European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

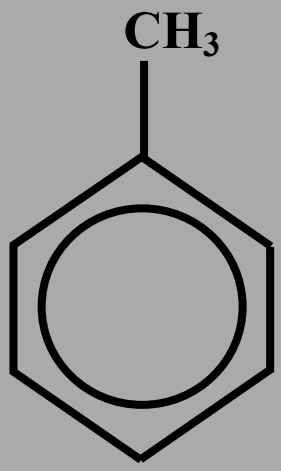
Existing Substances

European Union Risk Assessment Report

CAS No: 108-88-3

EINECS No: 203-625-9

toluene



2nd Priority List

Volume: 30

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

EUR 20539 EN

European Union Risk Assessment Report
toluene
CAS: 108-88-3
EC: 203-625-9
PL-2
30

European Union Risk Assessment Report

TOLUENE

CAS No: 108-88-3

EINECS No: 203-625-9

RISK ASSESSMENT

Cataloguing data can be found at the end of this publication
Luxembourg: Office for Official Publications of the European Communities, 2003

Printed in Italy

TOLUENE

CAS No: 108-88-3

EINECS No: 203-625-9

RISK ASSESSMENT

Final Report, 2003

Denmark

Rapporteur for the risk assessment report on toluene is the Danish Environmental Protection Agency.

Contact persons:

Henrik Tyle, Henrik Søren Larsen, Lotte Kau Andersen and Rasmus Brandt-Lassen
Chemicals Division
Danish Environmental Protection Agency
Strandgade 29
DK-1401 Copenhagen K
DENMARK

Acknowledgements:

The scientific assessments included in this report have been prepared by the following organisations in co-operation with and by request of the rapporteur:

- The Danish Technological Institute, Environmental and Waste Technology,
- Institute of Food Safety and Toxicology, The Danish Veterinary and Food Administration,
- The Danish National Institute of Occupational Health,
- The Danish National Working Environment Authority,
- TNO, The Netherlands.

Date of Last Literature Search:	**2000**
Review of report by MS Technical Experts finalised:	**2000**
Final report:	**2003**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

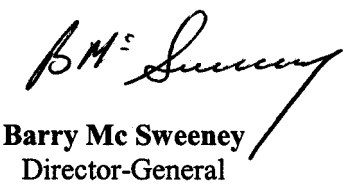
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

---

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

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

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

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS-No.: 108-88-3
EINECS-No.: 203-625-9
IUPAC name: Toluene

The present report assesses the risk associated with the production and use of the isolated commercial product toluene CAS 108-88-3 and the production and use of products containing the isolated commercial product toluene CAS 108-88-3. Gasoline and other crude oil products contain non-isolated toluene as a part of a complex mixture. According to Council Regulation (EEC) 793/93 non-isolated toluene is not a part of the present risk assessment. However, crude estimates of exposure to toluene from gasoline has been included for illustrative purposes and for evaluation of regional toluene concentrations.

Environment

Aquatic environment and sewage 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.

The conclusion applies in relation to releases from two production sites, one combined production and processing site and one off site production site. A risk is also identified for a number of downstream processing sites according to generic assessments for the following use categories:

- industry use as intermediate and as basic chemical,
- mineral oil and fuel formulation,
- formulation of polymers,
- formulation of paints,
- textile processing.

Atmosphere

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

The conclusion applies in the context of the Council Regulation (EEC) 793/93 of Existing Substances to the contribution of the commercial product toluene 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 be the most appropriate, it is recommended that under the relevant air quality Directives a specific in-depth evaluation is performed. Such an evaluation should focus on the contribution of isolated as well as non-isolated toluene to the complex issue of ozone and smog formation and the resulting impact on air quality.

Terrestrial compartment

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

The conclusion applies to release via sludge application to soil from one processing site and to a range of downstream processing sites according to generic assessments for the following use categories:

- industry use as intermediate and as basic chemical,
- mineral oil and fuel formulation,
- formulation of polymers,
- formulation of paints,
- textile processing.

Human health

Human health (toxicity)

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 acute toxicity as a consequence of dermal exposure arising from spraying painting or the use of adhesives,
- concerns for acute toxicity (headache, dizziness, feeling of intoxication, sleepiness and impaired functional performance) as a consequence of inhalation exposure arising from production and use as an intermediate, production of products containing the substance and use of products containing the substance,
- concerns for eye irritation as a consequence of exposure arising from production of products containing the substance and use of products containing the substance in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating),
- concerns for general systemic toxicity as a consequence of inhalation exposure arising from production of products containing the substance and use of products containing the substance in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating),
- concerns for general systemic toxicity as a consequence of dermal exposure arising from use of products containing the substance in the sectors of manual cleaning, use of adhesives and spray painting,
- concerns for general systemic toxicity as a consequence of the combined dermal and inhalation exposure arising the use of products containing the substance in the sectors of manual painting,
- concerns for specific organ toxicity (auditory system toxicity) as a consequence of inhalation exposure arising from production of products containing the substance and use of products containing the substance in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating),
- concerns for fertility and developmental effects and spontaneous abortions as a consequence of inhalation exposure arising from production of products and use of toluene containing

products in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating).

Risk reduction measures should therefore be considered that will ensure a reduction in the levels of toluene found in the workplace during the production and use of toluene and during the production and use of toluene containing products**.**

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 for acute toxicity (headache, dizziness, feeling of intoxication, sleepiness and impaired functional performance) and eye irritation as a consequence of inhalation exposure or eye exposure to vapours arising from spray painting and carpet laying.

The conclusion is based on the estimated exposure during use of toluene containing glues and paints. Risk reduction measures should therefore be considered that will ensure a reduction in the levels of toluene found when using consumer products containing toluene.

and

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

This conclusion is reached because of:

- concerns for effects on reproduction as a consequence of inhalation exposure.

The information and/or test requirement is:

- information on the relationship between the observed effects on reproduction and the duration of the exposure leading to these effects.

The need to actually obtain the information allowing the performance of the risk characterisation for this endpoint, will be considered when the recommended risk reduction strategy is published in the Official Journal.

Hence, any formal request for further information should be seen in the light of other possible risk reduction measures for the consumer scenarios based on the concerns for acute toxicity by inhalation and eye irritation identified for the Scenarios U2 (spray painting) and U4 (carpet laying).

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.

The conclusion applies in the context of the Council Regulation (EEC) 793/93 of Existing Substances to the contribution of the commercial product toluene to the formation of ozone and other harmful substances i.e. smog formation. Regarding which risk reduction measures would be 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 toluene to the complex issue of ozone and smog formation and the resulting impact on air quality.

Human health (physico-chemical properties)

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.

The risk assessment shows that risks are not expected. Risk reduction measures already being applied are considered sufficient.

CONTENTS

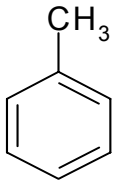
Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS-No.:	108-88-3
EINECS-No.:	203-625-9
IUPAC name:	Toluene
Synonyms:	Methylbenzene, phenyl methane, toluol, methyl benzol, methacide
Molecular formula:	$C_7 H_8$
Molecular weight	92.15 g/mole
Structure:	



1.2 PURITY/IMPURITIES, ADDITIVES

Purity:	≥ 99%	
Impurity:	benzene (CAS: 71-43-2)	≤0.02% w/w
	xylene, mixed isomers (CAS: 1330-20-7)	≤0.02% w/w
Additives:	No information	

1.3 PHYSICO-CHEMICAL PROPERTIES

Physical state:	liquid	
Melting point:	-95°C	(Merck Index, 1989)
Boiling point:	110.6°C at 1,013 hPa	(Merck Index, 1989)
Relative density:	0.871 g/cm^3 at 15°C	(IUCLID,1994)
	0.8669 g/cm^3 at 20°C	(Lide, 1996)
	0.866 g/cm^3 at 20°C	(Merck Index, 1989)
Vapour pressure:	3,000 Pa at 20°C	(measured, IUCLID, 1994)
	3,800 Pa at 25°C	(Mackay et al., 1992)
	28.7 mmHg ~3,826 Pa	(Weast, 1977)
Surface tension:	27.93 mN/m at 25°C	(Lide, 1996)
Water solubility:	515 mg/l at 20°C	(IUCLID, 1994)
	534.8 mg/l at 25°C	(Hansch and Leo, 1979)
Octanol/water (Kow):	log Kow = 2.65	(measured, IUCLID, 1994)
Flash point	4°C (closed cup)	(IUCLID, 1994)
Auto flammability	535°C	(IUCLID, 1994)

Air conversion factor:	1 ppmv ≅ 3.83 mg/m^3 at 20°C and 1,013 hPa	
	1 ppmv = 3.75 mg/m^3 at 25°C and 1 atm	(WHO, 1985)
	1 mg/m^3 = 0.266 ppm at 25°C and 1 atm	(WHO, 1985)
Viscosity:	>0.56 mPa s (>0.64 · 10^{-6} m^2/sec) at 25°C	(Lide, 1996)
	0.424 mPa s (0.49 · 10^{-6} m^2/sec) at 50°C	(Lide, 1996)

Comments

Toluene is a volatile liquid that is highly flammable.

Vapour pressure

The vapour pressure at 20°C was studied by four laboratories during the OECD chemicals testing programme. The results were 2,719, 2,870, 2,970 and 3,080 Pa. At 25°C, the same laboratories measured 3,530, 3,720, 3,810 and 3,940 Pa (Klein et al., 1981). In performing regression analysis on laboratory results, an equation was produced by BASF (1987) where the vapour pressure of toluene was expressed as ln p (bar) = 9.4709-3,145.05/(221.89 + t°C). The calculated pressure at 20°C was 2,930 Pa and 3,806 Pa at 25°C.

The values of 3,000 Pa at 20°C and 3,800 Pa at 25°C presented by the manufacturers are used in the risk assessment.

Water solubility

The experimental values are 514, 525, 535 mg/l (Bobra et al., 1983; Isnard and Lambert, 1989; Sutton and Calder, 1975; Adema, 1991). The solubility at 25°C in fresh water was observed to be 535 mg/l and in seawater 380 mg/l (Sutton and Calder, 1975). Rossi and Thomas (1981) using GC measured the solubility to be 507 mg/l in distilled water and 419 mg/l in seawater (3.5% salinity) at 25°C. In distilled water at 25°C and measured by HPLC, the water solubility was observed to be 524 mg/l (Banerjee, 1984). According to Rippen (1992), the water solubility between 16 and 30°C ranged from 420 mg/l to 735 mg/l and the mean value based on 21 literature values was 549±65 mg/l. This value is not used in the risk assessment because not all the values are validated.

The measured values of 515 mg/l (20°C) and 535 mg/l (25°C) are used in the risk assessment.

Octanol/water partition coefficient (Kow)

The log Kow ranged from 2.11 to 2.80, depending on temperature and pressure (Sloof and Blokzijl, 1988). Estimated from structure analysis, the log Kow is 2.54 (EPIWIN, 1995). Log Kow is experimentally found to be 2.63 (Isnard and Lambert, 1989), 2.65 (Doucette and Andren, 1988) and 2.69 (Hansch and Leo, 1979). Sangster (1989) recommended the value log Kow 2.73 (which is also the logPstar value recommended by Hansch and Leo (1985)). The geometric average of the measured results from four laboratories was calculated to be 2.65 by Eadsforth and Moser (1983), who also measured log Kow for toluene to be 2.65 and 2.77 by reverse HPLC. Because more weight is given to results from direct than indirect methods, the measured log Kow 2.65 is used in the risk assessment.

Conclusion

The data on physico-chemical properties used in the risk assessment are then: vapour pressure 3,000 Pa, water solubility 515 mg/l and log Kow 2.65 at 20°C.

The EUSES estimations require the values at 25°C, i.e. vapour pressure 3,800 Pa and water solubility 535 mg/l.

1.4 CLASSIFICATION

The classification and labelling of toluene has been agreed at technical level to be listed in Annex I to Directive 67/548/EEC following the adoption of the 29th Adaptation to Technical Progress, as follows:

Classification

F, R11	Highly flammable.
Repr.Cat.3; R63	Possible risk of harm to the unborn child.
Xn; R48/20-65	Harmful: danger of serious damage to health by prolonged exposure through inhalation. May cause lung damage if swallowed.
Xi; R38	Irritating to skin.
R67	Vapours may cause drosinessa and dizziness.

Labelling

F; Xn
R: 11-38-48/20-63-65-67
S: (2-)36/37-46/62

Environment: No classification.

R38 is justified because significant, persisting skin inflammation (score for erythema >2 at 72 hours and 7 days) has been observed in a skin irritation study in animals (Annex V B4 study), and because toluene has a degreasing effect on human skin (see Section 4.1.2.3.1).

R48/20 is justified because toluene causes several types of serious toxic effects after inhalation. Toluene-induced chronic impairment of auditory function has been demonstrated in a number of animal studies. This has been substantiated by morphological evidence of cell loss in the rat cochlea. Existing data suggest that humans are sensitive to this effect at exposure levels, which may be encountered in the working environment.

Toluene causes irreversible changes, including neuron loss, in the central nervous system of animals. In humans severe central nervous system effects including brain atrophy have been found at very high exposure levels. Neuropsychological effects at working environment exposure levels have been demonstrated.

Toluene causes an increase in the occurrence of non-malignant pituitary tumours in mice.

R65 is justified on the basis of viscosity and surface tension. A viscosity value at 40ºC has not been found.

However, as a 25°C value of >0.56 mPa·s (>$0.64 \cdot 10^{-6}$ m^2/sec), and a 50°C value of 0.424 mPa·s ($0.49 \cdot 10^{-6}$ m^2/sec) have been found (Lide, 1996), it can be assumed that toluene would fulfil the criteria for R65 of viscosity below $7 \cdot 10^{-6}$ m^2/sec at 40°C. The criteria for R65 state that substances with surface tension above 33 mN/m at 25ºC not necessarily should be classified, but since toluene has been reported to have a surface tension of 27.93 mN/m at 25ºC (Lide, 1996) no exemption is warranted.

R67 is justified since data from experimental exposure of human volunteers show that dizziness and sleepiness are experienced at air levels substantially below the level of 20 mg/l/4h mentioned in the criteria for R67 (for toluene this equals 5,300 ppm). In rats exposed to 20 mg/l/4h in the BASF (1980) study rocking gait and narcosis were observed.

Toluene was classified as Reproductive Category 3 (**R63**) for fertility at the Commission Working Group Meeting on Classification and Labelling of Dangerous Substances. It will be listed in Annex I to Directive 67/548/EEC following the adoption of the 29th Adaptation to Technical Progress.

2 GENERAL INFORMATION ON EXPOSURE

2.1 INTRODUCTION

Toluene formation

The chemical substance toluene occurs naturally and natural sources are volcanoes and forest fires (cf. Appendix A) and in low concentrations in crude oil. In the petroleum refinery process, where gasoline is produced, this toluene will be present in low concentrations in straight-run gasoline products.

The natural sources of toluene (the chemical substance) are small compared to the man-made quantities produced by different petroleum conversion processes. These processes (catalytic reforming, powerforming, catalytic cracking, hydrocracking, steam cracking etc.) are all important processes in modern refineries to upgrade the yield of useful products from crude oil (e.g. to produce high-octane gasoline from straight-run refinery streams or low boiling fuels from higher boiling refinery streams). These conversion processes produce olefinic and aromatic rich streams containing benzene, toluene and xylenes in varying concentrations. Most of the refinery/cracker streams containing toluene are used as a base or blending feedstock to produce motor gasoline.

In order to produce the commercial product toluene, CAS No 108-88-3, a fraction of the above toluene-rich streams is segregated, distilled and purified to produce the commercial toluene product.

Commercial toluene is mainly (80%) used as an intermediate in the production of other chemicals. Approximately 20% of commercial toluene is used as a solvent carrier in paints, thinners, adhesives, inks and finally as a processing aid ("extraction solvent") in the production of pharmaceutical and other chemical products.

Toluene formation/emission

The chemical substance toluene is formed naturally and emitted when some organic material is exposed to pyrolysis or combustion temperatures (e.g. forest fires, volcanoes, and smoke).

Toluene[4] will be released to the environment when substances containing toluene or preparations thereof are produced, distributed and handled.

Motor gasoline when used in a combustion engine, will emit unburned or formed toluene. Diesel engines will emit toluene when combusting diesel fuels.

The commercial product toluene will be released in varying quantities when:

- it is produced, distributed and handled,
- it is used as a chemical feed stock (intermediate),
- it is used, distributed and handled as such or as a preparation containing toluene as a solvent for:
  - closed systems and open systems with vapour recovery (toluene is recovered),
  - open systems without vapour recovery (toluene is mainly emitted to air).

4 It should be noted that the risk assessment covers the commercial product toluene with the CAS No 108-88-3 whereas other significant sources to toluene release are included for illustrative purposes, e.g. gasoline (cf. Appendix A).

Due to the physical-chemical properties of toluene, toluene preferentially partitions to the atmosphere. The main sources of atmospheric toluene are vaporisation of gasoline, vehicle exhaust emissions and solvent emissions.

The primary sources of emissions are (WHO, 1985):

- sources related to occurrence in fuels and creation in combustion processes: 65% (emissions from motor vehicles and aircraft exhaust and losses during gasoline marketing activities, spills and smoke),
- toluene production,
- processes in which toluene is used (32%),
- use of products in which toluene is a component.

The emission from motor vehicles during combustion may have changed considerable during the last decade due to increase of the toluene content in gasoline as a consequence of phase-out of lead and due to the introduction of catalytic exhaust purifiers.

2.2 PRODUCTION

As well as being a constituent of crude oil, toluene is a component of the condensate from natural gas production. Toluene is synthesised together with many other substances in petroleum refinery and chemical plant processes, primarily catalytic reforming, steam cracking, and dealkylation. Toluene is also recovered during the production of coal-derived chemicals, primarily from coke oven by-products. Part of the toluene so produced is separated from these sources and purified for industrial use to make the commercial grade toluene. The remaining refinery reformate streams are blended with other naphtha streams to make motor gasoline (Exxon, personal communication, 15.11.1996).

Toluene is mainly produced by continuous processes in closed systems.

The major amount of toluene is obtained by distillation of refinery streams. This is a process that does not involve any direct contact with water.

On basis of information provide by manufacturer task force (APA-TF, 1996), the total amount of toluene produced by the stakeholders that provided information was 2,600 kTonnes for 1995. This production volume does not include toluene in gasoline (i.e. non-isolated toluene).

The consumption of gasoline in the EU is approximately 120,000 kTonnes/year (CONCAWE, 1997). The content of toluene varies according to the intended final use, cf. Section 2.3.3.

The import of toluene was >48 kTonnes in 1995 (APA-TF, 1996). In an earlier communication, manufacturers have presented data on import volumes of 90 to 140 kTonnes/year. According to the realistic worst-case concept an import level of 150 kTonnes has been used in the risk assessment.

Table 2.1 EU production of commercial Toluene (information from manufacturers) in kTonnes/year

Source	Toluene, kTonnes/year		
	APA	CONCAWE	Total
Production approx.	2,600		
Imports of the same (worst scenario) is set at	150		
Export			
Toluene in gasoline from Refinery processes		14,000	
Total toluene molecules produced	2,750	14,000	16,750

Blank = not available

Thus a yearly consumption in the EU of 2,750 kTonnes toluene is used in this risk assessment.

2.3 USE PATTERN

Toluene is a high-production volume substance and is extensively employed in a broad spectrum of applications. Commercial toluene is used as a raw material in the production of benzene and a host of other chemicals (e.g. benzoic acid, nitrotoluenes, tolyl diisocyanates, as well as dyes, pharmaceuticals, food additives, plastics, etc.). The strong solvent powers of toluene make it a preferred solvent in many applications including coatings, adhesives, inks, pharmaceuticals and chemical processing (Fishbein, 1985). Toluene is present in many consumer products, including household aerosols, paints, varnishes, adhesives, and glues. Thus, toluene is used in several hundreds of products and in a large number of industrial branches.

Approximately half of the toluene production was processed at the production facilities where production took place (APA, 1996).

Table 2.2 Examples of processing and end use of isolated toluene

Process	End use	
Dealkylation	Benzene	
Oxidation	Benzoic acid	phenol terephthalic acid phthalates caprolactam
Nitration	Nitrotoluene	toluene diisocyanate, trinitrotoluene (TNT)
Chlorination		dyes, pharmaceuticals etc.
Sulfonation	Toluene sulfonic acids	
Alkylation	Alkylated toluene intermediates	

Fractionating the use of toluene as a feedstock in the production of other chemical products, Parpinelli Tecnon (1996) estimated the usage in Western Europe in 1994-1995 to average:

TDA (Toluene dealkylation (to benzene))	32%
Phenol	7%
Nitrotoluene / Caprolactam / Phthalates	2%
TDI (Toluene diisocyanate)	11%
Disproportionation (from toluene to C_6, C_8 or C_9)	16%
Motor gasoline (as additive solvent)	3%
Miscellaneous	10%
Total as feedstock and miscellaneous	81%
Used as solvent	19%
Total	100%

Based on the results of the Parpinelli Tecnon (1996) analysis (cf. above), 19% or approximately 400 kTonnes is used as a solvent. However, the European Industrial Toluene User Group (EITUG) has provided information on the industry toluene consumption of approximately 60 kTonnes/year (EITUG, 1998), later updated to approximately 180 kTonnes/year (EITUG, 1999) (cf. **Table 2.3**).

This discrepancy of toluene use as a solvent demonstrates the difficulties in estimating product end-use when such customers purchase the product, not from the producer, but from customers of the producer. APA informs that the majority of the toluene producers sell their product to large consumers (for conversion) and to distributors (for resale) in large volumes (ships and barges). Companies using toluene as a solvent use and store small volumes and normally purchase from established distributors in smaller volumes (trucks and smaller).

Table 2.3 Consumption of toluene by industry (EITUG 1998)

Industry	Industry	Tonnes/year	KTonnes/year
Printing	Ink making	1,600	
	Publication gravure	30,000	
	Packaging printing	5,000	
	Wall covering	1,000	38
Painting	Building industry	NA	
	Vehicle refinishing	NA	
	Wood and furniture	NA	90
Adhesives	Adhesive manufacturing	NA	
	Leather and footwear	NA	
	Floor coverings	NA	
	Wood and furniture	NA	19
Rubber	Rubber converting	30	30
Other uses	Laboratories	1	1
Industry total			178

Additional information has been obtained that toluene can also be used as processing aids (as "extraction solvent", not raw material) in the manufacture of caprolactam, pharmaceuticals and other chemicals. From limited information, it is estimated that the demand per site is small ≤300 t/y. As the actual number of users is not known, it is not possible to determine the total use in this category but it could be in the range 50-150 kTonnes.

According to APA, it is difficult to obtain an accurate estimate for the use of toluene as a solvent. Toluene is used in many solvent applications and there are no mechanisms in place to add up the quantities used. Not only is toluene used as a solvent in the rotogravure industry, in paints, varnishes and adhesives, it is also used in pesticides, wood preservatives and as a processing aid among others. The APA estimate of how much toluene that is used as a solvent (Parpinelli, 1996) is based on interviews of major producers/users and from published statistics. From the latest Parpinelli Technon study issued in 1998, a toluene solvent demand of 439 kTonnes is estimated. It is noted that the estimate should not be viewed as a statistically correct demand, but is instead an indication of the magnitude or range of demand. From another industry estimate (private communication to APA), a solvent demand of 382 kTonnes is estimated. The average value of the two sources would be 410 kTonnes based on 1998 data.

Table 2.4 Different estimates on the demand of toluene for use as a solvent

Country	Parpinelli		Industry [1]	Range
UK	70	74	128	75 - 125
Ireland	4			
Germany	87	103	69	70 - 100
Austria	4			
Switzerland	12			
Italy		72	60	60 - 70
France		63	48	50 - 60
Spain		57	40	40 - 55
Netherlands		24	10	10 - 25
Belgium		13	12	10 - 15
Portugal		19	10	10 - 20
Greece		9	-	10
Nordic Countries		5	5	5
Sweden	2			
Denmark	1			
Norway	1			
Finland	1			
Total		439	382	380 - 440
Average				410

[1] Private communication to APA

Toluene is used in the gravure printing process as a production aid for the printing of products such as magazines, leaflets, advertising brochures and catalogues.

In Denmark, the Danish Product Register (August 1998) data on toluene registered approximately 2,855 products containing 6,964 tonnes toluene. The distribution of the content is presented below and may be considered as a typical example of the distribution in products in the Nordic countries. The use of organic solvents like toluene has been reduced in the Nordic countries in certain use categories of products such as paints and lacquers during the last decades. The decreasing use of toluene in some types of products is reflected in the Product Register information which also shows that the total registered volume of toluene in products in the Danish market has decreased from approximately 19,000 t in 1995 to the present level of approximately 7,000 t (1998).

The Danish products types covering more than 50 functions/uses include solvents, adhesives and binding agents, paints, lacquers and varnishes, and intermediates. The industry groups were: chemical industry, manufacture of metal articles, textile and clothing industry, reprographic industry, wood and furniture industry, and construction industry distributed in 28 trades.

Table 2.5 Danish Product Register 1998 (tonnes and percentage differentiated in concentrations in preparations/products)

Use category	0-1%	1-5%	5-10%	10-20%	20-50%	50-80%	80 - 100%	Total	%
Solvents	<1	<1	6	42	274	1,971	2,242	4,536	65
Paints, lacquers and varnishes	28	16	65	156	336	133	3	737	11
Reprographic agents	<1	<1		698				698	10
Cleaning agents	<1	<1	<1	<1	59	292	10	362	5
Intermediates								633	9
Adhesives, glues	1	26	2	27	77	8	<1	141	2
Process regulators	<1	<1	<1	6	53	43	<1	104	1
Surface treatment	<1	6	<1	2	47	<1		56	1
Corrosion inhibitors	<1	3	2	2	37			45	1
Total	32	51	79	204	1,478	2,866	2,254	6,964	100

Note: Deviations in totals may be caused by the reporting method (less than 3 companies not specified due to confidentiality)

Table 2.6 Swedish Product register 1994

Use/function	Tonnes	%
Intermediates	12,000 – 17,000	66%
Diluents (paints etc.)	3,800 – 3,850	15%
Solvents	2,200	9%
Printing inks	1,000 – 1,200	5%
Paint and varnishes	640 - 720	3%
Binders, adhesives, glues	330 - 370	1%
Others		1%
Total	19,600 – 25,600	100%

Note: Approximately 1,000 products whereof 240 were consumer products

The differences in the distribution of toluene in various use categories of products in the Danish and Swedish product registers can be explained by the differences in the reporting requirements, use categorisation methodology and the structure of the industry between the two countries.

