

annual average local PEC in surface water (dissolved) [mg_{chem} * l_{water}^{-1}]	$PEClocal_{water\_ann} := 0.040 \cdot mg \cdot l^{-1}$
annual average local PEC in air (total) [mg_{chem} * m_{air}^{-3}]	$PEClocal_{air\_ann} := 0.197 \cdot mg \cdot m^{-3}$
local PEC in grassland (total), averaged over 180 days [mg_{chem} * kg_{soil}^{-1}]	$PEClocal_{grassland} := 0.0132 \cdot mg \cdot kg^{-1}$
local PEC in porewater of agriculture soil [mg_{chem} * $l_{porewater}^{-1}$]	$PEClocal_{agr\_soil\_porew} := 0.0048 \cdot mg \cdot l^{-1}$
local PEC in porewater of grassland [mg_{chem} * $l_{porewater}^{-1}$]	$PEClocal_{grassland\_porew} := 0.0052 \cdot mg \cdot l^{-1}$
local PEC in groundwater under agriculture soil [mg_{chem} * l_{water}^{-1}]	$PEClocal_{grw} := 0.0048 \cdot mg \cdot l^{-1}$

Result of calculation

$DOSE_{tot_{local}} = 0.043747 \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{drw_{local}} = 1.30621$ %

$DOSE_{air_{local}} = 96.496256$ %

$DOSE_{stem_{local}} = 0.108985$ %

$DOSE_{root_{local}} = 0.146658$ %

$DOSE_{meat_{local}} = 8.435713 \times 10^{-4}$ %

$DOSE_{milk_{local}} = 3.685553 \times 10^{-3}$ %

$DOSE_{fish_{local}} = 1.937362$ %

Site-specific emission to air, direct: maximum value

environmental concentrations

annual average local PEC in surface water (dissolved) [$mg_{chem} * l_{water}^{-1}$]	$PEClocal_{water\_ann} := 0.040 \cdot mg \cdot l^{-1}$
annual average local PEC in air (total) [$mg_{chem} * m_{air}^{-3}$]	$PEClocal_{air\_ann} := 0.184 \cdot mg \cdot m^{-3}$
local PEC in grassland (total), averaged over 180 days [$mg_{chem} * kg_{soil}^{-1}$]	$PEClocal_{grassland} := 0.0132 \cdot mg \cdot kg^{-1}$
local PEC in porewater of agriculture soil [$mg_{chem} * l_{porewater}^{-1}$]	$PEClocal_{agr\_soil\_porew} := 0.0048 \cdot mg \cdot l^{-1}$
local PEC in porewater of grassland [$mg_{chem} * l_{porewater}^{-1}$]	$PEClocal_{grassland\_porew} := 0.0052 \cdot mg \cdot l^{-1}$
local PEC in groundwater under agriculture soil [$mg_{chem} * l_{water}^{-1}$]	$PEClocal_{grw} := 0.0048 \cdot mg \cdot l^{-1}$

Result of calculation

$DOSE_{tot_{local}} = 0.040958 \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{drw_{local}} = 1.395154$ %

$DOSE_{air_{local}} = 96.26566$ %

$DOSE_{stem_{local}} = 0.108725$ %

$DOSE_{root_{local}} = 0.156644$ %

$DOSE_{meat_{local}} = 8.441519 \times 10^{-4}$ %

$DOSE_{milk_{local}} = 3.68809 \times 10^{-3}$ %

$DOSE_{fish_{local}} = 2.069284$ %

Site-specific emission to air, direct, 90%il-value

environmental concentrations

annual average local PEC in surface water (dissolved) [mg_{chem} * l_{water}^{-1}]	$PEClocal_{water\_ann} := 0.040 \cdot mg \cdot l^{-1}$
annual average local PEC in air (total) [mg_{chem} * m_{air}^{-3}]	$PEClocal_{air\_ann} := 0.136 \cdot mg \cdot m^{-3}$
local PEC in grassland (total), averaged over 180 days [mg_{chem} * kg_{soil}^{-1}]	$PEClocal_{grassland} := 0.0132 \cdot mg \cdot kg^{-1}$
local PEC in porewater of agriculture soil [mg_{chem} * $l_{porewater}^{-1}$]	$PEClocal_{agr\_soil\_porew} := 0.0048 \cdot mg \cdot l^{-1}$
local PEC in porewater of grassland [mg_{chem} * $l_{porewater}^{-1}$]	$PEClocal_{grassland\_porew} := 0.0052 \cdot mg \cdot l^{-1}$
local PEC in groundwater under agriculture soil [mg_{chem} * l_{water}^{-1}]	$PEClocal_{grw} := 0.0048 \cdot mg \cdot l^{-1}$

Result of calculation

$DOSE_{tot_{local}} = 0.03066 \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{drw_{local}} = 1.863741$ %