2.3.1 Information on use pattern according to the TGD and the literature

Toluene is used in the industry in closed systems, and with wide dispersive use. The main categories according to the TGD (1996) categorisation would then be:

Main category:	Continuous production, isolated intermediates (1b)
Production:	Type: used in closed system
Industrial category:	Chemical industry: basic chemical Chemical industry: chemicals used in synthesis Mineral oil and fuel industry Polymer industry Pulp, paper and board industry Paints lacquers and varnishes industry Textile industry Agricultural industry Electrical/electronic industry Personal/domestic industry
Use category	Intermediate Solvent Adhesives, binding agent processing: wide dispersive use

Table 2.7 Industrial and use categories (IUCLID, 1994)

Industrial category	IC no.	Use category	UC no.
Chemical industry: basic chemical Chemical industry: used in synthesis	2 3	Solvents Intermediates	48 33
Mineral oil and fuel industry	9	Additives in fuel, motor oil etc	28
Pulp, paper and board industry (printing process)	12	Solvent Coating Adhesives, binding agents	48 48 48
Textile processing industry	13	Coating	48
Paints, lacquers and varnishes industry	14	Solvents	48

Literature references on the sources of toluene

The principal source of toluene is catalytic reforming of refinery streams. This source accounts for ca. 87% of the total toluene produced. An additional 9% is separated from pyrolysis gasoline produced in steam crackers during the manufacture of ethylene and propylene. Other sources are an additional 2% recovered as by-product from styrene manufacture and 1-2% entering the market from separation from coal-tars (Kirk-Othmer, 1983).

Of the commercial toluene, the major part (80%) is used in chemical productions as an intermediate to other substances; e.g. toluene diisocyanate is the basic raw material for production of flexible polyurethane foams (Kirk-Othmer, 1983). Back-formation of toluene from some of its end-products may be possible.

The emissions to the environment were estimated by WHO (1985) to be the results of:

- use in fuels (exhaust emissions, evaporative losses and emissions due to marketing and distribution) 65%,
- use as solvent, release as a result of evaporation 34%,
- refining and production **2%,**
- the emission to the environment also comes from other manufacturing processes, by product formation (and cigarette smoking).

Three studies estimating sources of toluene released in the UK gave similar proportions:

- use in fuel 48-74%
- use as a solvent 25-52%
- refining and production <2%

Nielsen and Howe (1991) in: IUCLID (Shell, 1994).

2.3.2 Information on use pattern from main manufacturers

More recent information has been provided by the main manufacturers which is based on the result of a survey covering 1995 performed by CEFIC Aromatic Producers Association (APA, 1996):

Table 2.8 Production and processing of toluene

Production in refinery streams	**14,000 kTonnes/yr**	**(Estimate total motor gasoline at $1.40 \cdot 10^8$ tonnes/yr · ~10% toluene (CONCAWE, 1997)**
Production, isolated toluene:	2,600 kTonnes/yr	(APA, 1996)
Import:	≤150 kTonnes/yr	(>48 Kt, APA, 1996)
Processing at production	534 kTonnes/yr	(APA, 1996)
Processing by APA members	1,253 kTonnes/yr [1)]	
Formulation at production	2 kTonnes/yr [2)]	

[1)] The data from individual manufacturers do not all list production figures and some are indicted as processors only. These are omitted from the total of APA reporters who produce and process on the same site. A major portion of the onsite processing is as intermediates.

[2)] Only one responder who reported production volume also reported a formulation volume but no industrial category was reported.

According to APA (1997) the production, processing and use were distributed in industrial categories according to **Table 2.9**.

Table 2.9 Volumes of toluene used in various processes in the EU (APA, 1997; APA et al., 1999)

Industrial Category	kTonnes/year	IC no. [1)]	Use Category	UC no. [1)]	%
Chemical industry: Chemicals used in synthesis	534.0 1,411.0	3	On-site intermediate Off-site intermediate	33 33	20.2 79.8
Chemical industry: Basic Chemical	200.0	2	Solvent	48	
Chemical industry: Basic Chemical	150.0	2	Extraction agent	34	
Mineral oil and fuel industry	160.9	9	Solvent	48	
Polymers industry	113.4	11	Process regulator, dry	33	
Agricultural Industry	8.1	1	Intermediate	33	
Personal/domestic industry	8.1	5	Solvent	48	
Electrical/electronic industry	0.2	4	Solvent	48	
Textile processing industry	0.1	13	Coating	0	
Other	15.2	15	Other	0	
Paint, lacquer and varnish industry	90.0	14	Solvent	48	
Printing: *					
Ink making	1.6	14	Solvent	48	
Publication gravure	30.0	12	Solvent	48	
Packaging printing	5.0	12	Solvent	48	
Wall covering	1.0	12	Solvent	48	
Adhesives	19.0	12	Solvent	48	
Total	2,747.6				

* The printing industry subgroups could not be allocated to one specific IC and are therefore divided between the IC 14: Paint, lacquers and varnishes and IC12: Pulp paper and board industry

[1)] For explanation, see Table 2.7

With no specific knowledge of its uses, it is assumed that toluene is used as a solvent in the electronic and personal/domestic industries (either directly or in preparation such as adhesives). In the mineral oil and fuel industry, toluene is used in additives or as a solvent in additives in motor oil, gear oil, hydraulic fluid etc. Toluene is also used as a solvent in oil base paints. Specific emission scenarios exist for IC nos. 3, 5, 13 and 14 and appended to the Technical Guidance Document (TGD) in Section IV, Chapter 7. However, because of insufficient information on the release scenarios, the release estimations have been performed according to the general IC/UC categories in the TGD, Chapter 3, and Appendix A in the risk assessment report.

APA has performed a detailed study based on information from 31 sites: 19 sites were producing isolated toluene, 6 sites produced and performed on-site processing of toluene and 6 toluene processing sites. These sites will be considered separately in Section 3 and denoted “upstream” production and processing scenarios.

Table 2.10 Site-specific information

	No. of sites	Production volume, kTonnes	Processing volume, kTonnes
Production	19	2,080	
Production + processing on site	6	509	494
Processing	6		21
Total	31	2,589	515

2.3.3 Fuel component

The presence of toluene in fuel is not strictly a part of the risk assessment of the commercial product toluene but is used for illustrative purposes (cf. Appendix A for details).

The blending of unleaded gasoline has resulted in the incorporation of higher concentrations of reformates which are rich in aromatic hydrocarbons, including toluene.

The average composition of marketed gasolines has been studied in 48 German gasolines during 1992-1994. The range of toluene concentrations varied from 2.7% to 21.0% by weight with an average of 11.4% by weight (DGMK, 1994).

Table 2.11 Content of toluene in automotive gasolines

Fuel type	Country	Year	Range, %	Average %	Reference
Regular	The Netherlands	1977/78		ca. 5	Rippen (1992)
	Germany	1986	3.0 to 11.8	6.1	
Regular unleaded	Germany	1986	5.3 to 14.9	9.3	
Premium (Super)	The Netherlands	1977/78		ca. 8	
	Germany	1986	8.5 to 14.7	12.5	
Premium unleaded	Germany	1986	4.7 to 17.3	9.2	
48 Gasolines	Germany	1992-1994	2.7 to 21.0	11.4	DGMK (1994)

The annual consumption of motor gasoline in the EU for the years 1990-1994 has been about 120 million tonnes (IEA, 1995). Based on the German average, the total amount of toluene in gasoline consumed each year in the EU corresponds to approximately 13.7 million tonnes.

2.3.4 Summary on use of toluene

Toluene is a component of crude oil and is produced by different petroleum distillation conversion processes. Isolated toluene is used in industry as a chemical intermediate and as a solvent.

As an intermediate in the chemical industry, toluene is used as a raw material in the organic synthesis of other chemicals e.g. benzaldehyde, benzene, benzoic acid, benzyl chloride, phenol, toluene diisocyanate, xylene and other derivatives used as dye intermediates, resin modifiers and germicides. Toluene is also used in the synthesis of explosives (TNT), vinyl toluene, cresols and flavouring agents.

Toluene is used as a solvent for paints, lacquers, gums, resins in the extraction of various substances from plants. According to the main manufacturers approximately 20% of isolated toluene sold as solvent is used in paints, inks, thinners, coatings, adhesives, degreasers and other formulated products requiring a solvent carrier.

Because of the vast amount of products in which toluene is used either as intermediate or as solvent (the main uses), toluene could be allocated to most industrial categories.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

The environmental exposure assessments considered combine the relevant exposure scenarios for the substance and apply recommended assessment methods for deriving PEC at a local and regional scale according to information from the main manufacturers and/or the TGD.

3.1.1 Environmental releases

Emissions are expected from toluene production, from catalytic reformats, pyrolysis gases, and as a by-product from styrene production and from its use as a chemical intermediate in industry.

Emission takes place from its use as a solvent and thinner for paints, lacquers, etc. in industry and from downstream users including private use.

Releases to the environment also take place from toluene from the use of gasoline; for example emissions from motor vehicle exhaust, gasoline storage tanks, filling stations, petroleum spills, etc.

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

The risk assessment is primarily dealing with the releases from the production and processing of isolated toluene. Release from products containing toluene (e.g. gasoline) is therefore kept separated and only included/commented on for illustrative purposes in the following sections. It should be noted that monitoring data include both releases from isolated toluene production and use as well as from the use of products containing toluene and toluene produced by other actions (e.g. combustion). Emissions from other sources than production and use of the commercial isolated toluene are covered in Appendix A.

Toluene may be released into the environment during its production, processing (i.e. manufacturing of other chemical substances), formulation (i.e. mixing into other substances) and use. The atmospheric compartment is estimated to be the primary recipient based on the high vapour pressure. However, also release to surface water sand soil may occur. Toluene is furthermore released into the atmosphere principally from the volatilisation of petroleum fuels and toluene-based solvents and thinners and from motor vehicle exhaust. Emissions to aquatic environment and soil may occur during storage, transport and disposal of fuels and oils.

Toluene is used and emitted in large quantities. Because toluene is a volatile organic compound, the emissions mainly take place into the air and the emissions to soil and water partly leads to re-emission to the air. As a result most of the toluene is found in the air compartment.

Emission to air is dominated by road-traffic, which is the main source according to Sloof and Blokzijl (1988) and industry. Emissions are also caused by (other) combustion processes, laboratories and smoking. This risk assessment report, however, mainly concentrates on releases from the production, processing, formulation and use of isolated toluene.

3.1.1.1 Release estimates

The release estimates are based on the assumption that 2,600 kTonnes of toluene are isolated and that 150 kTonnes are imported per year in the EU.

Release from production and combined production and processing

Information from toluene production and processing sites has been gathered by the main manufacturers who have collected responses by means of a questionnaire from the involved industrial sites. The environmental exposure assessments were based on site-specific data when available, and TGD default values when such data were unavailable. The results covering sites of production, combined production and processing on the same site and a few processing sites are presented in **Table 3.1** and in detail with comments in Appendix B.

The data on production, and combined production and processing sites seem to cover an acceptable number of sites to be used as an alternative to generic scenarios according to the TGD covering "upstream" release and exposure.

In general, the environmental exposure estimation method employed by the main manufacturers is slightly different from the standard procedures of the TGD.

1. Data override default TGD emission factors and parameters (e.g. STP flow), if available.
2. The analysis is conservative in that the default values to water for a "wet" process are used regardless of whether or not the respondent characterised their manufacturing process as "wet" or "dry". These employed release factors are 0.003 for production and 0.007 for processing.
3. The default emission factor to air used (0.01) corresponds to main category 1c regardless of whether or not the response was a continuous process in a closed system.
4. The removal in the STP used was 94.21% (94.57% calculated by EUSES).
5. The production volume, emission factor, STP removal, and dilution were used to calculate local water concentration unless overridden by measured values in effluent or the local environment[5].

[5] Different degree of information and variable statistics were used, cf. Appendix B

Table 3.1 Data for production, production and on-site processing and processing sites in kTonnes, use categories, release fractions and emissions

Site	Production	Processed	Formulated	Sold for processing/ formulation elsewhere	MC	IC	UC	Release fraction to air	Release fraction to water	Emission to air (kg/day)	Emission to water (kg/day)
Production											
P1 [1)]	2	0	0	2	1c	3	33	0.01	0.003	41.1	12.3
P2	81	0	0	81	1c	3	33	0.01	0.000824	2,227.4	8.8
P3	180	0	0	180	1c	3	33	0.01	0.00002	4,931.5	9.9
P4	13	0	0	13	1c	3	33	0.000088	0.003	3.1	106.8
P5	37	0	0	37	1c	3	33	0.01	0.003	1,005.5	301.6
P6	103	0	0	103	1c	3	33	$7.28 \cdot 10^{-6}$	$3.14 \cdot 10^{-5}$	2.1	8.8
P7	75	0	0	75	1c	3	33	0 [2)]	0.003	0	0.4
P8	100	0	0	100	1c	3	33	0.01	0.003	2,739.7	821.9
P9	240	0	0	240	1c	3	33	0.0002	0.003	131.5	1,972.6
P10	8	0	0	8	1c	3	33	0.00023	0.003	5.1	66.3
P11	66	0	0	66	1c	3	33	0.01	0.003	25.0	542.5
P12	117	0	0	117	1c	3	33	0.01	0.003	43.8	35.2
P13	170	0	0	170	1c	3	33	0.01	0.003	4,657.5	0.0
P14	25	0	0	25	1c	3	33	0.01	0.003	679.5	203.8
P15	55	0	0	55	1c	3	33	$1.11 \cdot 10^{-6}$	0.003	0.2	452.1
P16	25	0	0	25	1c	3	33	$4 \cdot 10^{-7}$	0.003	0.0	205.5
P17	41	0	0	41	1c	3	33	$1.22 \cdot 10^{-6}$	0.003	0.1	337.0
P18	43	0	0	43	1c	3	33	$1.16 \cdot 10^{-6}$	0.003	0.1	353.4
P19	700	0	0	700	1b	3	33	0.0035	0.003	6,712.3	5,753.4
Production + processing											
PP1	9	3	6	0	1b	3	33	0.0012	0.003	27.9	69.9
PP2	49	158	2	0	1b	3	33	$1.09 \cdot 10^{-5}$	0.003	1.5	402.7
PP3	206	206	0	0	1b	3	33	0.000149	$4.85 \cdot 10^{-6}$	84.1	2.7
PP4	35	0	18	18	1c	3	33	0.01	0.003	958.9	287.7
PP5	194	123	0	71	1b	3	33	$1.55 \cdot 10^{-7}$	0.003	0.1	1,594.5
PP7	16	4	0	12	1b	3	33	0.001	0.003	10.7	32.1
Processing											
Pc1	0	1	0	0	3	3	33	0.025	0.003	68.5	8.2
Pc2	0	0.2	0	0	3	3	33	0.025	0.007	15.4	4.3
Pc3	0	33	0	0	3	3	33	0.025	0.007	2,260.3	632.9
Pc4	0	20	0	0	3	3	33	0.000125	0.007	6.8	0.4
Pc5	0	0.5	0	0	1b	3	33	0.0017	0.003	2.1	3.7
Pc6	0	0.2	0	0	1b	3	33	0.00001	0.003	0.0	1.3
Total	2,588	549	25	2,181						26,642	14,233

1) Production stopped in 1998
2) According to manufacturer

Summary statistics for "upstream" production and processing

Production sites

For production sites, 19 sites were identified covering the production of 2,080 kTonnes of toluene. The emissions to air vary from 0 to almost 7,000 kg/day and the emission to water varies from 0 to 5,700 kg/day. It is noted that the high values were based on the use of TGD default values. For details refer to the tables in Appendix B.

Production and processing sites

For sites where production and processing take place on the same site, 6 sites were identified covering 509 kTonnes of toluene production, processing of 494 kTonnes of toluene and formulation of 25 kTonnes.

The emissions to air vary from 0.08 to almost 1,000 kg/day and the emission to water varies from 3 to 1,600 kg/day. It is noted that the highest values were based on the use of TGD default values. For details refer to the tables in Appendix B.

Processing sites

Of processing sites, 6 sites are included in the main manufacturer study. The 6 sites cover the processing of approximately 21 kTonnes of toluene. It is noted that the highest values were based on the use of TGD default values. For details refer to the tables in Appendix B.

Thus, the site-specific information covers the production of 2,080 + 509 = 2,589 kTonnes toluene and processing of 494 + 55 = 549 kTonnes toluene.

Release estimations from processing and other downstream uses

For "downstream" uses site-specific information obtained by the main manufacturers was too scarce to be used as an alternative to default environmental release and exposure assessments according to the TGD. Therefore, downstream uses have been separated into industrial categories and use categories according to information from main manufacturers and releases estimated according to the TGD by EUSES ver.1.0 (cf. **Table 3.2,** scenarios 1 to 10).

The release estimations are mainly based on the scenarios presented in Section 2.2, **Table 2.9** with minor changes. For instance ink making is included in the paint scenario, resulting in 91.6 kT toluene allocated to IC 14. Adhesives and the remaining volume in the printing category have been allocated to IC 12 (pulp, paper and board industry). The mineral oil and fuel industry, IC 9, has been increased slightly based on revised data from the main manufacturers.

A total processing volume of 2,235 kTonnes of toluene is covered by the scenarios 1 to1 0 in **Table 3.2.** Adding this to the 549 kT accounted for by the data a total of 2,784 kTonnes is included in the risk assessment. The difference between production and processing of 195 kTonnes is assumed covering import.

The release scenarios used in the downstream risk assessment include formulation, processing and private use.

1. Chemical industry: Chemicals used in synthesis (IC 3). Use category: intermediate (UC 33). Processing of toluene and use as an off-site intermediate (i.e. processed elsewhere).
2. Chemical industry: Basic chemical (IC 2). Formulation and processing, toluene used as a solvent (UC 48).
3. Mineral oil and fuel industry (IC 9). Formulation: Toluene used in additives or as a solvent in additives (UC 48). The fraction of toluene in formulation is set at 10%. Processing of lubricants and fuels is equivalent to the private use in motor vehicles.
4. Polymers industry (IC 11). Use as intermediate (UC 33), e.g. in the production of rubber. Toluene used as process regulator in dry processes (without water). However, a few manufacturers use wet processes, which is therefore included as worst case. The fraction of toluene in formulation is set at 10%.
5. Paint, lacquer and varnishes industry (IC 14): Toluene used as solvent (UC 48) e.g. in the formulation of oil based paint and varnishes.
6. Chemical industry: basic chemical (IC 2): The use of toluene as an extraction agent (UC 38) is included in the processing as solvent since the same release fractions are used in the TGD.
7. Personal/domestic industry (IC 5). Toluene used as solvent (UC 48). Toluene is assumed released from private use of toluene as a solvent either directly or in preparations such as adhesives, cosmetics, additives in detergents, etc.
8. Pulp, paper and board industry (IC12). Toluene is used as a solvent (UC 48) in colorants, adhesives etc.
9. Textile processing industry (IC 4). Toluene is assumed used as a solvent (UC 48).
10. Other (IC15/0). The category includes minor industrial uses of toluene (electric industry, public domain, etc.).

The release from formulation and processing of toluene at sites, which is not accounted for in the site-specific scenarios performed by industry (APA) has been estimated by EUSES. The volumes have been allocated according to information provided by industry and have been revised after a review of the original data submitted.

The use of toluene as extraction solvent presented by APA et al. (1999) could not be allocated to a TGD defined IC. It was therefore decided in the risk assessment report to allocate this use as a separate scenario (scenario 6). The result that is presented in **Table 3.2** is used in the risk assessment estimations.

Table 3.2 Release scenarios in relation to current industrial toluene formulation and processing according to the TGD scenarios

Scenario	Life stage	Category	IC	UC	MC	Kt/yr	Release to	Release fraction	Fract. Local source	d/yr	Region release kg/d	Local release kg/d
1: Industry (intermediate)	Processing	Interme-diate	3	33	1c	1387.7	Air	0.001	0.15	300	380	69
							Water	0.007			2,660	486
2: Industry (basic)	Formulation	Solvent	2	48	3	200.4	Air	0.025	1.0	300	1,370	1,670
							Water	0.003			165	200
	Processing						Air	0.65	0.25	300	34,700	10,500
							Water	0.25			13,300	4,060
3: Mineral oil and fuel .	Formulation (10%)	Solvent	9	48	3	185.2	Air	0.025	0.7	300	1,270	1,080
							Water	0.003			152	130
	Private use						Air	0.4	0.002	365	19,700	39.4
							Water	0.0005			25	0.05
4: Polymers .	Formulation (10%)	Process reg., wet	11	33	1c	113.4	Air	0.02	0.4	300	311	151
							Water	0.003			93	45.4
	Processing				3		Air	0.05	0.05	300	1,530	93.3
							Water	0.003			31	1.87
5: Paint, etc.	Formulation (50%)	Solvent	14	48	1c	91.6	Air	0.01	0.7	300	251	214
							Water	0.003			75	64.1
	Private use						Air	0.95	2E-5	365	23,500	0
							Water	0.04			991	0.024
6: Industry (basic)	Formulation	Extraction agent	2	48	3	150.0	Air	0.025	0.4	300	1,030	500
							Water	0.003			123	60
	Processing						Air	0.65	0.15	300	26,000	4,740
							Water	0.25			9,990	1,820
7: Personal / domestic	Formulation	Solvent	5	48	4	8.1	Air	0.025	1	300	56	67.8
							Water	0.003			7	8.1
	Private use						Air	0.15	0.002	365	325	0
							Water	0.4			866	1.7
8: Pulp, paper and board	Formulation	Solvent	12	48	3	55.0	Air	0.025	0.4	300	377	183
							Water	0.003			45	22
	Processing						Air	0.65	0.333	300	9,520	3,860
							Water	0.001			15	5.9
9: Textile	Processing	Solvent	13	48	3	0.2	Air	0.15	0.4	38	8	30
							Water	0.75			39	150
10: Other	Processing	Other	15	0	3	43.6	Air	0.1	0.6	262	1,200	999
							Water	0.001			12	10
Total							Air				121,528	24,197
							Water				28,589	7,065
						2,235.1					150,117	31,262

It is noted that a large fraction (1/3) of the total environmental release is from private use of toluene. Furthermore it is noted that the release to air is approx. 80% of the total environmental release.

Based on the above scenarios, EUSES estimates the total continental and regional emissions:

	Continental	**Regional**
Total emission to air	1,090 t/d	122 t/d
Total emission to wastewater	180 t/d	20 t/d
Total emission to surface water	77 t/d	8.6 t/d
Total emission to industrial soil	2.4 t/d	0.3 t/d

Contribution of release of toluene from motor vehicles to total release of toluene

A rough estimation of the amount of toluene consumed by use of gasoline in the EU yields around 13.7 million tonnes (cf. Section 2.3.3).

The toluene emission at a realistic content of 8.6% (86 g/l) in the fuel was measured in an ECE 15 standard test. The result was an emission of 350 mg toluene/m^3 in the exhaust gasses, which was approximately equal to 370 mg toluene/km. The amount of toluene expelled unburned with exhaust gasses was measured to be 3.3% of the toluene in gasoline (Häsänen et al., 1981). A more recent estimate based on air monitoring at a road site in Copenhagen and taking into account actual traffic composition gives an estimate of 410 mg toluene/km (Christensen et al., 1999).

Assuming that these results are representative for the emission of toluene from motor vehicles engines, rough estimations of this source of toluene emission can be performed (cf. Appendix A). Regardless of whether the toluene emission rate per km or the amount toluene in exhaust gasses is used, these calculations indicate that the total emission in the EU approximates a level of around 500 kTonnes/year corresponding to around 50 kTonnes/year per region, i.e. a level of around the current level of toluene released to the air from the current production and processing of isolated toluene.

In a recent Dutch survey concerning environmental toluene emission sources which also includes emission from power plants, this survey concludes, however, that only around a third of the toluene environmental emission is caused by traffic (cf. Appendix A).

Another estimate on the total release of toluene from the use in gasoline is from The FOREMOVE model (Appendix A). The FOREMOVE model provides estimates of past annual toluene emissions for 12 EU countries (excluding Finland, Austria and Sweden) and also predicts future emissions on the basis of the regulatory constraints arising from Auto Oil I programme (DGXI, 1996). The figures for 2000/2005 project the effectiveness of control measures to reduce future toluene emissions from transport sources. These data are summarised below:

Table 3.3 Yearly estimates of toluene (kT/year) for 12 EU countries from car exhaust (DGXI, 1996)

	1990	**1995**	**2000**	**2005**
Gasoline exhaust	838	733	508	262
Diesel exhaust	4	4	4	3
Total	842	737	512	265

1995: 737 kT, cf. Table 3.4

The gasoline exhaust emissions include a contribution of about 10% due to evaporative losses from gasoline in vehicles. It is apparent from the above data that the contribution of toluene from diesel exhausts is not very significant.

The main manufacturers have estimated the emission to air including the release from use and from handling and use of gasoline. The results presented below illustrate that the release of toluene from handling and use of gasoline is about 3 times higher than the release from production and processing of isolated toluene.

Table 3.4 Emissions to air (APA, personal communication, 2000)

Emission to air from:	**Toluene, kTons/year**		
Exhaust pipe - gasoline cars [1)]		660	
Exhaust pipe - diesel cars [1)]		4	
Handling of gasoline [1)]		73	
Commercial toluene used as a feedstock (80%)[2)]	11		
Commercial toluene used as solvent in paint, adhesives, printing etc. [3)]	178		
Commercial toluene used as a processing aid (part of 50-150 kTons) [4)]	***50***		
Total toluene emitted	239	737	976

1) EU information for 1995 (CONCAWE, 1997).

2) 11 kT for emissions from toluene used as feedstock (to be reformated), is calculated as 80% of 2,800 kT = 2,240 kT. In the CONCAWE-report, it is stated that the gasoline exhaust emissions include a contribution of about 10% due to evaporative losses from gasoline in vehicles. Total gasoline emissions for 1995 are estimated to 733 kT. If 10% represents gasoline handling, this is 73 kT. Gasoline use in Europe is estimated at 14,000 kT. The calculation 73 · 2,240/14,000 yields 11.68 kT. This is rounded to 11 kT because gasoline handling involves much more open handling than toluene for feedstock. This number is certainly also an overestimate.

3) 178 kT for paint etc., is estimated in the following way: in the updated table from industry (EITUG), ca. 178 kT is estimated as the consumption. Because this is a use where toluene evaporates from paint, lacquers, varnishes and adhesives etc., the evaporation fraction is set to 100% to air. In rotogravure, toluene is recovered/collected in carbon filters and regenerated resulting in some toluene is released to water and some is incinerated but most is evaporated (at least the fraction in paint etc.).

4) The 50 kTonnes toluene emitted from uses as processing aid is a “guesstimate”, which is based on the assumption that 100 to 150 kT is used and part of the toluene is incinerated.

In conclusion the rough estimate of environmental emission of toluene from motor vehicles vary somewhat but two independent estimates indicate that this emission source may be about one to three times the emission from the industrial production, formulation and use of the commercial product toluene.

For illustration of the additional contribution to regional and continental concentrations from emission of toluene from the use of gasoline regional and continental concentrations have been estimated by addition of 737 kTonnes (**Table 3.4**) to the EUSES estimate on regional and continental emissions arising from the production and use of the commercial product toluene.

3.1.2 Environmental fate

3.1.2.1 Degradation

3.1.2.1.1 Abiotic degradation

Hydrolysis

No experimental data are available on hydrolysis. Toluene is not expected to hydrolyse under normal environmental conditions (Howard, 1990).

Photolysis

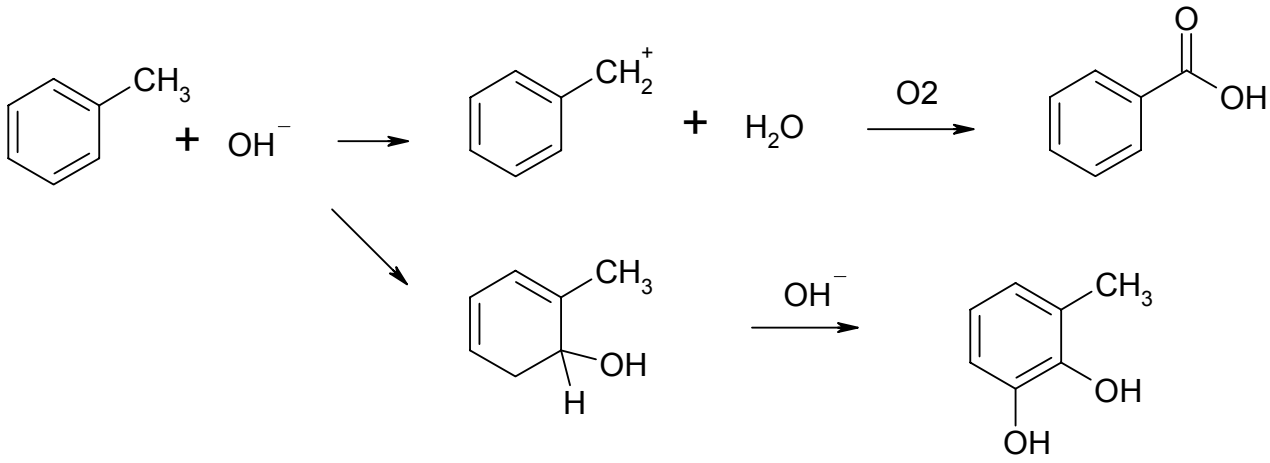
Direct photolysis is not expected to be essential because toluene adsorption maximum is below 290 nm. In a test where toluene was adsorbed on silica gel and irradiated with light at wavelengths >290 nm for 17 hours, 8.4% of applied amount was degraded (Freitag et al., 1985). The direct photolytical degradation of toluene is estimated to be negligible.

Photooxidation

Indirect photolysis by photochemical oxidative degradation was observed in air. The rate constant $k = 6 \cdot 10^{-12}$ cm^3/molecules/sec) equivalent to a half-life of 1.3 day (OECD draft method, IUCLID) was measured using OH sensitiser. A half-life of 30 days was measured using O_3 as sensitiser (IUCLID).

In a field study in California and Arizona, air samples during a two-week period included toluene. The rate constant with hydroxyl radicals (OH): $6 \cdot 10^{-12}$ cm^3/molecules/sec. The estimated residence time was 1.9 days, calculated assuming an average daily (24 hour) abundance of OH radicals of $1 \cdot 10^6$ molecules/cm^3. The daily loss rate calculated for 12 hours was 40.9% (Singh et al., 1981).

The most important atmospheric removal process for toluene is by reaction with the OH radical. The OH radical reactions proceed by two routes, H-atom abstraction from the C-H bonds in the methyl group or in the benzene ring and OH radical addition to the aromatic ring. For toluene the hydroxyl radical reaction leads to the initial formation of benzyl and hydroxycyclohexadienyl radicals or alkyl-substituted homologues (Atkinson, 1990):



The reactions result in the formation of o-, m- and p-cresol, o-, m- and p-nitrotoluene, benzylnitrate, glyoxal etc. The introduction of two oxygen atoms finally leads to the splitting of the aromatic ring.

The monocyclic aromatic hydrocarbons react slowly with O_3 and NO_3 radicals and atmospheric removal of toluene by these reactions is also of importance, especially at high concentrations. The occurrence of the pesticide DNOC (4,6-dinitro-o-cresol) in rain and groundwater long time after the substance was banned in Denmark may be caused by toluene transformation.

Table 3.5 summarises the indirect photodegradation data.

Table 3.5 Photooxidation rate constants

Sensitiser	Rate constant $cm^3/mol/sec$	Half-life days	Method	Reference
OH	$5.997 \cdot 10^{-12}$	1.3	Measured, OECD (draft 1990)	Palm and Zetsch (1992)
OH	$6.31 \cdot 10^{-12}$	1.8	Measured, OECD (1992)	Palm and Zetsch (1992)
OH	$6.0 \cdot 10^{-12}$	1.9	Measured	Singh et al. (1981)
OH	$5.226 \cdot 10^{-12}$	2.0	Estimated	AOPWIN (1995)
O_3	$1.5 \cdot 10^{-19}$	30	Measured	Palm and Zetsch (1992)

In Palm and Zetsch (1992), the concentration of the OH sensitiser was $1 \cdot 10^6$ molecules/cm^3 and the concentration of O_3 was $1 \cdot 10^9$ molecules/cm^3.

The photooxidation was calculated by the model Atmospheric Oxidation Program for Windows ver. 1.75 (AOPWIN, 1995) for comparison. The model is based on structure analysis. The estimated half-life of 2.047 days was based on the OH-radical concentration $1.5 \cdot 10^6$ molecules/cm^3 and a 12-hour daylight period.

Troposheric ozone formation

The formation of troposheric ozone involves complicated chemical reactions between NOx and VOC driven by the solar radiation. 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).

The relation between the ozone precursors in terms of VOC and thus toluene and ozone formation is complicated and depends on the speciation and concentrations of VOC, NOx, solar radiation and OH-radicals. The modelling of ozone formation from individual VOCs is difficult partly because the basic chemistry i.e. formation of breakdown products and their reactions is still under debate (Henrik Skov, personal communication). Within Europe very different environmental conditions prevail i.e. NOx / VOC ratio and solar radiation but also different meteorological conditions (wind speed etc.) meaning that a concentration of a VOC may lead to very different ozone concentrations.

For example the 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 (NOx 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

NOx regions). Thus there is no simple relationship between the VOC and NOx concentrations and the resulting troposheric ozone creation. The ozone concentrations may at some places of Europe even be higher at the same VOC concentration and at lower NOx concentrations than may be the case at other places. Likewise the time trends of the troposheric ozone concentration for Europe in general cannot be forecasted by predicting the future concentrations of VOC and NOx.

Nevertheless, the member countries in UNECE have 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) (Haushild and Wensel, 1998). Two sets of factors exist corresponding to a low and high NOx situation.

The POCP of toluene is 0.47 g C_2H_4/g toluene gas (4-day) (Andersson-Sköld et al., 1992). Haushild and Wensel (1998) give POCP equivalence factors of 0.5 g C_2H_4/g toluene gas in a low NOx situation and 0.6 g C_2H_4/g toluene gas in a high NOx situation based on the same study.

To evaluate the relative importance of toluene 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 toluene 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 NOx concentrations have to be taken into account. These will of course vary very much 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. For example " the VOC/NOx emission ratio in Milan (as also in Paris) is twice as high as for other cities." (Moussiopoulos et al., 1998).

An attempt to evaluate the relative contribution of non-isolated toluene (traffic emissions) to the ozone creation potential has been performed in Section 3.1.4.3.

Conclusion on atmospheric half-life

The conclusion is that photochemical oxidative degradation/transformation is assessed to be an important degradation pathway in air and that the half-life is estimated to be approximately 2 days according to the realistic worst-case concept. This value is used in the risk assessment.

3.1.2.1.2 Biotic degradation

Biodegradation

Several microorganisms that are able to degrade toluene have been isolated (Gibson and Subramanian, 1984) and the degradative pathway is reasonably well established. Several bacteria are known to use toluene as growth media (Gibson and Subramanian, 1984).

Even though toluene was readily biodegradable by microorganisms at high concentrations it appears that toluene may persist in natural waters at low concentrations. When the concentration falls below a threshold value, the metabolism of toluene can be too low to provide the cells with energy at a rate needed for the maintenance of their metabolism. A 10-day study to determine the minimum concentration of toluene needed for a bacterium population to use toluene as a carbon source was performed using a bacterium strain isolated from forest soil the mineralisation of radioactive toluene was determined by trapping $^{14}CO_2$. Concentrations of toluene below 31 µg/l were mineralised at low rates (1 to 16% during 8 days) by unadapted microorganisms. However,

in the presence of other carbon sources, 0.9 µg/l toluene could be mineralised to below the detection limit (2 ng/l) during 8 days. At 100 µg/l sufficient toluene was available to increase the metabolic activity of the bacteria (Roch and Alexander, 1997).

The factors affecting the ability of a bacterial species to degrade toluene in concentrations of 8.5 to 217 mg/g sorbed to granular activated carbon (GAC), in an aqueous solution of mineral salts were investigated by Roch and Védy (1999). After 144 days the amounts of toluene remaining on one type of GAC ranged from 7.5 to 9.5 mg/g, and the aqueous concentrations of toluene ranged from 2 to 7 µg/l. Neither bacterial death nor an inhibition by accumulating by-products could explain why the remaining toluene had not been degraded. However, at these low concentrations of toluene, and probably because of cell starvation, bacteria were observed to be more than 100-times less efficient to degrade toluene than at high concentrations (Roch and Védy, 1999).

The aerobic degradation of toluene may be inhibited in the presence of other organic chemicals. In a 16-day incubation study by Dyreborg et al. (1996) it was observed that the presence of thiophene, pyrrole, methylpyrrole and benzofuran reduced the degradation of toluene from 100% to 10% after 4 days. The medium was groundwater from a creosote-contaminated aquifer and toluene was added at 3 mg/l. The inhibition is stated to be caused probably by competitive inhibition (Dyreborg et al., 1996).

These studies illustrate some of the general problems by using degradation data from experimental standard tests with high concentrations of the test substance under laboratory conditions for estimating degradation half-lives under environmentally realistic concentrations and conditions. It seems thus that for toluene there is evidence for a significant slower degradation at environmentally realistic concentrations (µg/l range) due to sorption and the normal naturally occurring metabolic state of degrading bacteria. Inhibition of degradation caused by presence of other substances may also occur. Because of this evidence, the normal procedure for estimation of the half-lives for degradation of toluene at low concentration (µg/l range) in surface water, sediment and in soil should be performed in a more conservative way than by the standard estimation procedure of the TGD. It seems, however, reasonable to use the standard procedure of the TGD for estimation of the half-life of toluene in STP, where the conditions for degradation are much more favourable and the concentration generally would be much higher (i.e. mg/l range) than in the environment (except for contaminated sites which are not specifically dealt with in this risk assessment report).

Degradation in the sewage treatment plant (STP)

Toluene is degradable in several standard biodegradability tests using sewage sludge inoculums. Degradation is observed in several die away tests using seawater or estuarine water (Price et al., 1974; Bridie et al., 1979). The degradation rate is faster when adapted microorganisms/test systems are used.

Table 3.6 Results of biodegradation

Detection	Result	Day	Method	Conc. Toluene	Inoculum	Ref.
BOD	53% 62% 70% 80%	5 10 15 20	APHA 219 (1971)	10 mg/l	aerobic, domestic sewage, non-adapted	Price et al. (1974)
BOD	73% 74% 80% 86%	5 10 15 20	APHA 219 (1971)	10 mg/l	aerobic, domestic sewage, adapted	Price et al. (1974)
BOD COD	69% 81%	5 5	APHA 219 (1971) ASTM D 1252-67	1.5 mg/l	aerobic, predominantly domestic sewage, non-adapted	Bridie et al. (1974)

The adsorption in activated sludge from a municipal sewage treatment plant was measured during aerobic degradation at low concentration (0.05 mg/l) after 5 days of incubation. The accumulation factor (concentration in sludge/concentration in water) was 1900. The biodegradation after 5 days was 26.3% of applied amount based on CO_2 development (Freitag et al., 1985).

Based on this, toluene may be considered ready biodegradable respecting the 10-day time window and according to the TGD the first order rate constant for biodegradation in STP (k_{STP}) is set at $1 \cdot h^{-1}$ corresponding to a half-life of 0.0289 days.

Degradation in surface water

The removal in seawater was examined in mesocosmos studies including the volatilisation. The tanks were 5.5 m high and 1.8 m in diameter and contained 13 m^3 seawater. The dissipation of an initial concentration of 3.6 µg/l toluene was studied at the temperature intervals 3 to 7°C, 8 to 16°C and 20 to 22°C. The concentrations were measured during 1-2 months. A mixture of volatile organic compounds was used. The half-lives were found to be 13, 16 and 1.5 days, respectively (Wakeham et al., 1983). The dissipation was observed to be temperature dependent with higher volatilisation and degradation at higher temperatures. Besides the dissipation was observed to be dependent of the water depth and the turbidity.

The study does not present information detailed enough to estimate the degradation rates in surface water and therefore, the estimates employing the TGD for ready biodegradability were used as a starting point taking the above indications for slower degradation under environmental conditions including low concentration into account. Employing the test results for ready biodegradability and the recommended estimates based on the TGD (1996), but applying a factor of 2 for slower degradation at environmental conditions (cf. above) the first order rate constant for biodegradation in surface water, $kbio_{water}$ is estimated to $2.37 \cdot 10^{-2}$ d^{-1}, corresponding to a half-life of 30 days.

This result is used in the estimations of the regional environmental concentrations of toluene.

Degradation in soil

Biodegradation half-lives varying from 83 to 92 days in various soil systems under different experimental conditions are cited in Sloof and Blokzijl (1988), without further details.

The biodegradation of toluene in soil microcosms (50 g soil dw, 50 ml water) was observed to be proportional to the initial toluene concentrations and the degradation rates reached a maximum at

200 mg/kg. No degradation occurred above this concentration presumably due to the toxicity of the hydrocarbon to the soil microorganisms. The degradation half-lives were 3 and 2 days at 5 mg toluene/kg soil and 12 and 9 days at 200 mg toluene/kg soil at 14% and 100% moisture content, respectively (Davis and Madsen, 1996). They also report a degradation half-life of 31 hours and 172 hours in two different soil types at a concentration of 0.5 mg/kg. This study employed high concentrations of toluene, which may not be regarded of relevance for the degradation half-lives in soil in general except at contaminated sites.

Thus there is limited information available for interpretation of the first mentioned study but a large variation in the reported degradation half-lives in soil from 2 to 93 days. Taking the above-mentioned scientific studies on the dependency of the degradation kinetics on adsorption, metabolic state of microorganisms and concentration of the test substance into account, a conservatively derived half-life for aerobic degradation in soil based on experimental results of 90 days, are used in the regional and local estimations of soil concentrations.

Anaerobic degradation / degradation in sediment

Anaerobic degradation has been studied in an anaerobic microcosm employing aquifer material from the vicinity of a gasoline spill. Toluene (6 mg/kg) mineralisation. was observed in anaerobic microcosm prepared from gasoline-contaminated aquifer material. 34-49% of the added ^{14}C-toluene was removed during two weeks and of the removed toluene 77% was transformed into CO_2 (Haag et al., 1991). Thus toluene seems to be quickly anaerobicly degraded by adapted microorganisms when toluene occurs at high concentrations, No information is however available on the anaerobic degradability at environmentally realistic conditions and with non-adapted microorganisms. Thus the anaerobic degradability is by default set to zero for anaerobic sediment layers and the degradability half-life in sediments are according to the TGD set to one tenth of the half-life in soil, i.e. 900 days.

3.1.2.2 Distribution

The relatively high vapour pressure indicates that the atmospheric compartment is the primary recipient.

Volatilisation/Evaporation

Soil

In a laboratory experiment toluene was applied on the surface of a sandy soil system with an organic carbon content of 0.067%. It was observed that 38-66% of 0.2-0.9 mg/l of toluene evaporated during 45 days (cf. below “mobility”). The evaporation half-life of toluene added to sandy soil was experimentally found to be 4.9 hours (Wilson et al., 1981). After addition onto two soils with and without sludge, toluene was completely evaporated in 10 days and maximum 0.5% was degraded (Jin and O'Connor, 1990 cited in Rippen (1992)).

Based on these studies and the physico-chemical properties of toluene it is expected that evaporation may constitute an important removal mechanism in the top centimetres of soil.

Surface water

The volatilisation from water has been studied in several studies. The volatilisation half-life in a water tank at about 5 m water depth ranged 1.5-16 days (cf. above) (Wakeham et al., 1983). In a

laboratory study by Potera (1975) the volatilisation rate was 907 g/m^2/day and the observed half-life was 16.5 hours (range 13-17 hours). The tank size was 20·40 cm and 25 cm deep, contained about 19 l of water and the temperature was 20°C. These studies confirm that the volatilisation is dependent of the water depth.

The Henry's Law Constant can be estimated by using the measured vapour pressure 3,000 Pa and the water solubility 515 mg/l. Henry's Law Constant is then estimated to be 537 Pa m^3/mole at 20°C. This value indicates that volatilisation of toluene from surface water may be expected.

The rate of volatilisation of toluene from water to atmosphere is estimated by Mackay and Wolkoff (1973). They calculated the half-life based on a water volatilisation rate of 2,740 g/m^2/day from one cubic meter of water with 1 m^2 surface area to be 30.6 min.

Mobility in soil

Mobility was studied in a soil column study on a sandy soil in a 5 cm i.d. and 140 cm high column. The soil contained 92% sand, 2.1% clay, 0.067% organic carbon and pH was 6.4. The soil column received 14 cm water per day over 45 days with the measured concentrations 0.9 and 0.2 mg/l. When 0.9 mg/l was applied 38% of the applied toluene was volatilised, 2% was leached and 60% was degraded or not accounted for. When 0.2 mg/l was applied 66% was volatilised, 13% was found in the leachate and 21% was degraded or not accounted for, indicating that a higher degradation may take place at the 0.9 mg/l (Wilson et al., 1981).

Piwoni et al. (1986) constructed a microcosm to study the behaviour of organic pollutants during rapid infiltration of municipal wastewater into soil. The soil was a fine sandy soil from Oklahoma, USA, (92% sand, 6% silt, 2% clay and 0.087% organic carbon). The microcosm received 4.4 cm of water and equal amounts of wastewater each day. The soil columns were 15 cm internal diameter and 150 cm long. The wastewater was collected fresh daily. The microcosm was amended 31.4 mg toluene/l. A small proportion, 20% ±18 of added toluene volatilised and 9% was recovered in the microcosm effluent. 71% was not accounted for and may be either degraded or adsorbed. The result was comparable to measured values from publicly owned STPs.

The mobility in soil, based on Koc, indicates that toluene may be estimated as relatively mobile. Koc was experimentally found to range from 37 to 160 in three silt soils (37, 46 and 160 (Nathwani and Phillips, 1977)) indicating high to moderate mobility.

The adsorption coefficient Koc estimated from log Kow 2.65 according to the TGD (1996): log Koc = 0.81 log Kow + 0.1 = 2.24) would result in a Koc of 176.4. A QSAR estimation performed by a first-order molecular connectivity index estimated a Koc of 268 (PCKOC in EPIWIN; Meylan and Howard, 1994). The results are evidence supporting the conclusion that toluene may be considered to be a potential leacher, which may reach groundwater. The adsorption coefficient Koc of 177 is used in the risk assessment.

The distribution in the environment, based on the EQC model (developed by Di Guardo according to Mackay et al., 1996) using the relevant physico-chemical data from this report at 20ºC results in the distribution: 99.0% in air, 0.90% in water, 0.08% in soil, 0.002% in sediment, 0.0002% in suspended sediment, and 0.00002% in fish. Another Mackay Level I model calculation performed by Shell according to Mackay and Paterson (1981) (IUCLID, 1995) is included for comparison in the table below.

The distribution to the environment according to a EQC model level III has been estimated when emissions are distributed according to the TGD Scenario IC 2 (Table A 3.2 in the TDG, 1996).

The results are shown in **Table 3.7.**

Table 3.7 Distribution in the environment, Mackay Level I and III

Mackay Level I ref.:	Input data				Mackay distribution			
	Water-Solubility	Log Kow	Vapour Pressure	H Pa m³/mol	Air	Water	Sediment	Soil
Mackay level I. Iuclid 1995					99.47	0.49	0.02	0.02
Mackay level I. EQC 1.01 1997	515	2.65	3,000	537	99.00	0.90	0.002	0.08
Mackay level III. EQC 1.01 1997 *	515	2.65	3,000	537	35.8	63.3	0.254	0.683

* Emissions as for IC2: 65% to air, 25% to water and 1% to soil

Conclusion

Toluene is readily degraded in sewage water, and is degraded by a variety of soil microorganisms, especially when the microorganisms are adapted to toluene. At low environmental concentrations the degradation rate is significantly reduced. The half-life in STP was estimated to be 0.0289 days (1 h^{-1}), in surface water 30 days and in soil 90 days.

Toluene seems to be aerobically and anaerobically biodegradable at high concentrations and when exposed to adapted microorganisms, however, under aerobic and oligotrophic conditions, the substance seems not to be biodegradable if the concentration is low (0.05 mg/l level). The latter kinds of more detailed information regarding biodegradability are not easily employed by following the risk assessment methodology according to the TGD and are therefore not considered in this risk assessment. Because no information was available regarding anaerobic degradation at environmental concentrations and conditions, degradation in anaerobic sediment has been set to a half-life of 900 days according to the TGD.

The atmospheric compartment is the main recipient of toluene. In air, toluene is exposed to indirect photolysis by photochemical oxidative degradation with a half-life of 2 days. The fate of the degradation products has not been assessed in the risk assessment report.

Several studies confirm that the volatilisation of toluene may be substantial from water surfaces and from top soils. The adsorption potential seems low and may indicate a leaching potential. The leaching potential is confirmed by groundwater monitoring results (cf. Section 3.1.2.1).

3.1.2.3 Bioaccumulation

The log Kow is <3 indicating limited bioconcentration in aquatic organisms.

A number of bioaccumulation studies with aquatic organisms are available. The BCF value of 90 observed in the fresh water fish Golden Ide (*Leuciscus idus melanotus*), was the largest value found in fish studies and is used as a worst case in the risk assessment.

Table 3.8 Bioconcentration factors (BCF)

Organism	Exposure conc. mg/l	Exposure days	BCF	Reference
Fish:				
Anguilla japonica (eel)	0.13	10 days	13	Ogata and Miyake (1978)
Leuciscus idus melanotus (ide)	0.05	3 days	90	Freitag et al. (1985)
Clupea harengus (herring)	0.09	2 days	8	Korn et al. (1977)
Molluscs:				
Mytilus edulis (Mussel)	0.05-4	8 hours	4.2	Geyer et al. (1982)
Tapes semidecursata (Clam)	1.2	2-8 days	1.7	Nunes and Benville (1979)
Algae:				
Chlorella fusca	0.05	24 hours	380	Freitag et al. (1985)

The BCF (fish) employing the QSAR equation recommended in the TGD (1996) (log BCF = 0.85 log Kow - 0.7) is 36 indicating that the chosen experimental BCF may be regarded as a worst-case value.

Elimination of toluene from fish appears to be relatively rapid. The available information indicates the half-lives to be <2 days in two fish species: eel and herring (Ogata and Miyake, 1978; Korn et al., 1977). The low bioaccumulation potential in fish and molluscs and the rapid elimination rate indicate that toluene is unlikely to bioconcentrate in the aquatic food chain.

3.1.3 Aquatic compartment

3.1.3.1 Measured exposure data

3.1.3.1.1 Concentrations measured in STP

Toluene concentrations in industrial wastewaters were reported to range from 0.010 to 20 mg/l (WHO, 1985). Measured concentrations of toluene in wastewater influents and effluents have mainly been found in older literature references and may not be representative of current concentrations but they are mentioned in **Table 3.9** to give a general idea of the anticipated levels.