$DOSE_{air_{local}} = 95.05081$ %

$DOSE_{stem_{local}} = 0.107354$ %

$DOSE_{root_{local}} = 0.209256$ %

$DOSE_{meat_{local}} = 8.47211 \times 10^{-4}$ %

$DOSE_{milk_{local}} = 3.70146 \times 10^{-3}$ %

$DOSE_{fish_{local}} = 2.76429415$ %

Unintentional releases from road traffic; monitoring value

regional PEC in surface water (dissolved) [mg_{chem} * l_{water}^{-1}]	$PECregional_{water} := 2.75 \cdot 10^{-4} \cdot mg \cdot l^{-1}$
regional PEC in air (total) [mg_{chem} * m_{air}^{-3}]	$PECregional_{air} := 0.02\ mg \cdot m^{-3}$
regional PEC in agriculture soil (total) [mg_{chem}*kg_{soil}^{-1}	$PECregional_{agr\_soil} := 1.74 \cdot 10^{-5} \cdot mg \cdot kg^{-1}$
regional PEC in porewater of agriculture soils [mg_{chem}*l_{water}^{-1}	$PECregional_{agr\_soil\_porew} := 7.00 \cdot 10^{-6} \cdot mg \cdot l^{-1}$

Results of calculation

$DOSE_{tot_{regional}}$= 4.300596×10^{-3} $\frac{mg}{kg_{bw} \cdot d}$

$DOSE_{drw_{regional}}$= 0.091349 %

$DOSE_{air_{regional}}$= 99.653953 %

$DOSE_{stem_{regional}}$= 0.112547 %

$DOSE_{root_{regional}}$= 2.175615 × 10^{-3} %

$DOSE_{meat_{regional}}$= 8.356964 × 10^{-4} %

$DOSE_{milk_{regional}}$= 3.651148 × 10^{-3} %

$DOSE_{fish_{regional}}$= 0.135489 %

Appendix A V

of the Risk Assessment Report

Benzene CAS-No.: 71-43-2

Calculation of the evaporation time of benzene

June 2006

In the case of benzene, the predominant effect reducing potential dermal exposure is the high volatility of the substance (vapour pressure 91.7 hPa) which leads to considerable low retention times of the substance on the skin or on the protective gloves. This exposure reducing effect cannot be considered if workers have continuous direct contact with the substance, e.g. dipping hands into the substance.

For the purpose of determining the evaporation rate of benzene, an equation was used which was derived within the framework of a research project (Weidlich et al.1986, Gmehling et al., 1989). This project was aimed at calculating airborne concentrations of substances when emitted from liquid mixtures under consideration of the evaporation and the spreading of the substance at the workplace. For calculating the evaporation times of substances, an equation was derived based on the mass transfer at the interface between the liquid and the vapour (two-film-theory). Mass transfer during evaporation occurs until the equilibrium state is achieved. The main influence on evaporation is the transfer through the interface.

For pure substances, the following equation is used:

$$t_{(s)} = \frac{m \cdot R \cdot T}{M \cdot \beta \cdot p \cdot A} \cdot K$$

t: time [s]
m: mass, EASE estimate, [mg] (per cm²)
R: gas constant: 8.314 J K^{-1} mol^{-1}
T: skin temperature [K]
M: molar mass [g mol^{-1}]
β: coefficient of mass transfer in the vapour phase [m h^{-1}], for calculation: β = 8.7 m/h, see below
p: vapour pressure of the pure substance [Pa]
A: area, EASE: 1 cm^2
K: conversion factor

The skin temperature amounts normally to 28 – 32°C (ambient temperature: 20 – 22°C). The reduction of the skin temperature and accordingly of the vapour pressure caused by the evaporation process is not considered in the equation. This might be done by choosing a lower mean temperature for the evaporation process.

The coefficient of mass transfer β is described based on empirical studies:

$\beta = (0.0111 * v^{0.96} * D_g^{0.19}) / (\nu^{0.15} * X^{0.04})$

D_g : coefficient of diffusion, gas phase

v: velocity of air [m/h]
ν: kinematic viscosity of air [m²/h]
X: length of the area of evaporation in the direction of the air stream [m]

In the above given equation, the main influencing parameter the velocity of the air (v). At workplaces v is often between 0.3 m/s and 0.6 m/s (a velocity higher than 0.5 m/s is felt as non-convenient). Since the hands from which a substance evaporates are often in motion, the air velocity might be higher. For a conservative approach, the lower value (0.3 m/s) was chosen.

For different organic solvents, D_g is approx. 0.05 m^2/h. As a range might serve 0.03 – 0.06 m²/h, so that $Dg^{0.19}$ ranges between 0.58 and 0.51.

A literature value was taken for the kinematic viscosity of air (5.4396 10^{-2} m²/h).

The parameter X, representing the length of the area of evaporation in the direction of the air stream [m] is because of its low exponent (0.04) not very influencing. For the calculation, a length of 10 cm was taken.

Taking into account a rather low velocity of air (0.3 m/s), β is about 8.7 m/h. This value is in good correspondence with experimental values for benzene: for an air velocity of 0.27 m/s amounts to 7 m/s.