Table 3.9 Concentrations measured in wastewater

Location		No. or No./pos.	Range (µg/l)	average	Reference
DK, 3 STPs, weekly mixtures	1992				Grüttner and Jacobsen (1994)
Avedøre, municipal STP	inflluent	4	0.7-7.3	3.7 µg/l	
Skævinge, municipal STP	influent	3	1.3-2.6	8.7 µg/l	
Marselisborg, municipal STP	influent	3	4.9-9.0	6.6 µg/l	
Denmark, 2 STPs	1997-1998				Aarhus (1998)
Viby		3/3	0.31-0.82	0.63 µg/l	
Søholt		3/3	0.75-5.3	2.85 µg/l	
Germany ("tankstelle")	1983-1984	7	3.1-450	µg/l	Rippen (1992)
USA, Industrial effluent (TNT-prod)	1981			200 µg/l	Rippen (1992)
Industrial effluent,	1985	1,498/295		median 5.1 µg/l	Staples et al. (1985)
Municipal STP, Los Angeles	1980-1981	5		210 µg/l	Gossett et al. (1983)
Cincinnati, 3 STPs, influent	1982	26/2	<0.20-83	µg/l	Dunovant et al. (1986)
USA					Rippen (1992)
Municipal STP, effluent	<1982			1,100 µg/l	-
City STP, effl. to Niagara river	1978-1981	20		0.14 µg/l	-
USA, municipal effluent	<1986	1		48 µg/l	Marchand et al.
"	1985	40	max.1,600	320 µg/l	Piwoni et al. (1986)
"			max.12,900	290 µg/l	"
Calumet , Chicago, 1986	influent			85 µg/l	
	effluent			6.2 µg/l	
Chicago 1985	influent			22 µg/l	
	effluent			<0.4 µg/l	
USA					Piwoni et al. (1986)
40 Publicly owned STPs	influent		max.1,519	33.6µg/l	
Moccasin Bend STP, TN	influent		max.188.8	38.0µg/l	

3.1.3.1.2 Recent data on toluene in wastewater

In the APA (1996) study on toluene emissions covering 26 production sites, the STP influent concentrations were measured at 6 sites and ranged <0.01 to 6 mg/l with the mean 2.25 mg/l, the median 1.22 mg/l and the 90 percentile 5.6 mg/l. The STP effluent at 9 production sites ranged 0.01 to 0.05 mg/l with the mean 0.02 mg/l, median 0.01 mg/l and the 90%-ile 0.05 mg/l. At 11 processing sites, the STP influent concentration was measured at one site to 0.06 mg/l and the STP effluent at 5 sites ranged 0.01 to 0.42 mg/l with the mean 0.096 mg/l, median 0.01 mg/l and the 90 percentile 0.262 mg/l. Monitoring results from the receiving aquatic environment was below the detection limit which varied (0.005, 0.01 and 0.02 mg/l).

Releases of toluene in the Rhône-Alpes region in France

The effluents of 114 industrial sites were monitored in 1993 for several chemical substances. A single 24-hour mixing sample was taken at each site. Toluene was detected in 27 of the monitored effluents. The results are summarised in **Table 3.10**.

Table 3.10 Monitoring results from Rhône-Alpes in France

Industrial activity	Conc. in effluent (µg/l)	Daily release (g/d)	Dilution factor	C_{local} (µg/l) [1)]
Chemical industry	1,575	3.8	10^6	0.0002
Chemical industry	7,000	77	$2.2 \cdot 10^6$	0.0032
Metal working	8	0.02	7,400	0.001
Metal working	12	1.5	2,400	0.005
Paint manufacturing	67	35.9 *	500	0.0718
Paint manufacturing	3,766	0.45 *	$2 \cdot 10^6$	$2.25 \cdot 10^{-7}$
Paint manufacturing	3,546	27.8 *	$2.2 \cdot 10^6$	$1.26 \cdot 10^{-5}$
Paper-factory	120	660	50	2.4
Petrochemical industry	24,589	9,811	50	491.8
Petrochemical industry	147	25,946	1.5	98
Petrochemical industry	106	760	3,400	0.031
Petrochemical industry	117	1,653	1,700	0.069
Petrochemical industry	538	266 *	50,000	0.00532
Petrochemical industry	8,860	4,040 *	54,000	0.0748
Petrochemical industry	2,750	1,383	48,900	0.056
Petrochemical industry	762	2,771	6,770	0.113
Petrochemical industry	205	4,140	1,200	0.171
Petrochemical industry	28	1,728 *	400	4.32
Petrochemical industry	394	6,000 *	1,600	3.75
Petrochemical industry	16	221	315	0.051
Plastics and plastic fibres	359	9.87 *	850	0.0116
Plastics and plastic fibres	26	0.38	440	0.059
Plastics and plastic fibres	118	1.2	$4 \cdot 10^6$	0.00003
Solvent recycling	235	7.87 *	225,000	$3.50 \cdot 10^{-5}$
Surface treatment	19	2.3	120,000	0.0002
Tanning	12	4.9	30,500	0.0004
Textile dying	22	34	100	0.22

* Release into sewer; not clear whether further treatment or not.
Daily release (g/d) = Conc. in effluent (µg/l) · flow of discharge
ref: INERIS (1994) "Inventaire des micropolluants dans les entreprises de la région Rhône-Alpes".

1) Calculated on the basis of information in reference.

Releases of toluene in the Poitou-Charentes region in France

The effluents of 27 industrial sites were monitored in 1996-1997 for several chemical substances. A single 24-hour mixing sample was taken at each site. Toluene was detected in 1 of the monitored effluents. The results are summarised in **Table 3.11**.

Table 3.11 Toluene in effluents in the Poitou-Charentes region in France

Industrial activity	Conc. in effluent (µg/l)	Daily release (g/d)	Flow of receiving river (m^3/s)	C_{local} water (µg/l)
Chemical industry	9,800	1,323 *	135	0.114

* Release into sewer; not clear whether further treatment or not
Daily release (g/d) = Conc. in effluent (µg/l) · flow of discharge
ref: DRIRE Poitou-Charentes (1998) « Inventaire des rejets de micropolluants dans 27 établissements de la région Poitou-Charentes»

Releases of toluene in the Franche-Comté region in France

The effluents of 46 industrial sites were monitored in 1994-1995 for several chemical substances. A single 24-hour mixing sample was taken at each site. Toluene was detected in 1 of the monitored effluents. The results are summarised in **Table 3.12**.

Table 3.12 Toluene in the Franche-Comté region in France

Industrial activity	Conc. in effluent (µg/l)	Daily release (g/d)
Treatment of industrial effluents	124	9.3 *

* Release into sewer; not clear whether further treatment or not
Daily release (g/d) = Conc. in effluent (µg/l) · flow of discharge
ref: DRIRE Franche-Comté (1996) "Inventaire des rejets de substances toxiques dans les eaux".

Releases of toluene in the Picardie region in France

The effluents of industrial sites were monitored for several chemical substances. A single 24-hour mixing sample was taken at each site. The results are summarised in **Table 3.13**.

Table 3.13 Toluene in the Picardie region in France

Industrial activity	Conc. in effluent (µg/l)		Daily release (g/d)
Caoutchouc industry	4 1	(date: 23/07/97) (date: 10/11/94)	0.66 0.11
Caoutchouc industry	1.26 1.8	(date: 29/11/96) (date: 29/11/95)	8.16 9.94
Chemical industry	31	(date: 09/07/91)	17.52
Chemical industry	18	(date: 09/12/94)	0.72
Chemical industry	29 11	(date: 01/04/98) (date: 04/11/94)	6.26 1.95
Chemical industry	2 1.5 18 0.33	(date: 06/02/98) (date: 24/09/96) (date: 04/10/95) (date: 01/12/94)	0.35 0.32 1.53 0.74
Chemical industry	1.5	(date: 29/02/96)	0.26

Table 3.13 continued overleaf

Table 3.13 continued Toluene in the Picardie region in France

Industrial activity	Conc. in effluent (µg/l)		Daily release (g/d)
Chemical industry	6	(date: 22/11/94)	29.67
Chemical industry	169 11 80 250	(date: 19/02/98) (date: 12/03/97) (date: 20/02/96) (date: 17/10/95)	113.91 6.81 44.24 128.5
Chemical industry	305.5	(date: 15/11/94)	23.22
Chemical industry	2 1.5 42	(date: 29/04/97) (date: 07/02/96) (date: 31/10/91)	0.02 0.03 6.01
Chemical industry	3.5	(date: 18/02/97)	0.08
Farm-produce industry	12	(date: 09/10/97)	5.81
Farm-produce industry	5.5	(date: 17/10/96)	14.34
Farm-produce industry	1	(date: 18/06/97)	0.01
Farm-produce industry	1	(date: 10/10/96)	1.53
Farm-produce industry	1.4	(date: 20/12/94)	8.14
Farm-produce industry	1.3 3	(date: 10/04/96) (date: 13/08/91)	11.48 24.92
Glass bottle fabrics	27	(date: 18/05/95)	26.73
Mechanic construction	4	(date: 22/10/96)	0.12
Mechanic construction	2	(date: 09/07/91)	0.15
Mechanic construction	14	date: 06/12/94)	0.56
Mechanic construction	30	(date: 28/11/95)	7.2
Mechanic construction	1	(date: 11/12/96)	0.03
Metal industry	2	(date: 17/11/94)	1.63
Metal industry	3.2	(date: 08/12/94)	2.08
Paint manufacturing	9	(date: 08/11/94)	0.14
Paint manufacturing	4.5	(date: 05/12/95)	0.1
Paint manufacturing	1.5 4.3	(date: 03/03/98) (date: 14/12/94)	0.15 2.8
Paint manufacturing	3.5 13 140 1300	(date: 24/02/98) (date: 25/03/97) (date: 04/07/96) (date: 10/12/94)	0.17 0.47 2.8 33.8
Paint manufacturing	4.5 3	(date: 26/03/98). (date: 16/11/94)	0.85 6.93
Paint manufacturing	44	(date: 15/12/94)	0.97
Paper-factory	3.5 2.5	(date: 19/02/97) (date: 27/02/96)	6.76 5.61

Table 3.13 continued overleaf

Table 3.13 continued Toluene in the Picardie region in France

Industrial activity	Conc. in effluent (µg/l)		Daily release (g/d)
Surface treatment	1	(date: 18/11/96)	0.12
Surface treatment	3.5	(date: 24/07/96)	0.07
Surface treatment	1.5	(date: 04/12/96)	0.01
Surface treatment	0.75	(date: 29/11/94)	2.25
Surface treatment	13	(date: 15/05/91)	2.04
Textile dying	3.8	(date: 11/10/94)	3.1
Textile dying	1.4	(date: 07/12/94)	0.42
Textile dying	2.2	(date: 04/10/94)	1.1
Ttextile dying	2.5	(date: 26/02/97)	2.95
Textile dying	4.3	(date: 08/12/94)	4.12
Textile dying	2.4	(date: 08/12/94)	1.69
Textile dying	4	(date: 23/10/91)	1.37
Textile dying	1.5	(date: 06/05/97)	3.51
Transport of industrial liquids	32 23	(date: 25/03/97) (date: 19/10/94)	1.22 4.44

Daily release (g/d) = Conc. in effluent (µg/l) · flow of discharge
ref: DRIRE Picardie (1998) "Les micropolluants en Picardie"

Table 3.14 shows the estimated PECs based on the French monitoring data shown in **Tables 3.11-3.13** employing the default dilution factor of 10.

Table 3.14 Summary statistics of local PECs (µg/l) in France estimated from site-specific monitoring data using a default dilutionfactor of 10

Industry	Mean	Min	Max	Median	90th %ile	Number of sites
Chemical industry	5.23	0.0002	30.55	0.60	0.16	13
Farm-produce industry	0.40	0.1	1.20	0.22	0.88	6
Mechanic construction	1.02	0.1	3.00	0.40	2.36	5
Metal industry/working	0.13	0.001	0.32	0.10	0.28	4
Paint manufacturing	97.19	0.43	376.60	4.40	359.00	9
Petrochemical industry	131.00	0.031	886.0	1.49	452.4	12
Surface treatment	0.33	0.0002	1.30	0.13	0.83	6
Textile dying	0.27	0.14	0.43	0.24	0.41	9
Miscellaneous	6.76	0.00	35.90	0.37	37.65	12
All categories	34.32	0.00003	886.00	0.37	37.65	76

When combining the monitoring data on which dilution factors are available (**Table 3.10**) with those where only the effluent concentrations are available (**Tables 3.11-3.13**) the summary statistics are:

Table 3.15 Summary statistics of local PECs (μg/l) in France estimated from site-specific monitoring data combining data with dilution factors and the default dilution factor of 10

Industry	Mean	Min	Max	Median	90th %ile	Number of sites
Chemical industry	5.23	0.0002	30.55	0.60	0.16	13
Farm-produce industry	0.40	0.1	1.20	0.22	0.88	6
Mechanic construction	1.02	0.1	3.00	0.40	2.36	5
Metal industry/working	0.13	0.001	0.32	0.10	0.28	4
Paint manufacturing	15.22	0.0018	130.00	0.45	29.52	9
Petrochemical industry	49.2	0.0108	491.8	0.09	88.2	12
Surface treatment	0.33	0.0002	1.30	0.13	0.83	6
Textile dying	0.27	0.14	0.43	0.24	0.41	9
Miscellaneous	1.84	0.00	12.40	0.24	3.70	12
All categories	10.92396	0.00003	491.80	0.24	3.70	76

In the French studies the concentration of toluene in the STP effluents varied from 1 to 25,000 μg/l. The estimated concentrations in the receiving waters based on the mentioned dilution factors varied between <<0.01 to 490 based on dilution factors or up 886 μg/l based on default dilution factor of 10 ($PNEC_{aqua}$ 74 μg/l cf. Section 3.2.1.2).

In general the number of sites within each industrial category are too few to be regarded as representative for an EU risk assessment. However, the evaluation of these monitoring data indicate that locally high PECs may be found especially close to petrochemical industry and paint manufacturers.

3.1.3.1.3 Surface waters

Recent data

UK

In an UK monitoring data survey, the concentrations of toluene were measured at 22 sites in the Northumbria area. The sites appear to have been selected for their proximity to discharges that were anticipated to contain toluene. High values were reported at three sites: Site A adjacent to tank storage terminals, Site B adjacent to a components factory, and Site C a coastal site near the river mouth. For sites A and B, measurements were taken upstream and downstream of the main discharge sites. The most frequent measurements were taken twice a month over a three-year period (1993-1996); others were recorded less frequently or over shorter periods. The detection limit was 0.1 μg/l after 1995 and 0.3 μg/l before 1995. The range and average are presented in **Table 3.16**. In calculating the average, the detection limit has been assumed for individual measurements where toluene was not detected (UK Environment Agency, 1997).

Table 3.16 Toluene in UK surface water near relevant discharge zones

Site location	Date	Samples, No.	Samples > D.L.	Toluene concentration (µg/l)		
				Min.	Max.	Average
Tyne river, ~3 km upstream site A	01/02/93-25/01/95	5	2	<0.1	4.61	1.26
Tyne river, ~2 km upstream site A	25/01/95	1	0	<0.1	<0.1	<0.1
Tyne river, adjacent to site A	14/02/93-07/03/96	25	25	9.2	22,365	4,499
Tyne river, 3 km downstream site A	01/02/93-21/09/95	6	3	<0.1	4.69	1.11
Wear river, ~1 km upstream site B	26/01/93-07/03/96	23	7	<0.1	1.31	0.43
Wear river, Adjacent to site B	11/01/93-30/11/95	37	37	843.6	20,675	9,279
Wear, 200 m downstream site B	30/11/93-03/10/95	9	1	<0.1	50.46	5.7
Coastal, near mouth of Wear, site C	19/01/93-27/02/96	13	13	1,400	303,000	31,082

For information of sites cf. text

In an unpublished paper regarding the proposed COMMPS Procedure of the Water Framework Directive by DETR/Water Quality Div, Dept. of the Environment, Transport and the Regions (1998) some overview information and an analysis are presented of various statistical methods for providing summary information of concentrations in UK surface waters of 5 selected substances, including toluene. The data from 21 out of 228 stations with at least 5 data values and at least two measurements above the detection limit (DL) are analysed with eight different statistical methods. The results can be summarised to: the arithmetic mean, geometric mean and 90 percentiles may vary more than one order of magnitude depending on the treatment of values below DL and on the calculation method. For illustration varying the arithmetic mean from 134 to 618 µg/l depending on whether this value is based on the values >DL alone or whether values <DL is ascribed a value of half DL. The same phenomenon appeared for the geometric mean values. The 90 percentiles agreed well regardless of calculation methods on a level of 600 µg/l.

Germany

According to a Frauenhofer study (Herrchen and Müller, 1997) toluene has been measured above the determination limit in 7 out of 146 measurements (14%) during 1985 to 1996 in German surface waters (the rivers Rhine and Elbe). The mean concentration was 0.975 µg/l and the median concentration 0.5 µg/l.

A further analysis of the data from 1993 and 1994 in surface water is performed in a second study from Frauenhofer Institute (Klein et al., 1997). The results are presented below to show the difference in including values below the determination limit set equal to 0 or to ½ of the determination limit.

Table 3.17 Concentrations in German surface water (Klein et al., 1997)

Location	Year	Number	No. >d.l.	Mean (µg/l)		Median (µg/l)	
				c<d.l=0	c<d.l.=½d.l.	c<d.l=0	c<d.l.=½d.l.
Rivers*	1993	146	7	0.0329	0.975	0.01	2.5
NRW	1993/1994	20	17	0.256	0.257	0.34	0.34
Total	1993/1994	166	24				

* German rivers to the North Sea including their affluents. NRW: Nordrhein-Westfalen

Slovakia

The Morava River receives discharges from both industrial and domestic sources (cf. **Table 3.16**). In the Morava catchment, the oil fields and sugar works are the main sources of industrial pollution and domestic wastes from small cities enter the Morava River without being purified (Al-Rekabi et al., 1996). The concentrations changed by season and temperature.

Former data

Most data on toluene concentration in surface water are old data and mostly without information of the proximity to potential release sources.

Table 3.18 Surface water

Location	Date	Range	Mean	Reference
The Netherlands			0.1 µg/l	IUCLID; Sloof and Blokzijl (1987)
Germany Main river	1977	1-3000	µg/l	Arendt et al. (1977)
Rhine river	1978-1982	max. 2.0	µg/l	Meijers (1988)
Rhine at Düsseldorf	1982 1983 1984 1985 1986	 max. 4.0	0.100 µg/l 0.220 µg/l 0.110 µg/l 0.24 µg/l 0.02 µg/l	ARW (1984) Brauch and Kühn (1988)
Rhine at Wiesbaden Köln Düsseldorf Wesel	1986	<0.01-0.08 <0.01-0.05 <0.01-0.28 <0.01-0.05	0.02 µg/l <0.01 µg/l 0.02 µg/l 0.02 µg/l	ARW (1986) monthly averages
Wupper,D Emscher, D Lippe, D	1986		0.640µg/l 2.800µg/l 0.300 µg/l	NRW (1986)
Spain Besós river mouth Ilobregat river mouth Marine (coastal) Barcelona La Pineda Vil.Sitges	1985-1986		 22.000 ±0.120 µg/l 4.100 ±0.100 µg/l 0.100 ±0.077 µg/l 0.027±0.045 µg/l 0.100 ±0.050 µg/l 0.200 ±0.017 µg/l	Gomez-Belinchon et al. (1991)
Slovakia Morava River branches	1993 Winter Spring yearly	0.03-0.58 1.05-3.49 0.64-2.24	µg/l µg/l µg/l	Al-Rekabi et al. (1996)

The Netherlands

In surface water, the Netherlands survey programme observed on average in freshwater 0.1 µg/l (max. 2 µg/l), and in marine water 0.02 µg/l (IUCLID).

USA

In the USA, toluene was found in 83% of surface water monitored at concentrations <10 µg/l and 17% was >10 µg/l. In groundwater, 85% of the 39 wells analysed contained toluene; the

concentrations were <10 µg/l. Toluene was also detected in raw water and finished water supplies up to 19 µg/l (WHO, 1985).

Germany

Arendt et al. (1977) measured 1-3,000 µg/l in Main River, Germany. The maximum value of 3,000 µg/l was measured outside Hoechst Farbwerk (Manufacturer). The concentration decreased to 2,500 µg/l at 1.6 km downstream and further to 1,000 µg/l at 4 km downstream. Further downstream the concentrations ranged from 13 to 21 µg/l (Arendt et al., 1977).

Spain

The monitored rivers Besós and Llobregat are located north and south of Barcelona. Their waters share multiple uses (domestic, industrial, agricultural etc.) and receive a wide spectrum of unaccountable waste. Llobregat River is used as the major source of municipal water for the city of Barcelona. The samples were taken monthly at the river mouth and from open seawater in front of the rivers at maximum distance of 2 miles (3 km) (Gomez-Belinchon et al., 1988).

Table 3.19 Marine measurements

Location	Year	Concentration		Reference
		range	mean	
Marine waters (NL)			0.02 µg/l	IUCLID; Sloof and Blokzijl (1987)
North Sea 2-70 km from NL coast	1983-1984	<0.005-0.060	0.013 µg/l	van de Meent et al. (1986)
W. Mediterranean STP dispersion zone Rhône river mouth Rhône dispersal zone Corsica, E.+W. Coast -"-, Ajaccio -"-, open sea	1984	 0.240-0.830 0.004-0.415 0.005-0.017 	 µg/l 0.577 µg/l µg/l µg/l 0.040 µg/l 0.007 µg/l	Marchand et al. (1988) DL 0.02

In the studies in the North Sea, the concentrations decrease with increasing distance to the coast indicating dilution of the organic substances discharged from the rivers and the air-sea exchange by volatilisation and dry and wet deposition processes (van de Meent, 1986). The values should be compared to 0.02 µg/l measured in Rhine and the concentration found in rain also measured in 1983 at four locations in the Netherlands of 0.05 µg/l (van de Meent et al., 1986.)

In the coastal water in the western part of the Mediterranean outside Cortieu, toluene was measured at 4.5 ±2 ng/l (Marchand et al., 1988).

3.1.3.1.4 Sediments

Table 3.20 Measured concentrations in sediments

Location	Year	Concentration range	mean	Reference
United Kingdom, Tees river estuary	1984	1.2-6.4	µg/kg ww	Rippen (995) Harland et al. (1985)-(RIVM)
USA,	1985		5.0 µg/kg dw	Rippen (1995)
Slovakia Morava river branches	1993 winter	10.1-69.5	µg/kg ww	Al-Rekabi et al. (1996)
	spring	7.4-290	µg/kg ww	
	summer	6.2-166	µg/kg ww	
	yearly	4.3-192.2	µg/kg ww	

In water and sediment from the most industrialised part of the Tees estuary (UK) taken at two different locations at a depth of 1.5 m, average toluene concentrations were found at 6-60 µg/l in the water and 1.2-6.4 µg/kg wet weight in the sediment (Harland et al., 1985).

Slovakia

The Morava River receives discharges from both industrial and domestic sources. In the Morava catchment the oil fields and sugar works are the main sources of industrial pollution and domestic wastes from small cities enter the Morava River without being purified (Al-Rekabi et al., 1996). The concentrations changed by season and temperature. The concentrations in sediments were several orders of magnitude higher than in the water (cf. surface water data).

3.1.3.2 Model calculations

The estimation of environmental release and the PECs are based on information from main manufacturers. The main manufacturers have supplied the RAR with estimations based on combined data and TGD default values covering the toluene production sites, the combined production and processing sites and a few processors (Results and summary tables are included in the text and the detailed spreadsheet is included as appendix). For downstream uses not included, the generic scenarios of the TGD (1996) presented in Section 3.1.1.1 are used (scenarios 1-10). The distribution between industrial categories and scenarios are presented in **Table 3.2**.

3.1.3.2.1 PEC_{local} for the aquatic compartment

The removal and distribution in STP can be estimated by the values from the table in the TGD (Corrigendum 1997) using log Kow 2.65 and log H 2.7 for ready biodegradable substances. The model EUSES ver.1 estimates the removal in STPs to be approximately the same but the distribution a little different. The EUSES values are used in the risk assessment.

Table 3.21 Estimated fate of toluene in STP

Estimated according to	% to air	% to sludge	% degraded	% removal	% to water
TGD corrigendum 1997	50	8	37	95	5
EUSES ver 1.0	48.6	1.57	44.4	94.57	5.42

The estimated concentrations of toluene in surface waters for the and generic scenarios in Section 3.1.1.1 are presented in **Tables 3.20-21**.

Table 3.22 Site-specific releases to water and PEC estimated from production, production +on-site processing and processing sites
Bold values indicate that defaults have been overwritten by measured data (APA, 2000)

Site	E water (kg/d)	C influent mg/l	C effluent mg/l	PEC water mg/l
Production				
P1 [1)]	12.33	**5.1**	0.30	0.010
P2	**8.8**	2.93	0.17	$1.1 \cdot 10^{-3}$
P3	9.86	2.05	**0.005**	$1.39 \cdot 10^{-7}$
P4	106.85	53.42	**0.050**	0.002
P5	301.64	15.71	0.910	0.040
P6	8.85	4.42	0.256	$5.7 \cdot 10^{-6}$
P7	0.0037	0.19	**0.010**	0.001
P8	821.92	**1.44**	**0.013**	$3.9 \cdot 10^{-6}$
P9	1,972.60	**5.00**	0.290	$3.52 \cdot 10^{-6}$
P10	66.29	184.13	**0.010**	$1.8 \cdot 10^{-6}$
P11	542.47	85.56	$\mathbf{5 \cdot 10^{-4}}$	$4.17 \cdot 10^{-9}$
P12	35.20	**8.45**	$\mathbf{3.65 \cdot 10^{-4}}$	$3.65 \cdot 10^{-5}$
P13	**0.00**	0.00	0.000	0
P14	203.84	101.92	5.900	0.59
P15	452.05	16.74	**0.020**	$2 \cdot 10^{-8}$
P16	205.48	8.56	**0.005**	$3.33 \cdot 10^{-5}$
P17	336.99	11.70	**0.010**	$1 \cdot 10^{-8}$
P18	353.42	**1.00**	**0.050**	$2.97 \cdot 10^{-5}$
P19	5,753.42	958.90	**0.420**	**0.0014**
Production + processing				
PP1	69.86	0.97	**0.003**	0.000136
PP2	402.74	0.98	0.057	0.000369
PP3	2.74	1.37	0.079	0.000515
PP4	287.67	143.84	8.330	0.8300
PP5	1,594.52	30.20	**0.010**	$1.00 \cdot 10^{-8}$
PP7	32.05	**0.006**	0.00035	$5.32 \cdot 10^{-6}$

[1)] Production stopped in 1998

Table 3.22 continued overleaf

Table 3.22 continued Site-specific releases to water and PEC estimated from production, production +on-site processing and processing sites

Site	E water (kg/d)	C influent mg/l	C effluent mg/l	PEC water mg/l
Processing				
Pc1	8.22	4.11	0.24	0.024
Pc2	4.32	2.16	0.12	0.013
Pc3	632.88	316.44	18.32	1.830
Pc4	0.43	0.11	**0.01**	$3.22 \cdot 10^{-4}$
Pc5	3.70	0.17	**0.01**	0.0012
Pc6	1.32	0.44	0.025	$1.36 \cdot 10^{-5}$

Table 3.23 Summary statistics for local surface water PECs (mg/l) at production sites

Mean	Median	Min	Max	90th %	N
$3.40 \cdot 10^{-2}$	$5.7 \cdot 10^{-6}$	0.00	$5.90 \cdot 10^{-1}$	$1.63 \cdot 10^{-2}$	19

Table 3.24 Summary statistics for local PECs (mg/l) at production + processing sites

Mean	Median	Min	Max	N
$1.39 \cdot 10^{-1}$	$2.53 \cdot 10^{-4}$	$1.00 \cdot 10^{-8}$	$8.30 \cdot 10^{-1}$	6

Note: No site-specific data were provided for site PP4 other than the amounts produced and processed - as a result the local PEC is conservatively biased in comparison to PEC estimates for other sites where some relevant site-specific data were provided. If the default estimate from site PP4 is excluded the maximum local PEC derived from the remaining sites is 0.0084 mg/l. A similar concern applies to local air and soil PECs summarised below.

Table 3.25 Summary statistics for local PECs (mg/l) at processing sites

Mean	Median	Min	Max	N
$3.12 \cdot 10^{-1}$	$6.89 \cdot 10^{-3}$	$1.36 \cdot 10^{-5}$	1.83	6

The dilution factor is essential when calculating the environmental concentration. The data from APA demonstrate the variability in dilution. However, due to missing specified data, the TGD default dilution factor has been used for the generic scenarios not covered by APA, i.e. a dilution factor of 10 is used in the remaining scenarios.

Table 3.26 Generic scenarios for downstream uses: Estimated concentration in local surface water during emission episodes according to the TGD

Scenario	Life stage	E_{water} (kg/d)	$C_{influent}$ (mg/l)	$C_{effluent}$ (mg/l)	PEC_{water} (mg/l)
1: Intermediates	Processing	486	243	13.2	1.320
2: Basic chemicals	Formulation	200	100	5.43	0.549
	Processing	4,060	2,030	110	9.040
3: Mineral	Formulation (10%)	130	64.8	3.51	0.357
oil and fuel	Private use	0.049	0.0247	0.0013	0.004
4: Polymers	Formulation (10%)	45.4	22.7	1.23	0.129
	Processing	1.87	0.933	0.05	0.011
5: Paint, etc.	Formulation (50%)	64.1	32.1	1.74	0.180
	Private use	0.024	0.012	0.0007	0.006
6: Basic chemical	Formulation	60	30	1.63	0.169
	Processing	1,820	911	49.4	4.940
7: Personal /	Formulation	8.13	4.07	0.22	0.028
Domestic	Private use	1.73	0.866	0.047	0.011
8: Pulp, Paper and	Formulation	22	11	0.596	0.066
Board	Processing	5.93	2.97	0.161	0.022
9: Textile	Processing	150	75	4.06	0.413
10: Other	Processing	10	5	0.27	0.033

De Witt (1999) has performed a market analysis on processing sites using toluene in the manufacture of benzene, toluene diamine, phenol and other uses (IC3/UC33).

To provide a first step in refining the local exposure assessment for toluene processing sites, site-specific data for the 27 processing sites included in the DeWitt (1999) study were used by the main manufacturers (APA) to estimate the release to water and the resulting PECwater. In this analysis, processing capacity for each site is reported. These data were used to calculate a local PEC at each site using the following equation:

$$PEC_{\text{Local}} = \frac{C \cdot U\, E \cdot (1 - R)}{Z \cdot Q \cdot D} \cdot 1000$$

Where:
PEC_{Local} = local predicted exposure concentration [g/m^3 = mg/l)]
C = Site processing capacity [metric tons/a]
U = Fraction of capacity utilised
E = Emission fraction to wastewater
R = Fraction removed during WWTP [TGD default model estimate of 0.94 assumed]
Z = Number of days site operated [TGD default of 300 d/a assumed]
Q = WWTP flow [TGD default of 2,000 m^3/d assumed]
D = Receiving water dilution factor [TGD default of 10 assumed]
And 1,000 is required for the necessary unit conversions.

The De Witt (1999) analysis indicates that in 1998 the total toluene processing capacity in Western Europe was 3,176 kt/a while total production accounted for only 2,212 kt/a. These estimates suggest that the fraction of the total capacity utilised (U) on average cannot be more than 0.7. This estimate for U was assumed in local PEC calculations. The emission fraction to

wastewater was selected based on examination of the various defaults associated with the relevant industrial and use categories as summarised in **Table 3.2**. Based on these defaults, a conservative release fraction for processing applications of 0.003 was selected for local PEC calculations.

Based on the above assumptions, local PECs are summarised in **Table 3.27**. Local PECs for most sites are above the PNEC. As a result, results from this conservative screening assessment are not sufficient to exclude a potential environmental risk for downstream processors. The result is presented below.

Table 3.27 Summary of Local PEC calculations for toluene using De Witt 1999 market analysis data and TGD default emission and dilution factors
(APA, personal communication, 2000)

Site Number	Country	Purpose for toluene use [1)]	Site consumption capacity (kTons/yr)	Estimated release to wastewater (kg/d)	Estimated influent conc. (mg/l)	Estimated effluent conc. (mg/l)	Estimated PEC aquatic (mg/l)
38	D	B	63	441	220.5	11.907	1.1907
5	UK	B	119	833	416.5	22.491	2.2491
14	SP	B	124	868	434.0	23.436	2.3436
41	D	B	125	875	437.5	23.625	2.3625
35	D	B	15	1,050	525.0	27.81	2.781 [4)]
9	UK	O	2	14	7.0	0.378	0.0378
46	F	O	2	14	7.0	0.378	0.0378
3	UK	O	3	21	10.5	0.567	0.0567
2	UK	O	4	28	14.0	0.756	0.0756
1	UK	O	8	56	28.0	1.512	0.1512
45	F	O	9	63	31.5	1.701	0.1701
6	UK	O	10	70	35.0	1.89	0.189
7	UK	O	10	70	35.0	1.89	0.189
55	B	O	10	70	35.0	1.89	0.189
53	B	O	14	98	49.0	2.646	0.2646
37	D	O	15	105	52.5	2.835	0.2835
31	D	O	24	168	84.0	4.536	0.4536
27	D	T	23	161	80.5	4.347	0.4347
51	B	T	23	161	80.5	4.347	0.4347
47	F	T	26	182	91.0	4.914	0.4914
48	F	T	27	189	94.5	5.103	0.5103
29	D	T	35	245	122.5	6.615	0.6615
28	D	T	44	308	154.0	8.316	0.8316

Table 3.27 continued overleaf

Table 3.27 continued Summary of Local PEC calculations for toluene using De Witt 1999 market analysis data and TGD default emission and dilution factors

Site Number	Country	Purpose for toluene use [1)]	Site consumption capacity (kTons/yr)	Estimated release to wastewater (kg/d)	Estimated influent conc. (mg/l)	Estimated effluent conc. (mg/l)	Estimated PEC aquatic (mg/l)
30	D	T	79	553	276.5	14.931	1.4931
22	IT	T	84	588	294.0	15.876	1.5876
43	F	B,O [2)]	122	854	427.0	23.058	2.3058
16	NL	P,O [3)]	215	1,505	752.5	27.81	2.781 [4)]
Total			1,370				

1) Key to Purpose of Toluene Use
B = Benzene manufacture
T = Toluene Diamine manufacture
P = Phenol manufacture
O = Other uses

2) 119 KT capacity for benzene manufacture; 3 KT capacity for other uses

3) 165 KT capacity for phenol manufacture; 50 KT capacity for other uses

4) Estimated influent conc. exceeds water solubility therefore set to solubility limit (e.g. 515 mg/l)

Table 3.28 Summary statistics for default local PEC calculations (mg/l) at processing sites (APA personal communication, 2000)

Toluene uses	Site capacity kT/yr	Mean	Median	Min	Max	90th %	N
Benzene	581	2.18538	2.3436	1.1907	2.781	2.6136	5
Toluene diamine	341	0.80561	0.5859	0.4347	1.5876	1.52145	8
Other	111	0.17483	0.17955	0.0378	0.4536	0.28161	12
Mixed uses	337	2.5434	2.5434	2.3058	2.781	2.73348	2
All Uses	1,370	0.77879	0.4347	0.0378	2.781	2.3058	27

For the purpose of requiring data from these large processors identified in the De Wiit 1999 study, APA (2000) has tried to establish contact points to these companies. The answers show that there is a considerable uncertainty with regard to the extent that these processing companies process toluene if at all. Therefore the data given in the above tables can only be used as a very rough indication of the processing of toluene and the consequences for the receiving environment.

Comparison of measured and estimated concentrations in surface water

The estimated effluent concentrations are at the same concentration level as the average measured concentrations from localities adjacent to discharge zones <0.1 µg/l to 31 mg/l (**Table 3.16**) and in the French monitoring studies (**Tables 3.10** to **3.13**) where the effluent concentrations varied from 0.001 to 25 mg/l.

In local surface water, most of the estimated concentrations (3 to 9,000 µg/l) (**Table 3.22** and **Table 3.26**) seem to be close to the levels found in the French monitoring studies (**Tables 3.10** to **3.13**) where the estimated concentrations in the receiving surface water using the given dilution

factor indicate ranges from below 0.01 to 490 µg/l. However, only four model predictions are in the mg/l range, where several recent monitoring data (**Table 3.16**) and older monitoring data (**Table 3.18**) are found in this concentration range. Thus, the TGD estimations do not seem to be too conservative when compared to measured results (which include other toluene sources than industrial sources cf. Section 3.1.1).

The highest estimated PEC value is 9 mg/l which would be reduced if the estimated STP influent concentration was reduced to the toluene solubility level. Toluene concentrations above solubility level would be removed if oil-separation was included as STP-pretreatment (as presumed by the main manufacturer in the screening analysis of large processors **Table 3.27**). However, there is no information of such pretreatment and the toluene level is therefore not reduced in the estimation of PECs. Measured values from UK surface waters (**Table 3.16**) from near tank storage terminals were of the same level as the highest estimated PEC which on basis of this does not seem totally unrealistic.

The estimated PEC regional (6 µg/l) is higher than the measured concentrations from rivers at unknown distances to release areas.

3.1.3.2.2 PEC_{local} for sediment

The concentration in freshly deposited sediment is taken as the PEC for sediment, therefore, the properties of suspended matter are used. The concentration in bulk sediment can be estimated from the concentration in the corresponding water body assuming a thermodynamic partitioning equilibrium according to the TGD.

Table 3.29 Estimated concentration in local sediments

Scenario	Life stage	PEC_{water} (mg/l)	PEC_{sed} (mg/kg ww)
1: Intermediates	Processing	1.320	6.11
2: Basic chemicals	Formulation	0.549	2.54
	Processing	9.040	50.80
3: Mineral oil and fuel	Formulation (10%)	0.357	1.65
	Private use	0.004	0.030
4: Polymers	Formulation (10%)	0.129	0.597
	Processing	0.011	0.0522
5: Paint, etc.	Formulation (50%)	0.180	0.832
	Private use	0.006	0.029
6: Basic chemical	Formulation	0.169	0.780
	Processing	4.940	22.8
7: Personal / domestic	Formulation	0.028	0.131
	Private use	0.011	0.0505
8: Pulp, Paper and board	Formulation	0.066	0.304
	Processing	0.022	0.103
9: Textile	Processing	0.413	1.91
10: Other	Processing	0.033	0.154

Comparison of measured and estimated concentrations in sediment

The measured concentrations in sediments (**Table 3.20**) were in the range of 1.2 to 290 µg/kg ww. The estimated concentrations are one to two orders of magnitude higher than the measured concentrations. On the other hand, the proximity of the measured data to release points is unknown. The estimated concentrations vary from 30 to 50,800 µg/kg sediment. However, with the sparse monitoring data available, it is not possible to override the estimated toluene concentrations.

3.1.3.2.3 $PEC_{regional}$ and $PEC_{continental}$ for water and sediment

The concentrations of toluene in the various environmental compartments on the regional and continental scales were calculated with the EUSES v.1.0 programme. The regional and continental dimensions and properties as set out in the TGD are used.

EUSES estimates PEC continental in surface water to be 0.67 µg/l and the EUSES PEC regional in surface water to 6.25 µg/l, which is in the high end of measured values.

EUSES estimates PEC continental in sediments to be 3 µg/kg ww and the EUSES PEC regional in sediments to 26 µg/kg ww, which is in reasonable agreement with the measured values.

It should be noted that the estimated concentrations are based on isolated toluene whereas the measured values include other sources of toluene as well, e.g. non-isolated toluene from combustion processes etc. The estimated concentrations should therefore be expected to be in the lower end of the measured range, which seem to be the case for sediments but not for surface waters.

Including continental emissions of non-isolated toluene from the use of gasoline

EUSES estimates PEC continental in surface water to be 0.68 µg/l and the EUSES PEC regional in surface water to 6.26 µg/l;

EUSES estimates PEC continental in sediments to be 3 µg/kg ww and the EUSES PEC regional in sediments to 26 µg/kg ww.

The inclusion of the continental emission of non-isolated toluene from the use of gasoline has only little effect on continental and regional PECs for the aquatic environment.

3.1.4 Atmosphere

The removal in air may be by degradation by chemical- or sunlight-catalysed reactions or may be by adsorption onto particles that settle or are removed from the atmosphere by rain. A measure of the effectiveness of these factors is the atmospheric residence time.

Toluene released into the environment mainly enters the atmosphere because of the high vapour pressure. Release into surface waters will also relatively rapidly be transported to the atmosphere (the evaporation half-live is calculated to be about 3-5 hours (Mackay and Wolkoff, 1973)). The atmospheric oxidation is fast with a half-life of 12.8 hours (WHO, 1985). Other reported photooxidation rates range from 32 hours to 48 hours (cf. **Table 3.5**). A part of airborne toluene will be removed by precipitation. Toluene has been detected in rain water at 0.13-0.7 µg/l (Lahman et al., 1977 in WHO (1985)). Newer data were not submitted.

Toluene is removed from the atmosphere through free radical chain processes including hydroxyl radicals and oxygen.

The main emission sources are road traffic and industry.

A study by Guicherit and Schulting (1985) states that stationary source emissions of toluene in the Netherlands in 1980 were 6,278 tonnes/year and the mobile source emissions were 20,000 tonnes/year. Recent values from the Netherlands estimate stationary source emissions of toluene in 1995 to be 14,460 tonnes/year and the mobile source emissions to be 8,840 tonnes/year (cf. **Table A.4** in Appendix A).

3.1.4.1 Measured concentrations in the atmosphere

Table 3.30 Concentration in air

Locality	Concentration range	Average	Reference
The Netherlands Dutch countryside Dutch urban		2-4 µg/m³ 2-6 µg/m³ 13-21 µg/m³	Sloof and Blokzijl (1987)
The Netherlands	max. 42-152 µg/m³	3.6-19.0 µg/m³	Guicherit and Schulting (1985)
The Netherlands: inside football arena outside arena		 25 µg/m³ 4 µg/m³	Dueck (1996)
United Kingdom Remote rural Rural Urban	 ND-34.5 µg/m³ 0.8-15.3 µg/m³ 1.8-12.5 µg/m³	 8.43 µg/m³	Bertorelli et al. (1995)
USA Boundaries of six service stations, n=88	7-90 µg/m³	31 µg/m³	API (1991)
Los Angeles, CA 1979 Phoenix, AZ, Oakland, CA	4.3-202 µg/m³ 2.2-147 µg/m³ 0.6-64 µg/m³	44.5 µg/m³ 32.8 µg/m³ 11.8 µg/m³	Singh et al. (1981)
USA, Cincinnati airspace 3 STPs	<380-24,700 µg/m³		Dunovant et al. (1986)
USA, 8 Solid waste composting facilities: Background air Tipping Shredder Indoor Digester Fresh Midaged Old Curing	 	 9 µg/m³ 8,800 µg/m³ 11,500 µg/m³ 1,100 µg/m³ 860 µg/m³ 3,900 µg/m³ 700 µg/m³ 400µg/m³ 88 µg/m³	Eitzer (1995)

Calculation factor at 20°C, 1,013 hPa: 1ppb = 3.8 µg/m³ (Rippen 1992)

The background concentration measured in the Dutch countryside averaged from 2 to 6 $\mu g/m^3$, Dutch urban sites 13 to $21 \cdot 10^{-6}$ g/m^3, and in the Netherlands averaged 3 to 4 $\mu g/m^3$ (Slooof and Blokzijl, 1988).

In urban areas, a toluene level in ambient air of 0.1-204 μg/m^3 has been detected (WHO, 1985). In 1971 to 1980, atmospheric concentrations of toluene were estimated in Canada, Europe and the USA. The concentrations varied from rural areas with low concentrations to cities and airports where high levels were found. The average concentrations ranged from 5 to 1,310 μg/m^3. The highest level was 5,500 μg/m^3 (WHO, 1985).

The air concentrations in urban environments were measured at three sites in the USA during 2 weeks at hourly intervals. The min/max and average results are presented in **Table 3.30** (Singh et al., 1981)

The toluene concentration downwind from an automobile painting plant was at a distance of 1.6 km 600 μg/m^3, at 6 km 75 μg/m^3; and at 16 km the "background value" of 5.5 μg/m^3 was found (Sexton and Westberg, 1980 in WHO (1985)).

Eitzer (1995) studied the air concentrations of toluene from eight municipal solid waste composting facilities. The 8 facilities chosen, span a size range from 5-10 to 660 tons/day capacity using different techniques of aeration. The results from 10-20 minutes air sampling by portable sampling pumps are presented in **Table 3.30** as the average concentrations in the air background, and at different stages in the composting process. The emissions were high at the tipping floors where the waste is dropped off, at the shredder and at the initial active composting region where the temperature rose to normal composting conditions (>55°C) (Eitzer, 1995). This indicates that toluene was emitted early in the composting process. However, the highest toluene concentrations were from a pile of tipped waste that had a load of paint dropped off. Shredding of the waste increased the surface area and exposed the surfaces to the atmosphere and as expected toluene was observed at the highest concentration at this part of the waste procedure.

Studies on air pollution have demonstrated that 35% of the anthropogenic volatile organic compound (VOC) emissions are due to vehicle exhaust and evaporative losses. In urban areas, the contribution to the VOC emissions from traffic may reach 60-80% of the total emissions. VOC emissions from petrol storage and distribution systems represent some 500,000 tonnes per year, i.e. 5% of total man made VOC emissions in the EU. Petrol stations situated in urban areas are considered critical locations with high emissions from evaporative losses during tank filling from the vent pipe of the storage reservoir as well as during fuel spillage while refilling (Ballesta and Saeger, 1995).

Relating to the measured/estimated total VOC, the toluene part varies according to source, location etc. For motor vehicle engines exhaust, some variation in the composition of VOC and NM-VOCs have been observed. However, the values may be used for a crude estimation in the evaluation of for instance street air situations where the major part of the VOCs is assumed to be from motor vehicles exhaust.

In the composition of NM-VOC emissions of motor vehicles, toluene in weight % of exhaust (Veldt in EEA, 1999):

Gasoline exhaust gas	4-stroke engine conventional	12%
	4-stroke engine 3way catalyst	7%
	Evaporation	1%
Diesel		1.5%

In the composition of VOC emissions of motor vehicles toluene w/w% cited from Derwent in EEA (1999)

Petrol engines exhaust	7.2%
Diesel exhaust	0.8%
Petrol evaporation	5.66%

In the composition of VOC emissions of motor vehicles toluene w/w% cited from Loibl et al. in EEA (1999):

Gasoline exhaust gas	Conventional	10%
	Catalyst	11%
	cold start (all cars)	14% [6]
Diesel		-
Evaporation		1%

The emissions from four petrol stations were examined in 1994 based on volume of fuel sales, type of fuel, number of pumps etc. The vapour emissions were composed of 80% paraffinic, 15% olefinic and 5% aromatic compounds. Of the aromatics, BTX was measured. Active sampling by charcoal tubes were performed in station A, B and C at 1,000 cm^3/min in 24 hours. Diffusive sampling was performed at 3 m above ground at fixed positions at the station and in the vicinity, 3 sampling periods of 14 days in 4 stations.

Table 3.31 Toluene monitoring in cities at service stations

Petrol station, City	Season	Average (µg/m³) active sampling	Variation (µg/m³) diffusive sampling
C, Brussels	Winter	23.8	6.3-66.3
D, Brussels	Winter		10.2-49.8
A, Murcia	Autumn	190.6	34.2-325.1
B, Murcia	Autumn	104.8	29.9-213.4
C, Brussels	Autumn	30.1	13.6-118.1
D, Brussels	Autumn		12.4-51.5

In Murcia, higher concentrations were found due to higher temperatures which increase the volatilisation. The level in the service area was 5-15 times higher than background level. Emissions from petrol stations not above background level (mainly from automotive emissions) at a distance of 100 m in Murcia and 30 m in Brussels.

Table 3.32 Average concentrations for one month in the service area and the surroundings of petrol stations.

	Temperature, avg.	Wind speed, avg.	Background, µg/m³	Service area, µg/m³
Murcia	20ºC	1.7 m/s	34	78-325
Brussels	12ºC	3.5 m/s	13	30-113

[6] The reported value is 140%, however this must be because of a typing error and the correct value is possibly 14%.

The reported air concentrations of toluene near petrol stations are generally around an order of magnitude higher than the typically reported urban air concentrations (cf. below).

Air monitoring in Brussels 1994

In an air monitoring campaign in Brussels, 68 sampling sites covering 17·18 km around city center during 6 weeks in January to March 1994. Sampling at 3 m height away from busy traffic road. Thus a minimum value should be expected. The measured toluene concentrations varied between 4.52 µg/m^3 to 48.34 µg/m^3, the average was 13.56 µg/m^3 and the median value 12.42 µg/m^3 (Saeger et al., 1995).

Air monitoring in Catania 1996

In an air monitoring campaign in Catania, Italy, 22 sampling sites covering 6.5 km^2 around city centre during two sampling periods of 1 month, February/March and July/August 1996. Sampling at 3 m height away from busy traffic road. Thus a minimum value should be expected (background). The measured toluene concentrations varied between 12.2 µg/m^3 and 54.8 µg/m^3, the average was 29.1 µg/m^3 and the median value 26.5 µg/m^3 (Ballesta et al., 1997).

Air monitoring in Copenhagen 1997

The monitoring results of toluene in the centre of Copenhagen 1997 averaged 27.7 µg/m^3 (24 hours), the median hour level was 21.3 µg/m^3 and the 98 percentile (hour) was 89.9 µg/m^3 (Kemp et al., 1998).

Air monitoring in Bologna 1997-98

In an air monitoring campaign in Bologna, Italy, 40 sampling sites covering 34 km^2 around city centre during two sampling periods of 1 month, May 1997 and March 1998. Sampling at 3 m height away from busy traffic road. Thus a minimum value should be expected (background). The measured toluene concentrations varied between 1.5 µg/m^3 and 37.4 µg/m^3, the average was 10.3 µg/m^3 and the median value 8.5 µg/m^3 (Ballesta et al., 1998).

Table 3.33 Toluene monitoring in Bologna

Period, No.	Min-Max µg/m^3	Average µg/m^3	Median µg/m^3
May 1997, 39	1.5-18.1	6.8	6.4
March 1998, 45	2.9-37.4	13.3	12.8
Total, 84	1.5-37.4	10.3	8.5

In conclusion typical air concentrations of toluene are in the order of 10 to 30 µg/m^3. As for the air near petrol stations the main sources of toluene in urban air are generally toluene as a component of evaporated gasoline or as a component of motor vehicle exhaust.

Deposition by rain

Wet deposition

A rain sampler with a 0.89 m^2 collection surface recovered from 4 rain storm events in a semi-rural area in Oregon, USA (1982), a concentration in the rain of 5.4, 19, 13, and 0.91 ng/l,

resulting in a mean sample concentration of 9.6 ng/l. The collector opened automatically at rain events to exclude dry deposition (Pankow et al., 1984). Based on the equilibrium scavenging for raindrops falling through the atmosphere the authors estimated the predicted concentration in the atmosphere to be 2800 ng/m^3 (Pankow et al., 1984).

At the same location, sampling was conducted for seven storm events during the winter and spring of 1984. In the rain, toluene was detected in 5 samples with the mean concentration 88 ±75 ng/l (range 40-220 ng/l). The mean atmospheric gas phase concentration was 3800 ng/m^3 (range 1,800-8,600 ng/m^3) (Ligocki et al., 1985).

At observations in the Netherlands 1983 at four locations, a concentration of 50 ng/l in rain was measured (van de Meent, 1986).

3.1.4.2 Calculations of PEC_{local} for air

The estimated concentrations in the atmosphere are based on emissions from production, formulation, processing and use and from the emissions from STP.