For benzene and the EASE estimate of 1 mg/cm², an evaporation time of 8 seconds (T = 30°C) is calculated. For benzene on the gloves, an assumed temperature of 20°C leads to a evaporation time of 13 seconds. As a rough estimation for given an order of magnitude, 10 s should be taken as the evaporation time. It is not known in how far the interaction of the skin with the substance influences the evaporation time. The error caused by this interaction is regarded to be higher than the one caused by the uncertainty of the calculation of β. For different substances (7 substances were investigated) β differs about ± 15 %.

In case of gasoline being in contact with the skin skin, dermal exposure is also reduced due to evaporation. On account of the high vapour pressure of gasoline (350 - 900 hPa (CONCAWE 1992)) the resulting retention time of the substance on the skin is considerably shortened thus lowering dermal exposure. For a rough estimation it can be stated that the evaporation time is below the one estimated for pure benzene (< 10 s).

Appendix A VI

of the Risk Assessment Report

Benzene CAS-No.: 71-43-2

Benzene metabolic pathways (Concawe 1996)

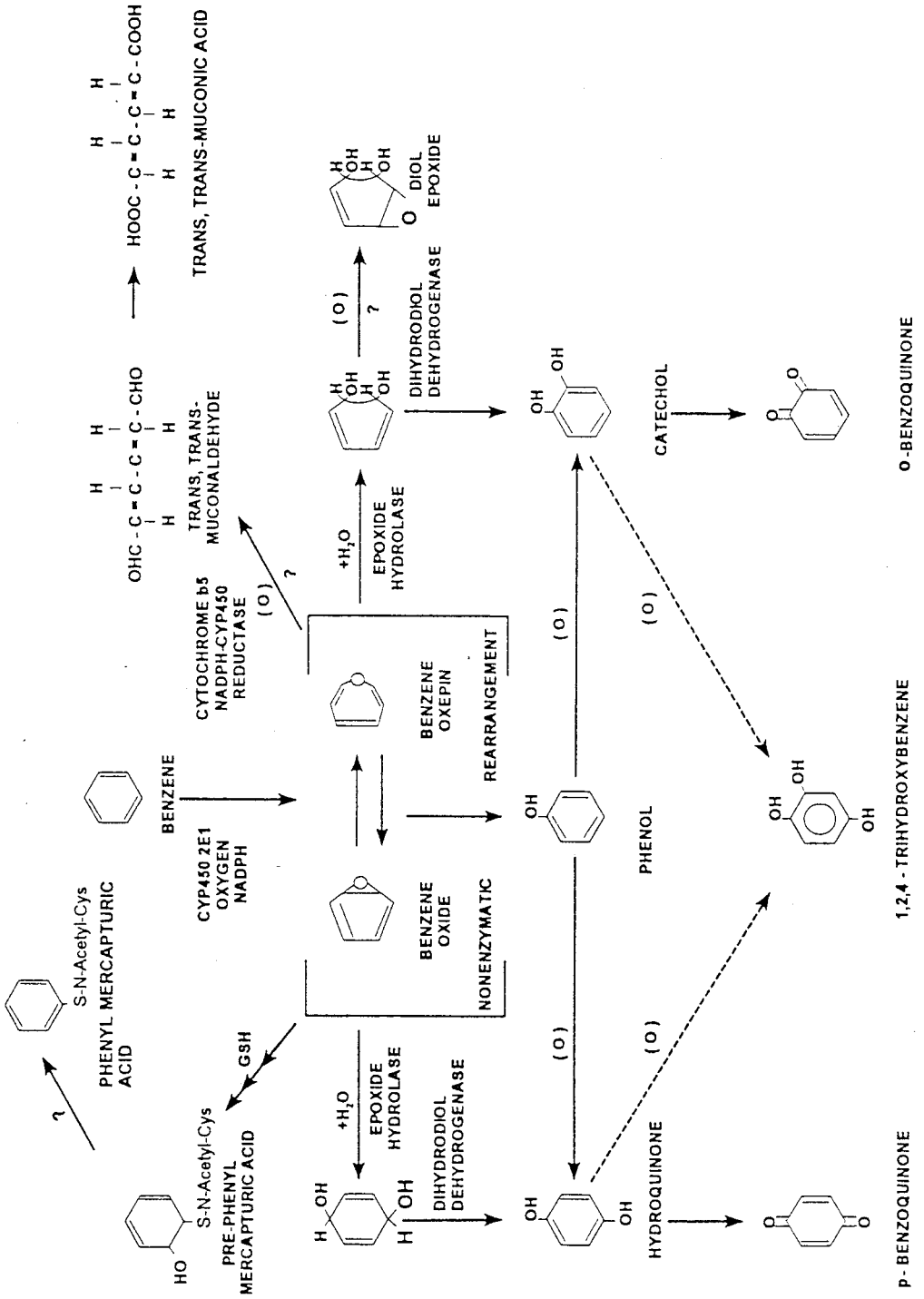

Figure 4.1.2.1: Benzene metabolic pathways (Concawe 1996)