Table 3.34 Releases and PEC local air at production, production+processing and processing sites

Site	Release to air (kg/d)	PEC air mg/m^3
Production		
P1 [1)]	41.1	0.0114
P2	2,227.4	**0.010**
P3	4,931.5	1.3710
P4	3.13	0.0144
P5	1,005.5	0.2795
P6	2.05	0.00120
P7	30.3	$5.04 \cdot 10^{-5}$
P8	2,739.7	0.7616
P9	131.5	0.2665
P10	5.08	**0.00023**
P11	**25.00**	0.0733
P12	**43.83**	**0.0040**
P13	4,567.53	1.295/**53.6** [2)]
P14	679.45	0.1889

Table 3.34 continued overleaf

Table 3.34 continued Releases and PEC local air at production, production+processing and processing sites

Site	Release to air (kg/d)	PEC air mg/m³
P15	0.17	0.0611
P16	0.03	0.0278
P17	0.14	0.0455
P18	0.14	0.0478
P19	6,712.33	1.8700
Production and processing		
PP1	27.95	0,009439
PP2	1.47	0,05441
PP3	84.11	0,02338
PP4	958.90	0,2666
PP5	0.08	0,2154
PP7	10.68	**0.045**
Processing		
Pc1	68.49	0.0190
Pc2	15.41	0.0043
Pc3	2,260.27	0.6284
Pc4	6.85	0.0019
Pc5	2.10	**0.043**
Pc6	0.0044	$1.78 \cdot 10^{-4}$

1) Production stopped in 1998
2) Suspect data point. Calculated PEC used in the summarised statistics

Table 3.35 Summary statistics for air PECs (mg/m³) at production sites

Mean	Median	Min	Max	90th %	N
$3.33 \cdot 10^{-1}$	$4.78 \cdot 10^{-2}$	$5.04 \cdot 10^{-5}$	1.87	1.31	19

Table 3.36 Summary statistics for air PECs (mg/m³) at production + processing sites

Mean	Median	Min	Max	N
$1.02 \cdot 10^{-1}$	$4.97 \cdot 10^{-2}$	$9.44 \cdot 10^{-3}$	$2.67 \cdot 10^{-1}$	6

Table 3.37 Summary statistics for air PECs (mg/m³) at processing sites

Mean	Median	Min	Max	N
0.116	0.0117	$1.78 \cdot 10^{-4}$	0.628	6

Table 3.38 Generic scenarios: estimated concentration in local air during emission episodes

Scenario	Life stage	$E_{local, air}$ (kg/d)	$E_{STP, air}$ (kg/d)	$Clocal_{air}$ (µg/m³)	$PEClocal_{air,ann}$ (µg/m³)
1: Intermediates	Processing	69.4	236	65.6	56.7
2: Basic chemicals	Formulation	1,670	97	464	384
	Processing	10,500	1,970	2,930	2,410
3: Mineral oil and fuel	Formulation (10%)	1,080	62.9	300	250
	Private use	39.4	0.024	11	13.8
4: Polymers	Formulation (10%)	151	22	42	37.3
	Processing	93.3	0.906	25.9	24.1
5: Paint, etc.	Formulation (50%)	214	31.1	59.4	51.6
	Private use	0	0.012	0.003	2.8
6: Basic chemical	Formulation	500	29.1	139	117
	Processing	4,740	885	1,320	1,090
7: Personal / domestic	Formulation	67.8	3.95	18.8	18.3
	Private use	0	0.84	0.23	3.0
8: Pulp, Paper and board	Formulation	183	10.7	51	44.7
	Processing	3,860	2.88	1,070	883
9: Textile	Processing	30	72.8	20.3	4.9
10: Other	Processing	999	4.85	278	202

Comparison of measured and estimated concentrations in the atmosphere

The measured concentrations were in the range of <1 to 300 µg/m³ (cf. **Table 3.30-33**). The estimated local concentrations are in several situations above the measured concentrations (cf. **Table 3.34 and Table 3.38**). The proximity of the measured data to release points is unknown. The estimated concentrations 100 m away from the point source are therefore hardly comparable to the measured values in **Table 3.30**. It should be noted that the measured data include contributions from "non-isolated" toluene, e.g. fuel and gasoline, and therefore would be expected to be somewhat higher than the PEC estimations based on the commercial product toluene. However, in general the employed estimation scenarios for local air concentrations seem to be in reasonable agreement with measured air concentrations based on the proximity to the source.

EUSES estimates PEC continental in air to be 0.91 µg/m³ and the EUSES PEC regional in air to 2.79 µg/m³.

Because the continental and regional PECs are based on the commercial product toluene, the values are expected to underestimate the actual PEC including the contribution from combustion processes, gasoline, etc. The EUSES estimations are as expected in the lower end of the measured range. In the USA for instance, toluene is routinely measured by the statewide Air Resource Board (ARB) air toxics network. The network mean concentration of toluene from January 1996 through December 1996 is estimated to be 8.29 µg/m³ or 2.2 ppb (ARB, 1997). The US EPA has also reported concentrations of toluene from 14 study areas during 1989 to 1991. The overall mean concentration from these areas was 10.2 µg/m³ (US EPA, 1993). In a

study for US EPA, the USA background concentration of toluene is estimated to be 3.8 μg/m^3 (Rosenbaum et al., 1999).

Including continental emissions of non-isolated toluene from the use of gasoline, EUSES estimates PEC continental in air to be 2.35 μg/m^3 and the EUSES PEC regional in air to 6.92 μg/m^3.

The inclusion of the continental emission of non-isolated toluene from the use of gasoline increase the continental and regional PECs with a factor 2-3 for the air environment. Other major sources of toluene are not included in this evaluation e.g. emissions from power plants.

Deposition

The deposition of toluene from air to soil and surface water is estimated based on the direct releases from production, formulation, processing and use and the indirect releases from STP.

The estimations of the total deposition flux (DEP_{total}) and the annual average total deposition flux ($DEP_{total, ann}$) are shown in **Table 3.39**.

Table 3.39 Estimations of depositions from local air

Scenario	Life stage	$E_{local, air}$ (kg/d)	$E_{STP, air}$ (kg/d)	DEP_{air} (μg/m²/d)	$DEP_{total,ann}$ (μg/m²/d)
1: Intermediates	Processing	69.4	236	91.6	75.3
2: Basic chemicals	Formulation	1,670	97	530	436
	Processing	10,500	1,970	3,760	3,090
3: Mineral	Formulation (10%)	1,080	62.9	343	282
oil and fuel	Private use	39.4	0.024	11.8	11.8
4: Polymers	Formulation (10%)	151	22	52	42.7
	Processing	93.3	0.906	28.3	23.2
5: Paint, etc.	Formulation (50%)	214	31.1	73.5	60.4
	Private use	0	0.012	0.004	0.003
6: Basic chemical	Formulation	500	29.1	159	130
	Processing	4,740	885	1,690	1,390
7: Personal /	Formulation	67.8	3.95	21.5	17.7
domestic	Private use	0	0.84	0.25	0.25
8: Pulp, Paper and	Formulation	183	10.7	58.2	47.8
board	Processing	3,860	2.88	1,160	952
9: Textile	Processing	30	72.8	30.9	3.2
10: Other	Processing	999	4.85	301	216

3.1.4.3 Local concentrations due to car exhaust

Local concentrations due to car exhausts can be estimated with computer models, e.g. the CAR-model (Eerens et al., 1993). This has been done for cyclohexane in the EU risk assessment report on cyclohexane (Draft of February 1999). By assuming that all traffic is by gasoline driven vehicles a worst-case estimate can be given for toluene. The emission factor for cyclohexane is 0.006 times the emission factor for VOC (Nelson and Quigley, 1984) in the Cyclohexane risk assessment report). The emission factor for toluene is 0.191 [7] times the emission factor for VOC (DG XI, 1996 in CONCAWE, 1999). Therefore, the air concentration of toluene can be estimated as: conc. $(\text{cyclohexane})_{\text{car model}} \cdot 0.191/0.006$, cf. **Table 3.31**.

Table 3.40 CAR model results (annual average toluene concentration in µg/m³ air)

Type of road			Distance [m]					
			5	10	15	20	25	30
Urban	1	Exhaust	6.781	5.316	4.043	2.961	2.069	1.369
	2	Exhaust	12.192	8.850	6.271	4.457	3.406	3.120
	3A	Exhaust	14.612	10.760	7.704	5.444	3.979	3.343
	3B	Exhaust	21.933	16.140	11.524	8.149	5.985	4.998
	4	Exhaust	20.978	15.025	10.314	6.812	4.584	3.565
Motorway	1	Exhaust	2.006	1.592	1.210	0.891	0.605	0.414
	2	Exhaust	3.629	2.642	1.878	1.337	1.019	0.923

1: Road in open terrain, no or very few buildings
2: Basic street type not defined by 1, 3A, 3B, or 4
3A: Street with buildings at least 3 m heigh on both sides, no gaps larger than 25 m and at least 75 m buildings per 100 m street
The ratio between height of buildings and distance of these to road axes is from 1.5 to 3 on one side and less than 3 on the other
3B: As 3A but with the ratio less than 1.5 for both sides of the road
4: Street with buildings at least 3 m heigh on one side with the ratio building-height/road-axis distance less than 3. The other street side has no buildings or a ratio much greater than 3 (preferably greater than 10)

Evaporation of toluene from gasoline in vehicles is estimated to be 1.8% of total VOCs i.e. less than 10% of the emission of VOCs from vehicles (DG XI, 1996 in CONCAWE, 1999).

The concentration of toluene predicted by the model is in the lower end of the measured data from cities shown in Section 3.1.3.1. However, it has to be taken into account that the measured data include all sources of toluene including emissions from the industrial use of commercial toluene and evaporation from transport, handling and from gasoline in vehicle.

The concentrations of toluene at the road site predicted by the worst-case approach employed above are low compared to most $PEC_{local,\ air}$ predicted in generic scenarios for industrial sites cf. **Table 3.38**. However, the concentrations predicted for road sites are at the same level as the $PEC_{local,\ air}$ predicted for production sites cf. **Table 3.37**.

[7] In Veld in EEA (1999) the equivalent value is 12% for 4-stroke engines (cf. Section 3.1.4.1). However based on "the realistic worst-case approach" the value reported by CONCAWE (1999) of 19.1% is used here.

Creation of ozone due to non-isolated toluene in car exhaust

In **Table 3.41** is shown the mean road site concentrations of individual NMVOCs at a site in Copenhagen during 5 days in December 1997. Using the POCP equivalence factors it is possible to estimate the relative contribution of non-isolated toluene to the potential overall troposheric ozone creation for such a NMVOC composition. It has to be emphasised that the toluene concentrations measured are closely correlated to benzene and CO concentrations. This clearly indicates that the toluene in this case arise from car exhaust. Further, 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 toluene concentrations due to low solar radiation and the prevailing wind conditions.

Table 3.41 Monitoring results of different NMVOCs at Jagtvej, Copenhagen on December 1-5 1997, and the relative contribution to potential ozone creation
(Christensen, 1999)

Substance	Mean	Range	S.D.	Median	POCP g C_2H_4/g gas [1]		Relative O_3 creation [2]	
	ppbv	ppbv	ppbv	ppbv	low NOx	High NOx	low NOx	high NOx
Pentane	2.4	0.4-5.7	1.2	2.5	0.3	0.4	$2.12 \cdot 10^{-3}$	$2.83 \cdot 10^{-3}$
trans-2-Pentene	0.2	0.01-0.5	0.1	0.2	0.4	0.9	$2.29 \cdot 10^{-4}$	$5.16 \cdot 10^{-4}$
2-Methyl-2-butene	0.4	0.02-0.9	0.2	0.3	0.5	0.8	$5.73 \cdot 10^{-4}$	$9.17 \cdot 10^{-4}$
cis-2-Pentene	0.1	0.01-0.3	0.1	0.1	0.4 [3]	0.9	$1.15 \cdot 10^{-4}$	$2.58 \cdot 10^{-4}$
2,2-Dimethylbutane	0.9	0.04-2.3	0.5	0.9	0.3	0.3	$9.51 \cdot 10^{-4}$	$9.51 \cdot 10^{-4}$
Cyclohexane	0.5	0.04-1.1	0.3	0.5	0.25	0.25	$4.30 \cdot 10^{-4}$	$4.30 \cdot 10^{-4}$
2,3-Dimethylbutane	0.4	0.03-1.0	0.2	0.4	0.4	0.4	$5.64 \cdot 10^{-4}$	$5.64 \cdot 10^{-4}$
2-Methylpentane	2	0.2-5.2	1.1	2.1	0.5	0.5	$3.52 \cdot 10^{-3}$	$3.52 \cdot 10^{-3}$
3-Methylpentane	1.1	0.1-2.7	0.6	1	0.4	0.4	$1.55 \cdot 10^{-3}$	$1.55 \cdot 10^{-3}$
n-Hexane	0.8	0.1-2.3	0.5	0.8	0.5	0.4	$1.41 \cdot 10^{-3}$	$1.13 \cdot 10^{-3}$
Isoprene	0.2	0.01-0.6	0.1	0.2	0.6	0.8	$3.34 \cdot 10^{-4}$	$4.46 \cdot 10^{-4}$
2-Methyl-1-Pentene	0.04	0.01-0.1	0.02	0.02	0.5 [4]	0.9	$6.88 \cdot 10^{-5}$	$1.24 \cdot 10^{-4}$
cis-2-Hexene	0.03	0.01-0.1	0.01	0.02	0.5	0.9	$5.16 \cdot 10^{-5}$	$9.29 \cdot 10^{-5}$
2,4-Dimethylpentane	0.2	0.01-0.7	0.1	0.2	0.4 [5]	0.4	$3.28 \cdot 10^{-4}$	$3.28 \cdot 10^{-4}$
Methyl-cyclohexane	0.3	0.02-0.6	0.1	0.3	0.5	0.6	$6.02 \cdot 10^{-4}$	$7.22 \cdot 10^{-4}$
2- and 3-Methylhexane	1.4	0.1-3.7	0.8	1.3	0.5	0.5	$2.87 \cdot 10^{-3}$	$2.87 \cdot 10^{-3}$
n-Heptane	0.7	0.1-1.9	0.4	0.6	0.5	0.5	$1.43 \cdot 10^{-3}$	$1.43 \cdot 10^{-3}$

[1] POCP equivalence factors from Hauschild and 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

Table 3.41 continued overleaf

Table 3.41 continued Monitoring results of different NMVOCs at Jagtvej, Copenhagen on December 1-5 1997, and the relative contribution to potential ozone creation

Substance	Mean ppbv	Range ppbv	S.D. ppbv	Median ppbv	POCP g C_2H_4/g gas [1] low NOx	POCP g C_2H_4/g gas [1] High NOx	Relative O_3 creation [2] low NOx	Relative O_3 creation [2] high NOx
Benzene	3.4	0.2-8.0	1.7	3.3	0.4	0.2	$4.34 \cdot 10^{-3}$	$2.17 \cdot 10^{-3}$
2- and 3-Methylheptane	0.4	0.01-1.0	0.2	0.3	0.5	0.5	$9.34 \cdot 10^{-4}$	$9.34 \cdot 10^{-4}$
Toluene	**10.2**	**0.8-21.5**	**5.6**	**8.9**	**0.47** [3]	**0.6**	$\mathbf{1.81 \cdot 10^{-2}}$	$\mathbf{2.31 \cdot 10^{-2}}$
Ethylbenzene	2	0.1-4.9	1.1	1.9	0.5	0.6	$4.34 \cdot 10^{-3}$	$5.21 \cdot 10^{-3}$
o-Xylene	2.7	0.1-6.2	1.4	2.6	0.2	0.7	$2.34 \cdot 10^{-3}$	$8.20 \cdot 10^{-3}$
m- and *p*-Xylene	5.5	0.3-12.7	2.9	5.5	0.5	0.95	$1.19 \cdot 10^{-2}$	$2.27 \cdot 10^{-2}$
Relative contribution of non-isolated toluene %							**30.55**	**28.48**

[1] POCP equivalence factors from Hauschild and Wensel (1998) except for cyclohexane from EU RAR
[2] Calculated at STP
[3] Andersson-Sköld et al. (1992)

The result of this calculation shows that if the VOC composition is as measured in the Copenhagen study non-isolated toluene potentially would exhibit approx. 30% of the total VOC contribution to ozone creation.

Creation of ozone due to isolated toluene

As described in Section 3.1.2, the creation of troposheric ozone is dependent on the occurrence of VOC, NOx, 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 toluene 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.

The total NMVOC emitted in the 15 EU countries is shown in **Table 3.42**.

Table 3.42 Emission of ozone precursors in the 15 EU countries (EEA, 2000)

NMVOC in the 15 EU countries (Kilotonne)									
1980	1985	1990	1991	1992	1993	1994	1995	1996	1997
14,434	14,315	14,852	14,388	14,037	13,494	13,683	13,257	12,904	12,687

Total continental emission to air of isolated toluene is calculated by EUSES to be 1,090 t/d based on the production volume from 1995 (cf. **Table 3.2**). The total emission of NMVOC in 1995 is approx. 36,000 t/d. The proportion of isolated toluene relative to total NMVOC is approx. 3%.

The POCP equivalence factor for the total NMVOC is not known because the composition of individual NMVOC species is not available. Toluene 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 toluene relative to total NMVOC.

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

To conclude isolated toluene contributes in the order of 3% to the total NMVOC emission. Thus isolated toluene in general only contributes to a small extent to the total SMOG problem, however, for a single substance among hundreds of different VOCs the contribution is significant.

3.1.5 Terrestrial compartment

The main part that reaches soil would be expected to evaporate. The adsorption, which is dependent on the content of organic matter, is generally low, and toluene will also be transported to deeper layers/groundwater by leaching. In the soil biodegradation is expected to take place.

3.1.5.1 Measured concentrations in soil

The concentration found in soil in the Netherlands averaged 0.001 mg/kg (Sloof and Blokzijl, 1987). From uncontaminated sites in Florida (USA), seven samples resulted in <0.04 µg/kg soil (CONCAWE, 1997). In Canada urban areas near refineries, the concentration of toluene was <10-70 µg/kg, found in 1/30 samples, and in soils from refineries, concentrations <0.1-10 µg/kg were found in 5 out of 10 samples (CONCAWE, 1997).

3.1.5.2 Measured concentrations in sludge

The concentrations measured in STP sludge are presented below.

In a Danish report from 1996, the sludges from 19 typical Danish STPs representing average Danish STP types with municipal and industrial loading were analysed during Sept. 1995 and Feb. 1996. From the 19 STPs, 20 sludge samples were analysed and 15 were measured to have a concentration of toluene above the detection limit of 0.05 mg/kg dw. The range was <0.05-370 mg/kg dw, and the mean value was 20.69 mg/kg dw including values below detection limit (Kristensen et al., 1996).

In a German study, monitoring was performed on a STP receiving effluents from domestic and textile industries using high amounts of solvents. Nine sludges were analysed. The wintertime analyses were significantly higher than the summer analyses and in 4 sludges above 1 mg/kg dw were measured (Schnaak, 1995). The winter analyses are included in **Table 3.43**.

Table 3.43 Concentrations in STP sludge

Location	Range	Mean	Median	Ref.
Denmark, 20 sludges	<0.05-370 mg/kg dw	20.69 mg/kg dw	0.29 mg/kg dw	Kristensen et al. (1996)
Denmark, Aarhus amt, 9 sludges	<0.005-4.4 mg/kg dw	0.7 mg/kg dw		Aarhus (1998)
Sweden, 27 sludges	0.3-310 mg/kg dw			Swedish EPA (1992)
Sweden	0.3-310 mg/kg dw		16.2 mg/kg dw	Danish EPA (1995)
Literature	0.11-140 mg/kg dw			Danish-EPA (1995)
USA: before 1982, n=12	1.4-705 mg/kg dw	15 mg/kg dw		Rippen (1992)
Germany *	<0.005-143.4 mg/kg dw	19.9 mg/kg dw	0.11 mg/kg dw	Schnaak et al. (1995)

dw: dry weight
* cf. text

In general therefore measured concentrations in sludge are in the range 0.1-100 mg/kg dw with extreme values up to 700 mg/kg dw.

3.1.5.3 Estimation of PEC_{soil}

Toluene is not applied directly to the soil or crops, but it does occur in sewage sludge and may thus be applied to soil. The main manufacturers have informed that most sludges from production and processing are incinerated or landfilled, however, in a few instances it does end up on agricultural soil. Besides, the measured values of toluene in municipal sludge also indicate that toluene does find its way to sludge, which may be applied to agricultural soil. Toluene is also released to air and may undergo deposition to soil. The $PEC_{local, soil}$ is a summation of the concentration due to these two separate processes.

The values used are referring to the generic model and for the initial risk assessment the estimation procedures of the TGD are followed.

Concentration due to sludge application

The initial concentration in soil (C_{soil}) is governed by the input of the chemical through sludge application and later by input from aerial deposition.

The concentration in dry sewage sludge is calculated from the emission rate to water, the fraction of emission sorbed to sludge and the rate of sewage sludge production: according to the TGD and presented in **Table 3.49**.

Some of these values seem unrealistically high. According to the main manufacturers, the sludge from the production and processing industries where high levels may be anticipated is incinerated. The highest measured value of 370 mg/kg dw is observed in a municipal STP without serious known toluene production and/or processing. Therefore this value cannot be considered representative for a risk assessment on the production and use of toluene. On this basis it has been decided to use the EUSES estimations on soil concentrations.

Removal from soil

Toluene is removed from soil by degradation volatilisation and leaching. The estimated removal rates are:

Table 3.44 Removal rates from soil

Soil	Degradation rate (d^{-1})	Volatilisation rate (d^{-1})	Leaching rate (d^{-1})	Removal rate (d^{-1})
Agricultural soil	0.0077	0.119	0.000432	0.1271
Grassland	0.0077	0.238	0.000864	0.2465

Concentration in soil due to atmospheric deposition

The contribution to the soil concentration from atmospheric deposition is estimated from the highest emission rate from local source or STP. The deposition fluxes are presented in **Table 3.39**. The deposition to soil from atmospheric deposition alone is included in the **Table 3.45**.

Estimated local concentration in soil

The local concentration in soil for production sites and for production + on-site processing is based on air deposition alone since sludge is incinerated or landfilled. For site-specific processing sludge may be applied to soil at three sites and the sludge concentration and the resulting estimated soil concentration are presented (**Table 3.45**).

Table 3.45 Production, production+processing and processing site-specific estimations (APA)

Site	PECsoil local mg/kg dw
Production	
P1 [1)]	0.0002
P2	0.0105
P3	0.0233
P4	0.0003
P5	0.0054
P6	0.00003
P7	$8.55 \cdot 10^{-7}$
P8	0.0148
P9	0.0052
P10	0.0002
P11	0.0014

1) Production stopped in 1998

Table 3.45 continued overleaf

Table 3.45 continued Production, production+processing and processing site-specific estimations

Site	PECsoil local mg/kg dw
P12	0.0003
P13	0.0220
P14	0.0037
P15	0.0010
P16	0.0005
P17	0.0008
P18	0.0008
P19	0.0449
Production + Processing	
PP1	0.0003
PP2	0.0009
PP3	0.0004
PP4	0.0052
PP5	0.0037
PP7	0.0001
Processing	
Pc1	0.000342
Pc2	$8.27 \cdot 10^{-5}$
Pc3	0.0121
Pc4	$3.39 \cdot 10^{-5}$
Pc5	$1.84 \cdot 10^{-5}$
Pc6	$3.04 \cdot 10^{-6}$

Table 3.46 Summary statistics for soil PECs (mg/kg dry) at production sites

	Mean	Median	Min	Max	90th %	N
Local	$7.12 \cdot 10^{-3}$	$1.04 \cdot 10^{-3}$	$8.55 \cdot 10^{-7}$	$4.49 \cdot 10^{-2}$	$2.22 \cdot 10^{-2}$	19
Agricult.	$7.12 \cdot 10^{-3}$	$1.04 \cdot 10^{-3}$	$8.55 \cdot 10^{-7}$	$4.49 \cdot 10^{-2}$	$2.22 \cdot 10^{-2}$	19
Grassland	$3.67 \cdot 10^{-3}$	$5.35 \cdot 10^{-4}$	$4.41 \cdot 10^{-7}$	$2.31 \cdot 10^{-2}$	$2.22 \cdot 10^{-2}$	19

Table 3.47 Summary statistics for soil PECs (mg/kg dry) at production + processing sites

	Mean	Median	Min	Max	N
Local	$1.77 \cdot 10^{-3}$	$6.67 \cdot 10^{-4}$	$1.24 \cdot 10^{-4}$	$5.19 \cdot 10^{-3}$	6
Agricult.	$1.77 \cdot 10^{-3}$	$6.67 \cdot 10^{-4}$	$1.24 \cdot 10^{-4}$	$5.19 \cdot 10^{-3}$	6
Grassland	$9.11 \cdot 10^{-3}$	$4.80 \cdot 10^{-4}$	$6.39 \cdot 10^{-5}$	$2.67 \cdot 10^{-3}$	6

Table 3.48 Summary statistics for soil PECs (mg/kg dry) at processing sites

		Mean	Median	Min	Max	N
Local	air only	$2.10 \cdot 10^{-3}$	$5.83 \cdot 10^{-5}$	$3.04 \cdot 10^{-6}$	$1.21 \cdot 10^{-2}$	6
	air + sludge	$2.50 \cdot 10^{-1}$	$2.45 \cdot 10^{-1}$	$3.94 \cdot 10^{-2}$	$4.67 \cdot 10^{-1}$	3
Agric.	air only	$2.10 \cdot 10^{-3}$	$5.83 \cdot 10^{-5}$	$3.04 \cdot 10^{-6}$	$1.21 \cdot 10^{-2}$	6
	air + sludge	$4.28 \cdot 10^{-2}$	$4.18 \cdot 10^{-2}$	$6.74 \cdot 10^{-3}$	$7.98 \cdot 10^{-2}$	3
Grassland	air only	$1.08 \cdot 10^{-3}$	$3.01 \cdot 10^{-5}$	$1.57 \cdot 10^{-6}$	$6.25 \cdot 10^{-3}$	6
	air + sludge	$1.71 \cdot 10^{-2}$	$1.67 \cdot 10^{-2}$	$2.70 \cdot 10^{-3}$	$3.20 \cdot 10^{-2}$	3

The estimated concentrations in soil from atmospheric deposition and from sludge deposition for the generic sites not included in estimation were calculated by EUSES according to the TGD.

Table 3.49 Local concentrations in soil, generic scenarios

Scenario	Life stage	C_{sludge} (mg/kg dw)	$PEClocal_{soil}$ [1] (mg/kg)	$PEClocal_{agr.\ soil}$ (mg/kg)	$PEClocal_{grassland}$ (mg/kg)
1: Intermediates	Processing [2]	9,650	3.64	0.622	0.13
2: Basic chemicals	Formulation	3,980	1.51	0.266	0.0632
	Processing	80,600	30.5	5.25	1.14
3: Mineral oil and fuel	Formulation (10%)	2,580	0.977	0.172	0.041
	Private use	0.98	0.0007	0.0004	0.0003
4: Polymers	Formulation (10%)	901	0.341	0.0589	0.0130
	Processing	37.1	0.0145	0.0030	0.0011
5: Paint, etc.	Formulation (50%)	1,270	0.482	0.0833	0.0183
	Private use	0.479	0.0002	0.00006	0.00004
6: Basic chemical	Formulation	1,190	0.452	0.0796	0.0189
	Processing	36,200	13.7	2.36	0.5130
7: Personal / domestic	Formulation	162	0.061	0.0108	0.0026
	Private use	34.4	0.013	0.0023	0.0005
8: Pulp, paper and board	Formulation	437	0.166	0.0292	0.0070
	Processing	118	0.067	0.0296	0.0243
9: Textile	Processing	2,980	1.120	0.1920	0.0396
10: Other	Processing	199	0.080	0.0178	0.0078

[1] PEClocal for soil: 20 cm soil depth, 30 d averaging, sludge application 0.5 kg m^{-2}
PEClocal agricultural soil: 20 cm soil depth, 180 d averaging, sludge application 0.5 kg m^{-2}
PEC local grassland: 10 cm soil depth, 180 d averaging, sludge application 0.1 kg m^{-2}

[2] Scenario include sludge application. However, most large processors are assumed to incinerate the sludge or deposit sludge on landfill

Comparison of measured and estimated concentrations in soil

The estimated values are in general within the same order of level as the measured values e.g. the average value found in Dutch soil according to Sloof and Blokzijl (1988) cf. Section 3.1.5.1.

Estimated continental and regional PEC_{soil}

The EUSES estimated that:
PEC continental in agricultural soil was 0.079 µg/kg ww
PEC continental in natural soil was 0.011 µg/kg ww
PEC regional in agricultural soil was 0.703 µg/kg ww
PEC regional in natural soil was 0.033 µg/kg ww

Including continental emissions of non-isolated toluene from the use of gasoline.
PEC continental in agricultural soil was 0.095 µg/kg ww
PEC continental in natural soil was 0.028 µg/kg ww
PEC regional in agricultural soil was 0.749 µg/kg ww
PEC regional in natural soil was 0.081 µg/kg ww

The inclusion of the continental emission of non-isolated toluene from the use of gasoline has only little effect on continental and regional PECs for the soil compartment except for natural soils where PECs are increased with a factor 2-3.

Ground- and drinking water

The results on measurements in groundwater are summarised in **Table 3.50**.

Table 3.50 Measurements of toluene in groundwater

Location	Year	Concentration Range	mean	Reference
DK Groundwater n= 126 / 980 positive Water works well n= 113 / 1216	 1990-1997 1990-1997	 <DL-6.6 <DL-42	 median 0.1 µg/l median 0.1 µg/l	GEUS (1998)
DK Groundwater GRUMO, n=28	1990	0.1-0.42	0.12 µg/l	Nyegaard (1991)
NL Groundwater	before 1980	max. 300	µg/l	Rippen (1992)
NL Groundwater/percolate under waste tip 8 m depth, travelled 0 m 39 m depth, trav. 30 m 33 m depth, trav. 100 m 33 m depth,trav. 130 m			 300 µg/l 100 µg/l 0.3 µg/l 0.3 µg/l	Zoeteman et al. (1981) T½ based on 1.order 0.1 year T½ based on adsorption in study 0.3 year
USA Drinking water wells well water		max. 6400 5-100	µg/l µg/l	Pancorbo and Varney (1986) WHO (1985)
Canada drinking water raw water		 0-27 max. 15	 2 µg/l <1 µg/l	WHO (1985)

A water works using bank filtrated water measured a decreasing amount of toluene after bank passage. The time for filtration in the riverbanks was estimated at 4-6 weeks. The measured geometric mean in the river Rhine was 0.06 µg/l, after bank filtration (Uferfiltrat) 0.03 µg/l, after

ozonation of the raw water 0.03 µg/l and after filtration by active carbon below detection level at 0.03 µg/l (ARW, 1984).

In Canada, toluene has been detected in drinking water (the average and maximum concentration in treated Canadian water were reported to be 0.002 mg/l and 0.027 mg/l), well water (0.005-0.1 mg/l) and in raw water (0.001-0.015 mg/l (average and maximum values <0.001 and 0.015 mg/l) (WHO, 1985).

The available monitoring data are scarce. A national groundwater survey programme in Denmark (GRUMO) has detected over the years 1990 to 1997 toluene in 126 samples out of 980 samples with the maximum value of 6.6 µg/l and a median value of 0.1 µg/l. In a water works well monitoring program toluene was detected in 113 out of 1,216 samples with a maximum value of 42 µg/l and a median 0.1 µg/l (GEUS, 1998).

Estimated concentration in groundwater

An indication of the potential levels in groundwater is established by the concentration in the pore water of agricultural soil as a worst-case assumption according to the TGD.

Table 3.51 Local concentrations in groundwater

Scenario	Life stage	$PEClocal_{agr.\ Soil}$ (mg/kg)	$PEClocal_{grw}$ µg/l
1: Intermediates	Processing	0.622	190
2: Basic chemicals	Formulation	0.266	81
	Processing	5.25	1,610
3: Mineral	Formulation (10%)	0.172	52.7
oil and fuel	Private use	0.0004	0.11
4: Polymers	Formulation (10%)	0.0589	18
	Processing	0.0030	0.9
5: Paint, etc.	Formulation (50%)	0.0833	25.5
	Private use	0.00006	0.027
6: Basic chemical	Formulation	0.0796	24.4
	Processing	2.36	722
7: Personal /	Formulation	0.0108	3.31
domestic	Private use	0.0023	0.69
8: Pulp, Paper and	Formulation	0.0292	8.95
board	Processing	0.0296	9.07
9: Textile	Processing	0.1920	58.7
10: Other	Processing	0.0178	5.45

Comparison of measured and calculated concentrations in groundwater

It is highly questionable whether the available monitoring data may reflect the current levels of toluene in the various regions of EU. The toluene level measured in Danish groundwater (**Table 3.50**) seems to be three orders of magnitude below the estimated levels employing EUSES

for several use scenarios such as processing industry, paint, mineral oil and polymers formulation. However, the highest measured values are within the same range as the predicted values. The reason why most predicted values deviate substantially from the majority of monitoring data may probably be that EUSES employs worst-case assumptions which are not relevant at all for Danish conditions (e.g. groundwater 1 meter below fields where sludge containing toluene are being deposited and immediately being mixed with the top soil layer).

3.1.6 Secondary poisoning

Not relevant.

3.1.7 General comments regarding measured and estimated environmental concentrations

It is noted that the measured environmental concentrations also reflect other sources than the sources from current industrial production and processing of toluene, which are covered by this risk assessment report. The other sources of toluene are e.g. toluene emitted in exhaust gasses and natural sources such as forest fires and volcanos. Emissions from other sources to air may later be redeposited to the aquatic and terrestrial environment, cf. Section 3.1.1.1. Therefore, besides the general uncertainty regarding the proximity of the sites of the measurements to the emission sources and other uncertainties and variability in the monitoring data, the lack of a general discrepancy between the measured and estimated environmental concentrations presented in the previous sections may be surprising. However, the lack of general disagreements in most of the previous sections may illustrate that the employed PEC estimations, which only takes the toluene emissions from industrial production and processing but not toluene emissions from other sources (such as toluene in exhaust gases) into account, actually are performed according to a realistic worst-case concept.

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

3.2.1 Aquatic compartment

3.2.1.1 Toxicity test results

3.2.1.1.1 Short-term toxicity to fish

Several short-term studies on toluene toxicity have been performed. **Table 3.52** below is a summary of the results of acute toxicity tests on various species of fish. The included tests are considered representative and valid. When evaluating the validity of ecotoxicity tests results, it was considered whether standardised test methods have been followed but also whether the effect concentrations were measured or nominal, from flow-through, semi-static or static tests, from experiment with nominal concentrations only but performed in closed systems or open systems and whether or not solvents were used. When evaluating the test data validity information about the physico-chemical and environmental fate related properties of the substance were also considered. Generally, the results from static tests have been excluded due to the chemical nature of the substance (toluene is volatile) unless effect data are based on measured data or closed systems have been used. For example, the study by Pickering and Henderson (1966) was assessed to be less valid due to the use of nominal concentrations in a static study and the fact that the resulting LC50 for 4 fish species were twice as high as the LC50 observed in other studies. In a recent study on a range of organic test substances, it was generally shown that a liquid/liquid stock generator for archieving maximum stock water concentrations for acute fish toxicity tests generally delivered water concentrations lower than the water solubility of the substances (Kahl et al., 1999). For toluene, the maximum stock water concentrations was around half of the water solubility concentration, which is greater than all of the below reported aquatic effect concentrations, but which illustrates the uncertainty of basing effect concentrations on nominal concentrations maybe especially for volatile substances like toluene. During the test period in an open, static test system, a substantial decrease of toluene levels may occur by evaporation: up to 85% within 24 hours and up to 100% within 48-96 hours (Heijden et al., 1988) which mean that even initial measured concentration may result in underestimation of toxicity.

Aquatic organisms are exposed to toluene via respiration, resulting in changes in gill permeability and internal carbon dioxide poisoning. Toluene causes acute effects through the mechanism of narcosis (minimum toxicity).

The short-term toxicity studies for fish are summarised in **Table 3.52**.

Table 3.52 Short-term toxicity to fish

Species	Duration (hours)	LC50 (mg/l)	Method, conditions	Ref.
Pimephales promelas Fathead minnow	96 96 96	63 (55-72) embryos 29 (25-36) 1-day old 26 (18-31) 30-day old	flow-through, 25°C, 45 mg $CaCO_3$/l, pH 7.6, US EPA 1975. Measured conc.	Devlin et al. (1982)
Pimephales promelas Fathead minnow	96	31.7	Flow-through, 25°C, soft water (47 mg $CaCO_3$/l), pH 7.6, US EPA. Measured conc. EC_{50} < 12.1 mg/l	Geiger et al. (1990)
Carassius auratus Goldfish	96	22.8	Flow-through, 18°C, soft water, measured	Brenniman et al. (1976)
Lepomis macrochirus Bluegill sunfish	24 96	17 13	Static (closed), 22°C, 40 mg $CaCO_3$/l, pH 7.3, US EPA 1975, Nominal conc.	Buccafusca et al. (1981)
Cyprinodon variegatus Sheepshead minnow	96	13	Early life stage test MATC: 5 mg/l	Suter and Rosen (1988)
Oncorhynchus kisutch Coho salmon	96	5.5	Flow-through, 7.6-10.4°C, Measured. LC_{50}: 6.3 ml/l ~6.3*0.866=5.5 mg/l	Moles et al. (1981)
Oncorhynchus gorbuscha Pink salmon	24	5.4	Static, 12°C,seawater, Measured conc.	Thomas and Rice (1979)
Oncorhynchus gorbuscha Pink salmon	96	7 (6.4-8.1)	Static, 4-12°C, 28%.seawater, Measured conc.	Korn et al. (1979)
Morone saxatilis Striped bass	24 96	6.3 (7,300 ml/l)	Static, 16°C, 25o/oo seawater, Measured conc.	Benville and Korn (1977)

Several acute studies are performed on fish of which most do not consider the volatilisation potential of toluene. The studies included in **Table 3.52** are the studies considered valid for this risk assessment. The lowest LC50 (96 hours) value for fish was 5.5 mg/l in freshwater and 5.4 mg/l in seawater and both from valid tests using flow-through methods and measured concentrations. The value 5.5 mg/l is used in the risk assessment.

This value is in general agreement with the QSAR estimation according to the TGD (1996) which results in a fish (96 hours) LC50 22 mg/l for non-polar narcotic acting substances and QTOXMIN (Pedersen et al., 1995) which result in LC50 (96 hours) of 16 mg/l. The ECOSAR model, which is a computer program for estimating the ecotoxicity of industrial chemicals, based on structure activity relationships estimates a freshwater fish LC50 (96 hours) to be 16.8 mg/l for neutral organics (US EPA, 1994). These QSAR predictions are somewhat higher than the chosen experimental LC50 level concluded here.

3.2.1.1.2 Short-term toxicity to crustaceans

Table 3.53 Short-term toxicity to crustaceans

Species	Duration (hours)	L(E)C50 (mg/l)	Method, conditions	Valid	Ref.
Daphnia magna	48	11.5	static (closed system), Daphnids 4-6 days old, 23°C, pH 7, US EPA 1975. Nominal conc.	Valid	Bobra et al. (1983)
Daphnia magna	48	14.9	Static, 22°C, 100 mg $CaCO_3$/l, nominal conc. (measured ≤20% deviation)	Valid	Hermens (Adema, 1991)
Ceriodaphnia dubia	48	3.78	Renewed daily, closed, measured conc., EC50 (168 hrs) = 3.41 mg/l	Valid	Niederlehner et al. (1998)
Other crustaceans					
Cancer magister Crab	96	28	Flow-through	Valid	RIVM/Caldwell et al. (1976)
Artemia salina Brine shrimp	24	33	Static, closed, 25°C, seawater	Valid	Price et al. (1974)
Crangon franciscorum Bay shrimp	96	3.5	Static, 25 ‰ seawater	Valid ?	Benville and Korn (1977)
Palaemonetes pugio Larval grass shrimp	24	30.6; 25.8	Static, 20°C, APHA 1965, meas. Results 15 and 25 ppt salinity	Valid	Potera (1975)
Palaemonetes pugio Mature grass shrimp	24	20.2; 17.2	Static, 20°C, APHA 1965, meas. Results 15 and 25 ppt salinity	Valid	Potera (1975)
Nitocra spinipes Copepod	24	24.2; 74.2	Static, 20°C, APHA 1965, meas. Results 15 and 25 ppt salininity	Valid	Potera (1975)
Chaetogammarus marinus Marine crustacea	48	18	Static, Initial conc. 96% of nominal.	Valid	Adema (1991)

Several studies on crustaceans have been performed. Most of the studies have not taken the volatility into account. *Daphnia magna* in static tests (apart from the above mentioned) were observed to have LC50 values of 60-470 mg/l (average 278) which may be based on methodological problems (open or not sufficiently closed vessels). There are no indications in the test reports that concentrations have been measured during the tests. A study by Leblanc (1980) where the result of a static test and based on nominal concentrations was: EC50 (24 and 48 hours) 310 mg/l, was considered invalid. The EC50 (48 hours) values for *Daphnia* considered valid were 3.8 mg/l, 11.5 mg/l and 14.9 mg/l. It is noted that lower effect concentrations were observed with a marine species, the bay shrimp *Crangon franciscorum* (EC50 = 3.5 mg/l) and with the freshwater species *Ceriodaphnia dubia* (EC50 = 3.8 mg/l).

The experimental EC50 (48 hours) for Daphnia is in reasonable agreement with the QSAR estimations according to the TGD (1996) which results in a *Daphnia* (48 hours) EC50 13.4 mg/l for non-polar narcotic acting substances and QTOXMIN (Pedersen et al., 1995) which results in an EC50 (48 hours) of 17 mg/l. The ECOSAR model estimates the *Daphnia* LC50 (48 hours) to 18.8 mg/l for neutral organics (US EPA, 1994).

3.2.1.1.3 Toxicity to algae

Table 3.54 Short-term toxicity to algae

Species	Duration	EC50 (mg/l)	NOEC (mg/l)	Method, conditions	Reference
Selenastrum capricornutum	72 h 96 h		12.5 10	closed, nominal	Koch (1995) US EPA (1980)
Skeletonema costatum	72 h		10	closed, nominal	Heijden et al. (1988)
Chlorella sp. (salt marsh sp)	12 h	> 342	<34	closed system, 20°C, inhibition on photosynthesis/respiration ratio, APHA 1965	Potera (1975)
Chlorella vulgaris	72-96 h	207		closed, nominal 19°C, 400 ft candle,CO_2-uptake, $20 \cdot 10^4$ cells/ml	Hutchinson et al. (1980)
Chlamydomonas angulosa	72-96 h	134		closed, nominal 19°C, 400 ft candle,CO_2-uptake, $5 \cdot 10^4$ cells/ml	Hutchinson et al. (1980)
Chlorella vulgaris	24 h 10 d	245	 250	open system, nominal	Koch (1995), US EPA (1980)
Scenedesmus quadricauda	7 d	>433	>400	partly closed (metal caps), nominal	Bringmann and Kühn (1980)

In a study by Hutchinson et al. (1980), toluene effect on photosynthetic inhibition was tested on two algal cultures using ^{14}C-labelled toluene and glass stoppered flasks. Three-to-four day exponential phase cells were used at a cell density of $20 \cdot 10^4$ cells/ml for *Chlorella vulgaris* and $5 \cdot 10^4$ cells/ml for *Chlamydomonas angulosa* and the $^{14}CO_2$ uptake over three hours was used as an indication of photosynthesis. The EC50 values were 207 and 134 mg/l, respectively.

The concentrations in the algae studies were apparently all nominal. It was considered whether to reject the validity of the studies because of this. It is however not an absolute requirement according to OECD TG 201 to include analytical verification of the concentration of the test substance. Furthermore to use analytical measurement at the end of the test as a basis for the estimation of algae toxicity may underestimate the exposure, because of significant adsorption or bioaccumulation to the exponentially growing algae biomass. Based on that employment of a closed system is likely to control loss by volatilisation of toluene, all tests employing nominal concentrations and closed systems were considered valid. In two algae studies the NOECs were 10 mg/l, which is used as the basis for the assessment of toxicity toward algae.

These experimental values are around one order of magnitude higher than QSAR estimations according to the TGD (1996), which results in an algae (72-96 hours) EC50 of 8.8 mg/l and QTOXMIN (Pedersen et al., 1995), which results in EC50 (72 hours) of 11 mg/l. The ECOSAR model estimates the green algae EC50 (96 hours) to 12.2 mg/l and the NOEC value to 1.8 mg/l for neutral organics (US EPA, 1994).

3.2.1.1.4 Chronic toxicity to aquatic organisms

Table 3.55 Chronic toxicity to aquatic organisms

Species	Duration	EC50 mg/l	LOEC mg/l	NOEC mg/l	Method, conditions	Ref.
Fish						
Carassius auratus (fry)	30 d	14.6			FT, US EPA	Brenniman et al. (1976)
Pimephales promelas (embryo-larvae)	32 d		6	4	FT, measured	Devlin et al. (1982)
Oncorhynchus kisutch (fry)	40 d		3.2	1.4	FT, measured	Moles et al. (1981)
Cyprinodon variegatus (egg-juvenile)	28 d		7.7	3.2	FT, 25 0/00 salinity	Ward et al. (1981)
Oncorhynchus mykiss (ELS)	27 d	0.02	0.0029		FT, meas., LC10: 2.9 µg/l	Black et al. (1982) cf. text below
Oncorhynchus mykiss (ELS)	27 d		4.4/10.8	1.4/4.7	FT, meas, two tests	WRc in UK, 2 test results from an attempt to reproduce Black et al. study (1982)
Daphnia						
Daphnia magna	21 d			1.0-2.0	S-S, closed syst.,meas.	Kühn et al. (1989) (2.0 mg/l based on nominal concentration. 1.0 mg/l lowest measured concentration)
Daphnia magna (immobilisation)	16 d	3.8 *			S-S, closed, meas.	Hermens et al. (1984) (*EC50 value calculated from QSAR, NOEC pers comm. H Canton (Heijden et al., 1988))
Daphnia magna (reproduction)	16 d	1.4 *		0.53	S-S,*QSAR, pers.comm	”
Ceriodaphnia dubia (reproduction)	7 d	3.23	2.76	0.74	S-S, measured conc.	Niederlehner et al. (1998)

FT: Flow-through
S-S: Semi -static

The chronic toxicity to fish was studied on *Pimephales promelas* in a 32-day embryo-larval flow-through study using the weight of young fish as endpoint. LOEC was observed at 6 mg/l and NOEC set to 4 mg/l. The actual concentrations were measured (Devlin et al., 1980). Moles (1981) observed that growth reduction was significant at 3.18 mg toluene/l in a 40-day flow-through study using Coho salmon fry. The lowest chronic fish toxicity LOEC was thus 3.18 mg/l and employing the recommended procedure for extrapolation to NOEC by TGD equivalent of a NOEC of 1.4 mg/l.

Black et al. (1982) found in an early-life-stage test with rainbow trout an LC50 of 20 µg/l and a 27-day LC10 of 2.9 µg/l. In this study, the eggs were exposed in a flow-through system to the test substance within 30 minutes of fertilisation. The concentration was measured daily. A study attempting to reproduce the results by Black et al. conducted by WRC (1991) in the UK reports NOEC values in two independent studies of 1.4 and 4.7 mg/l, respectively. Experts have examined both studies. Reasons for the large discrepancy between the original and new studies were not found and both studies are regarded as valid. Even though an evaluation of the original study by Black et al. (1982) did not reveal any obvious invalidating factors, this study seems not reasonable to include for consideration of the long-term NOEC for fish, because four other independently conducted long-term valid fish studies (including one with the same fish species) report NOECs within the same range but several magnitudes higher than the NOEC reported by

Black et al. Thus a chronic fish NOEC of 1.4 mg/l is concluded based on the available valid experimental data.

The chronic toxicity to *Daphnia* reproduction was studied in a 21-day semi-static study using closed vessels (Kühn et al., 1989). Using measured concentrations the NOEC was 1 mg/l (Kühn et al., 1989). Hermens et al. (1984) used renewal (semi-static) conditions in a 16-day *Daphnia* reproduction study and observed a NOEC of 0.53 mg/l. The Hermens et al. study is a QSAR study and the experimental procedures are not quite clear.

The reproductive toxicity study on *Ceriodaphnia dubia* in a 7-day semi-static closed glass vial system reports a NOEC of 0.74 mg/l, a LOEC of 2.76 mg/l and an EC50 of 3.23 mg/l.

Based on this a chronic NOEC for reproduction to crustaceans of 0.74 mg/l is used and because this is the lowest reported valid chronic effect concentration of aquatic species carried over for derivation of $PNEC_{water}$. The value is supported by being approximately the average of the two *Daphnia magna* studies and a little higher than the QSAR estimated value for long-term *Daphnia* toxicity.

The reported experimental aquatic effect concentrations are in general agreement with QSAR estimations of values for chronic toxicity on fish and *Daphnia* by the TGD for non-polar acting substances of 2.0 mg/l (30 days, FELST) and 2.3 mg/l (16 days, reproduction), respectively, and with ECOSAR estimations (US EPA, 1994) where chronic values were: fish 30-day NOEC 2.4 mg/l, Daphnia 16-day NOEC 1.3 mg/l.

Another EU body (CSTE) has previously performed an evaluation of short- and long-term aquatic toxicity data on toluene [8].

3.2.1.2 PNEC for aquatic organisms

A full base set of acute EC50 from fish, daphnia and algae and the long-term NOECs from fish, Daphnia and algae are available. The assessment factor to apply is 10 according to the TGD on the lowest long-term NOEC of 0.74 mg/l on *Ceriodaphnia* reproduction.

$PNEC_{aquatic\ organisms} = 0.74/10 = 0.074$ mg/l.

[8] CSTEE (1993) recommends a value of 10 µg/l for toluene as water quality objective (WQO) value defined as a maximum acceptable concentration that should not be exceeded to avoid hazards to the aquatic environment, including the marine environment. Thus, this evaluation also takes into account the difference in characteristics between salt water and fresh water (Council Directive 76/464/EEC, art.6.2). Other differences between the current PNEC and the WQO may be caused by the methods used in calculating WQO and PNEC. WQCs are in general given as the lower rounded value of the PNEC.

3.2.1.3 Toxicity to microorganisms in STP

Table 3.56 Toxicity to microorganisms relevant for STP

Species	Duration (hours)	EC50 (mg/l)	NOEC (mg/l)	Method, conditions (nominal conc.)	Reference
Entosiphon sulcatum (protozoa)	72 h		456	Static (partly closed, metal caps), 25°C, US EPA	Bringman and Kühn (1980) (partly close: flasks stoppered with cotton-lined plastic caps)
Tetrahymena pyriformis	48 h	289		Static	Schultz et al. (1996)
Pseudomonas putida (Bacteria)	16 h		29	Static (partly closed,cotton lined plastic caps), 25°C,	Bringman and Kühn (1980) (partly close: flasks stoppered with cotton-lined plastic caps)
Pseudomonas putida	3 h	193		Static,30°C (LD50: 2.1 mM)	Heipieper et al. (1995)
Nitrosomonas (nitrification)	24 h	84		eq to ISO/DIS 9609,	Blum and Speece (1991)
Aerobic heterotrophs (from mixed liquor of an activated sludge STP)	49 h	110		Static, closed bottles	Blum and Speece (1991)
Activated sludge	12 h	292		Respiration	Nirmalakhandan et al. (1994)
Polytox (mixture of 12 stream bacteria): respiration	6 h	207 189		Batch reactor, respirometry, 25°C	Nirmalakhandan et al. (1994)

The concentrations were not measured. Bringman and Kühn (1980) present the results as toxicity thresholds that are equal to NOEC. The studies were performed in partly closed vessels.

The effect on activated sludge was studied using a sludge from a municipal STP in a respirometric test procedure where the respiration from capped reactors was measured during 12 hours. The IC50 was calculated to be 292 mg/l. Using Polytox (standardised microbial culture) the IC50 (6 hours) was 207 mg/l (Nirmalakhandan et al., 1994).

The toxicity to each of 3 bacterial groups: aerobic heterotrophs, *Nitrosomonas* and methanogens, were studied by Blum and Speece (1991). All assays were carried out in sealed serum bottles under similar conditions. Water and the inoculum were obtained from the mixed liquor of an activated sludge wastewater treatment plant. The 50% inhibition concentration relative to controls (IC50) was 84 mg/l for *Nitrosomonas* (nitrification) and 580 mg/l for methanogens. IC50 for aerobic heterotrophs was 110 mg/l (respiration*)* (Blum and Speece, 1991).

3.2.1.4 PNEC for microorganisms

The cell density inhibition studies on *Pseudomonas putida* resulted in a NOEC (16 hours) of 29 mg/l. Using an assessment factor of 1 would result in a $PNEC_{microorganisms}$ of 29 mg/l. However, using the values from the *P. putida* 3-hour EC50 test and an assessment factor of 10 would result in a $PNEC_{microorganisms}$ of 19.3 mg/l.

The studies on degradation in activated sludge used concentrations of 1.5 and 10 mg/l and no inhibitions seemed to appear; though the degradation at 1.5 mg/l was slightly faster than at 10 mg/l.

According to the TGD, available data suggest the following range of increasing sensitivity: respiration test <*P. putida* inhibition test < inhibition of nitrification.

For toluene the respiration test gives EC50 values that vary between 110 to 292 mg/l. The lowest value is therefore used in the risk assessment

The EC50 for respiration of microorganisms in STPs was 110 mg/l and using an assessment factor of 100 would result in:

$PNEC_{microorganisms}$ = 110/100 = 1.1 mg/l (respiration)

However inhibition of microbial nitrification is the preferred endpoint for STPs, because this process is more sensitive than inhibition of microbial respiration. Using the inhibition of nitrification and the assessment factor of 10 results in a:

$PNEC_{microorganisms}$ = 84/10 = 8.4 mg/l (nitrification), which will be used in the risk characterisation.

3.2.1.5 Sediment

No studies on sediment dwelling organisms were available and because log Kow is less than 5, the PNECsed is not calculated. The reason is that employment of the equilibrium partition method and the PNECsed calculation method would result in the same PEC/PNEC ratio for sediment dwelling organisms as for pelagic organisms.

3.2.2 Atmosphere

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

Direct effects on plants

In plant studies conducted by an American institution in 1982, for instance for carrots, tomatoes and barley, 11.5 mg/m^3 toluene in air for more than 30 minutes is claimed to be toxic (Overcash et al., 1982). No details are given. A new study with much more details refer to much higher toxic air concentrations for toluene. Christ (1996) investigated the harmful effects of 49 organic substances including toluene on various plants of approximately 10 cm length (tomato, sunflower, soya, Tropaeolum, sugar beet and wheat) in short-term experiments with 3 hours of air exposure. Visible effects occurred at air concentrations between 15 and 50 g/m^3, effects on growth at 1 g/m^3 and on photosynthesis at 3.6 g/m^3.

Currier (1951) examined effects on tomato, carrot and barley of exposure to high air concentrations of toluene in short-term experiments (15 – 30 min.). Leaf damages were observed in barley at a concentration of 6,400 mg/m^3, and extensive leaf damages at a concentration of 12,000 mg/m^3 in tomato, carrot and barley.

Sauter and Pambor (1989) examined degradation of the epistomatal wax layer in spruce (*Picea abies*) and fir (*Abies alba*) needles exposed at roadsides. A comparable degradation of the epistomatal wax layer was observed when shoots of spruce and fir were incubated in enclosed 1 l beakers together with paper towel moistened with 1 ml of benzene or xylene for three days. However, no degradation was observed when shoots were exposed to toluene in a similar experiment but no precise information is available about the air exposure concentration.

In a study by Schubert et al. (1992) tobacco pollen germination was examined. At a concentration of 29,000 mg/m^3 the germination was reduced by 50% after 2 hours of exposure.

One screening study with 14-day-exposure period of toluene gas exposure was found. Trifolium, radish, cress, bean and tobacco were exposed and the maximum concentration without any observed effect was 60 mg/m^3 (Van Haut et al., 1979). The parameter examined was growth recorded as increase in fresh and dry weight. Authors conclude that "toluene…. are practically inactive and thus of no concern with regard to vegetation oriented protective matters".

The phytotoxicity of hydrocarbons o.a. toluene in a mixture with white oil was tested by spraying a 0.75% toluene emulsion on cucumber. The phytotoxic symptoms 10-14 days after spraying were recorded in a point system ("10": dead, "5": moderately phytotoxic, "2": slight damage and "0" undamaged). Toluene was given the point 3 to 5 with a mean value of 3.6 point, i.e. effect severity rated between "slight" and "moderate" damage (Heringa, 1951). This study seems not relevant.

To conclude, toluene seems not to be of concern with regard to plant toxicity exposed via air except at very high concentrations. No formal PNEC will be established because of lack of appropriate long-term studies, however, the NOEC of 60 mg/m^3 based after a 14-day exposure period given in Van Haut et al. (1979) can be used to evaluate the risk for terrestrial plants exposed via air.

Indirect effects

Toluene contributes to ozone formation in the surface near atmosphere (Derwent et al., 1998), and may also contribute to the formation other harmful substances e.g. DNOC. 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 toluene 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 toluene 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 troposheric 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 CO_2 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 effects are described in the relevant human health section.

The current threshold values in use in the EU according to Directive 92/72/EEC are shown in **Table 3.57**.

Table 3.57 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 current 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

In plants, a yield decrease was observed after 2-4 weeks of exposure to 1,000 mg/kg soil w/w (Heijden et al., 1988).

For maize, fescue and soybean, 200 to 20,000 mg/kg soil is toxic depending on soil type and plant species: A 10% yield reduction on a sand soil was evident at 200 ppm for maize, 800 ppm in soybean and 2,000 ppm in fescue. At 2,000 ppm or more there was at least 50% reduction in the fresh weight of all three crops. The lowest LOEC for phytotoxic effects observed was thus 200 mg/kg soil dw (Overcash et al., 1982).

For lettuce, *Lactuca sativa*, a 14-day EC50 was >1,000 mg/kg soil (Hulzebos et al., 1993). The study was performed according to OECD TG 208 in an agricultural loam (pH 7.5, org. matter 1.4%, clay 12%, moisture-holding capacity 80%). The toluene content was analysed at the start of the test but not at the end. The EC50 value was based on initial nominal concentration, fresh weight biomass (seedlings) after 7 and 14 days. The measured initial concentration of toluene in soil is stated to be <50% of the nominal. The reported EC50 value by Hulzebos et al. (1991) is therefore likely underestimated and, thus, regarded as invalid for risk assessment.

The combined effect of volatilisation and degradation was observed in a study cited in Overcash et al. (1982) where 0.1% to max. 6.25% of applied toluene remained in a clay loam soil 1 week after application.

The effects on earthworms are studied on *Eisenia foetida* in a 28-day study using artificial soil. LC50 was observed to be >150 but <280 mg/kg soil. NOEC on mortality and cocoon production was ≤150 and <250 mg/kg, respectively. However, the earthworm condition (visual inspection) showed a NOEC between 15 and 50 mg/kg soil (Heijden et al., 1988).

The soil microbial processes respiration and ammonification were affected at high concentrations in loam and humid sands. The NOEC values were found between 360 and 1,300 mg/kg soil for respiration and between 100 and 1,100 mg/kg for ammonification. The nitrification in the same two soils was observed to be more sensitive as the NOEC value in a 28-day test was < 26 mg/kg soil dry weight (Heijden et al., 1988).

In another experiment, NOEC >25 mg/kg soil for soil respiration and N-mineralisation measured in experiments with frequent sampling between 1.5 and 80 days, and 7 and 56 days, respectively (Kirchmann et al., 1991). However, analysis of the soil immediately after addition of toluene showed that very low concentrations of toluene were found, 0.09 mg/kg after the addition of 25 mg/kg and no detectable toluene after the addition of 0.5 mg/kg. It was assumed that toluene was volatilised during addition and mixture with the soil. Thus, the Kirchmann et al. study demonstrates that toluene <0.09 mg/kg soil had no effect on respiration and nitrification.

The microbial toxicity in soil medium was studied in a Polytox test. The test culture consisted of a mix of 12 strains of aerobic microbial cultures. The test medium was a sandy loam soil collected from a depth of 15 cm at an agricultural field. After addition of the cell culture to soils at varying moisture capacities, the respiration up to 10 hours was measured in the laboratory at 25°C, and the inhibition relative to control calculated. IC50 was 310, 370, 380 and 430 mg/kg for soil at 33%, 50%, 80% and 100% moisture holding capacity, respectively (Regno et al., 1998).

3.2.3.1 PNEC for soil organisms

In a single 28-day study on *Lactuca sativa,* a yield decrease was observed at 1,000 mg/kg soil. In a 28-day study on earthworms, mortality, cocoon production and visual conditions were affected and the NOEC ranged between 15 and 50 mg/kg. In 28-day studies on soil microorganisms, the process of nitrification was the most affected process with a NOEC < 26 mg/kg soil.

For earthworm, the NOEC (28-day) for mortality and cocoon production was ≤150 and <280 mg/kg, respectively. However, based on visual inspection on the earthworm condition, the NOEC was by the authors concluded to be between 15 and 50 mg/kg. For microorganism nitrification, the NOEC (28-day) was <26 mg/kg. Thus both the earthworm and the microorganism studies indicate the "true" NOEC in these studies were below 150 and 26 mg/kg, respectively. The inclusion of cocoon production in the earthworm study and extending the study period to 28 days (short-term studies usually 14 days) may support that the results be considered a long-term study. For microorganisms, longer-term studies tend to result in higher NOECs than short-term studies, whereas the opposite generally applies to studies with multicellular longer living organisms like earthworms. Furthermore, use of long-term test data on microorganisms in the context of effect assessment on soil organisms is presently not explicitly covered by the recommendations given in the TGD. Based on these considerations and since the reported NOEC for nitrification was <26 mg/kg, 15 mg/kg from the earthworm study is used in the risk

assessment. Thus, based on two long-term studies on plants and earthworm an assessment factor of 50 may be used to reach an indicative $PNEC_{soil}$:

$PNEC_{soil} = 15/50 = 0.3$ mg/kg.

For comparison this value is in close agreement with estimation of PNEC employing the equilibrium partitioning method:

$PNEC_{soil} = (K_{soil\text{-}water}/RHO_{soil}) \cdot PNEC_{water} \cdot 1{,}000 = 0.26$ mg/kg w/w.

3.2.4 Secondary poisoning

Not relevant because the worst-case BCF for fish is <100. Furthermore, the substance has not a high lipophilicity and seems to be readily degradable.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

3.3.1.1 Surface water

The regional PEC/PNEC is 0.04 for the aquatic compartment.

The PEClocal $_{water}$ is presented in **Table 3.58** along with the PEC/PNEC-ratios.

The PNEC $_{aquatic\ organisms}$ is 0.74/ 10 = 0.074 mg/l.

3.3.1.1.1 Production

Table 3.58 Risk characterisation for surface water at production sites and combined production and processing sites

a) Summary of local PECs (mg/l) for surface water at production sites

Production sites	Mean	Median	Min	Max	90th %	N
PEC water (mg/l)	0.03	$5.7 \cdot 10^{-6}$	0.00	0.590	0.016	19
PEC/PNEC	0.5	<0.01	-	8.0	0.2	

b) Summary of local PECs (mg/l) for surface water at production + processing sites

Production + processing	Mean	Median	Min	Max	N
PEC water (mg/l)	0.14	0.00025	$1.00 \cdot 10^{-8}$	0.830	6
PEC/PNEC	1.9	<0.01	<0.01	11.2	

c) Site-specific PEC/PNEC ratio for surface water estimated for production and, production + on-site processing (APA, 2000). Bold values in the PEC_{water} column indicate that defaults have been overwritten by measured data

Site	PEC water mg/l	PEC/PNEC water mg/l	Conclusion
Production			
P1 [1)]	0.010	0.14	ii
P2	$1.1 \cdot 10^{-3}$	0.015	ii
P3	$1.39 \cdot 10^{-7}$	$1.88 \cdot 10^{-6}$	ii
P4	0.002	0.027	ii
P5	0.040	0.546	**iii** [2)]
P6	$5.70 \cdot 10^{-6}$	$7.7 \cdot 10^{-5}$	ii
P7	0.001	0.013	ii

Table 3.58 c) continued overleaf

Table 3.58 c) continued Site-specific PEC/PNEC ratio for surface water estimated for production and, production + on-site processing. (APA, 2000). Bold values indicate that defaults have been overwritten by measured data

Site	PEC water mg/l	PEC/PNEC water mg/l	Conclusion
P8	$3.90 \cdot 10^{-6}$	$5.27 \cdot 10^{-5}$	ii
P9	$3.52 \cdot 10^{-6}$	$4.76 \cdot 10^{-5}$	ii
P10	$1.80 \cdot 10^{-6}$	$2.43 \cdot 10^{-5}$	ii
P11	$4.17 \cdot 10^{-9}$	$5.64 \cdot 10^{-8}$	ii
P12	$3.65 \cdot 10^{-5}$	$4.93 \cdot 10^{-4}$	ii
P13	**0.00**	<<	ii
P14	0.59	7.97	**iii**
P15	$2.00 \cdot 10^{-8}$	$2.7 \cdot 10^{-7}$	ii
P16	$3.33 \cdot 10^{-5}$	$4.5 \cdot 10^{-4}$	ii
P17	$1.00 \cdot 10^{-8}$	$1{,}35 \cdot 10^{-7}$	ii
P18	$2.97 \cdot 10^{-5}$	$4.04 \cdot 10^{-4}$	ii
P19	**0.0014**	0.0189	ii
Production + Processing			
PP1	0.000136	0.00183	ii
PP2	0.000369	0.00499	ii
PP3	0.000515	0.00696	ii
PP4	0.8300	11.2	**iii**
PP5	$1.00 \cdot 10^{-8}$	$1.35 \cdot 10^{-7}$	ii
PP7	$5.32 \cdot 10^{-6}$	$7.19 \cdot 10^{-5}$	ii

1) Production stopped in 1998
2) No information available on the basis for the site-specific dilution factor. Assuming the given dilution is a mean value a PEC/PNEC > 1 would be the result of low flow conditions

Risk characterisation for production

Conclusion (iii) applies for production sites P5, P14.

Conclusion (ii) applies for production sites P1, P2, P3, P4, P6, P7, P8, P9, P10, P11, P12, P13, P15, P16, P17, P18, P19.

Risk characterisation for combined production and processing

Conclusion (iii) applies for site PP4.

Conclusion (ii) applies to PP1, PP2, PP3, PP5, PP7.

3.3.1.1.2 Off-site processing

Table 3.59 Risk characterisation for surface water at processing sites

a) Summary of local PECs (mg/l) for surface water at some processing sites (APA, 2000)

Processing	Mean	Median	Min	Max	N
PEC water (mg/l)	0.312	0.0069	$1.36 \cdot 10^{-5}$	1.83	6
PEC/PNEC	4.2	0.1	<0.01	24.7	

b) Local PECs (mg/l) for surface water at some processing sites (APA, 2000)

Site	PEC water mg/l	PEC/PNEC water mg/l	Conclusion
Processing			
Pc1	0.024	0.324	ii
Pc2	0.013	0.175	ii
Pc3	1.830	24.72	**iii**
Pc4	$3.22 \cdot 10^{-4}$	<0.01	ii
Pc5	$1.28 \cdot 10^{-3}$	0.017	ii
Pc6	$1.36 \cdot 10^{-5}$	<0.01	ii

c) Summary of local PECs (mg/l) for surface water at processing sites identified in De Witt (1999). PEC estimation based on site capacity and TGD defaults (APA, 2000)

Processing	Mean	Median	Min	Max	90th %	N
PEC water (mg/l)	0.779	0.435	0.038	2.781	2.306	27
PEC/PNEC	10.5	5.9	0.5	37.6	31.2	

Risk characterisation for off-site processing

Conclusion (iii) applies for processing site Pc3.

Conclusion (ii) applies for processing sites Pc1, Pc2, Pc4, Pc5 and Pc6.

Generic risk characterisation

Conclusion (iii) also applies for the generic scenario 1 (use as an intermediate) and most large identified processors (see **Table 3.27**) that presumably cover the major part of the total tonnage processed in the EU.

3.3.1.1.3 Downstream uses

Table 3.60 Estimations of PEC/PNEC local surface water

Scenario	Life stage	PEC_{water} (mg/l)	$PEC/PNEC_{water}$
1: Intermediates	Processing	1.320	**17.8**
2: Basic chemicals	Formulation	0.549	**7.4**
	Processing	9.040	**122.2**
3: Mineral	Formulation (10%)	0.357	**4.8**
oil and fuel	Private use	0.004	0.1
4: Polymers	Formulation (10%)	0.129	**1.7**
	Processing	0.011	0.2
5: Paint, etc.	Formulation (50%)	0.180	**2.4**
	Private use	0.006	0.1
6: Basic chemical	Formulation	0.169	**2.3**
	Processing	4.940	**66.8**
7: Personal /	Formulation	0.028	0.4
domestic	Private use	0.011	0.2
8: Pulp, Paper and	Formulation	0.066	0.9
board	Processing	0.022	0.3
9: Textile	Processing	0.413	**5.6**
10: Other	Processing	0.033	0.5

Bold: risk indicated

For downstream uses the scenarios in **Table 3.60** indicate that locally there may be risks for aquatic organisms for:

- intermediates, processing (scenario 1),
- basic chemicals (including processing aid, "extraction" agent or solvent), processing and formulation (scenarios 2 and 6),
- mineral oil and fuel formulation (scenario 3),
- formulation of polymers (scenario 4),
- formulation of paints (scenario 5),
- textile processing (scenario 9).

For these scenarios, **conclusion (iii)** applies, based on the recognition that it is unlikely that sufficient information can be gathered and be considered representative for the numerous downstream uses to exclude a risk.

3.3.1.2 STP, microorganisms

The preferred endpoint to be used for risk characterisation is inhibition of nitrification:
$PNEC_{STP,\ microorganisms}$ = 8.4 mg/l.

Table 3.61 Site-specific PEC/PNEC ratio for STP, microorganisms estimated for production, production + on-site processing, and processing off-site (APA, 2000)
Bold values in the $C_{STP, effl}$ column indicate that defaults have been overwritten by measured data

Site	$C_{STP, effl}$ mg/l	PEC/PNEC STP, microorganisms (nitrification)	Conclusion
Production			
P1 [1)]	0.30	0.035	ii
P2	0.71	0.09	ii
P3	**0.005**	<0.01	ii
P4	**0.050**	0.01	ii
P5	0.910	0.11	ii
P6	0.256	0.03	ii
P7	**0.01**	<0.01	ii
P8	**0.013**	<0.01	ii
P9	0.290	0.03	ii
P10	**0.010**	<0.01	ii
P11	**0.0005**	<0.01	ii
P12	**0.000365**	<0.01	ii
P13	0	<<	ii
P14	5.900	0.70	ii
P15	**0.020**	<0.01	ii
P16	**0.005**	<0.01	ii
P17	**0.010**	<0.01	ii
P18	**0.050**	0.01	ii
P19	**0.420**	0.05	ii
Production + Processing			
PP1	**0.003**	<0.01	ii
PP2	0.057	0.01	ii
PP3	0.079	0.01	ii
PP4	8.330	0.99	ii
PP5	**0.010**	<0.01	ii
PP7	$3.47 \cdot 10\text{-}4$	<0.01	ii
Processing			
Pc1	0.24	0.03	ii
Pc2	0.12	0.01	ii
Pc3	18.322	**2.18**	**iii**
Pc4	**0.010**	<0.01	ii
Pc5	**0.010**	<0.01	ii
Pc6	0.025	<0.01	ii

[1)] Production stopped in 1998

Risk characterisation for production

Conclusion (ii) applies for all production sites.

Site-specific risk characterisation for combined production and processing

Conclusion (ii) applies to PP1, PP2, PP3, PP4, PP5, PP7.

Risk characterisation for off-site processing and generic risk characterisation

Conclusion (iii) applies for processing site Pc3 and most large identified processors (**Table 3.27**) that presumably cover the major part of the total tonnage processed in the EU.

Conclusion (iii) also applies for the generic scenario 1 (use as an intermediate).

Conclusion (ii) applies for processing sites Pc1, Pc2, Pc4, Pc5 and Pc6.

Downstream uses

Table 3.62 Estimations of PEC/PNEC for microorganisms in STPs

Scenario	Life stage	$C_{STP, effluent}$ (mg/l)	$PEC/PNEC_{microorganism}$ (nitrification)	Conclusion
1: Intermediates	Processing	13.2	1.57	**iii**
2: Basic chemicals	Formulation	5.43	0.65	ii
	Processing	110	13.10	**iii**
3: Mineral	Formulation (10%)	3.51	0.42	ii
Oil and fuel	Private use	0.0013	<0.01	ii
4: Polymers	Formulation (10%)	1.23	0.15	ii
	Processing	0.05	0.01	ii
5: Paint, etc.	Formulation (50%)	1.74	0.21	ii
	Private use	0.0007	<0.01	ii
6: Basic chemical	Formulation	1.63	0.19	ii
	Processing	49.4	5.88	**iii**
7: Personal /	Formulation	0.22	0.03	ii
Domestic	Private use	0.047	0.01	ii
8: Pulp, paper and	Formulation	0.596	0.07	ii
Board	Processing	0.161	0.02	ii
9: Textile	Processing	4.06	0.48	ii
10: Other	Processing	0.27	0.03	ii

The results in **Table 3.62** indicate that locally there may be risks for microorganisms in STPs from several downstream uses of toluene (**conclusion (iii)**):

- industry use as an intermediate (scenario 1),
- industry use as basic chemicals (scenarios 2 and 6).

3.3.1.3 Results of the risk characterisation for the aquatic environment

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

This conclusion applies to a number of production and processing sites where insufficient information has been available to exclude a risk.

This conclusion applies to the use of toluene in

- industry use as an intermediate and as basic chemicals (scenarios 1, 2 and 6),
- mineral oil and fuel formulation (scenario 3),
- formulation of polymers (scenario 4),
- formulation of paints (scenario 5),
- textile processing (scenario 9).

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

This conclusion applies to a number of production and processing sites where sufficient information has been available to exclude a risk.

3.3.2 Atmosphere

Due to the high-vapour pressure of toluene the atmosphere is a major recipient of toluene. The photodegradation by photochemical oxidative degradation/ ransformation is fast with a half-life of approximately 2 days. Atmospheric concentrations on a regional scale are in the $\mu g/m^3$ level, while on local scale at the perimeter of production/processing plants average levels are estimated to be at $\mu g/m^3$ level up to more than 1 mg/m^3. Local atmospheric concentrations due to emission of toluene in exhaust gases expelled from motor vehicles are expected to be less than the atmospheric concentrations in close proximity of larger industrial plants.

Some information regarding short-term effects of toluene on plants has been obtained indicating little concern at concentrations below 60 mg/m^3 and most studies indicate that short-term effects occur at much higher exposure levels. No information on possible effects caused by long-term exposure (more than 14 days) is at present available. The TGD (1996) does not give guidance on how to assess the risk for plants exposed via air e.g. how to apply assessment factors or when to request a plant fumigation test. The margins of safety (MOS) using the 60 mg/m^3 (14-day exposure) as the NOEC are in general two to three orders of magnitude or higher. For the generic scenarios “Basic chemicals, processing” and “Pulp, paper and board, processing” the MOS are 25-70. Also for some identified production or processing sites the MOS are lower than two orders of magnitude using TGD default release fractions on site-specific production or processing volumes. However, taking all the available information into account it seems reasonable, on borderline and as no guidance is given in the TGD (1996) to conclude that there is no risk for plants at the present exposure levels.

It is known that toluene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone and volatile air pollutants e.g. DNOC. The photochemically 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 NOx, 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 toluene may differ substantially between different regions in the EU.

The industrial use of the commercial product toluene contributes significantly to the overall emission of toluene, however, emission of toluene 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 toluene from the use and production of the commercial product toluene may be in the order of 3% 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 toluene. Even a simple evaluation of the photochemical ozone creation potential of the emission of isolated toluene is difficult to perform, when the emission pattern of individual NMVOCs is not available.

The current risk assessment does not cover non-isolated toluene. Thus evaluation of the possible effects of emission of toluene from motor vehicles is outside the scope of this risk assessment. However, on the basis of monitoring of NMVOCs in street air there is indication that non-isolated can contribute substantially (~ 30%) to the overall ozone formation due to NMVOCs.

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 $\mu g/m^3$, 8-hour 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 ($\geq$240 $\mu g/m^3$) were recorded in Italy and Greece (WHO, 1999, cf. also De Leeuw et al., 1996).

In 1999, the threshold for information of the public in the EU (180 $\mu g/m^3$, 1-hour average) was not exceeded in 4 Member States while up to 70% of the monitoring stations in other Member States did exceed this threshold (Sluyter and Camu, 1999). On average 27% of all monitoring stations in the EU did exceed the threshold. The number of days that the threshold was 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 $\mu g/m^3$, 8-hour average) has been estimated by WHO (1999). The 1995 summer ozone incidence is estimated to have caused 1,500-3,700 deaths (0.1-0.2% of all deaths) and further 300-1,000 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 $\mu g/m^3$ level.” (WHO, 1999).

If these figures are used to estimate the impact of emissions from the production and use of the commercial product toluene through formation of ozone, then this emission may have caused in the order of 100 deaths in the summer of 1995 if a linear relationship exists between the emission of toluene, the emission of NMVOCs and the creation of ozone. Similarly, the vegetation and

wildlife may be severely affected by ozone incidences and toluene is likely to contribute to these effects.

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

Cf. also Section 4.1.3.4.

Results of the risk characterisation for the atmosphere

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

This conclusion applies in the context of the Council Regulation (EEC) 793/93 of Existing Substances to the contribution of the commercial product toluene 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 toluene 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 or testing or risk reduction measures beyond those which are being applied already.

This conclusion applies to plants exposed via air.

3.3.3 Terrestrial compartment

The volatility and relatively fast degradation under aerobic conditions suggest that toluene would have a relatively short half-life on soil surfaces.

The PEC/PNEC (soil) is calculated based on the few data on terrestrial organisms.
$PNEC_{soil} = 15 / 50 = 0.3$ mg/kg.

Table 3.63 Risk characterisation for soil

a) Summary statistics for soil PECs (mg/kg dry) at production sites

	Mean	Median	Min	Max	90th %
Local PEC soil (mg/kg)	0.007	0.001	$8.55 \cdot 10^{-7}$	0.045	0.022
PEC/PNEC	0.02	<0.01	<0.01	0.15	0.1

b) Summary statistics for soil PECs (mg/kg dry) at production + processing sites

	Mean	Median	Min	Max
Local PEC soil (mg/kg)	0.002	0.0007	0.0001	0.005
PEC/PNEC	<0.01	<0.01	<0.01	0.02

c) Summary statistics for soil PECs (mg/kg dry) at processing sites

		Mean	Median	Min	Max	N
Local	air only	0.002	$5.83 \cdot 10^{-5}$	$3.04 \cdot 10^{-6}$	0.012	6
	air+sludge	0.250	0.245	0.039	0.467	3
PEC/PNEC	air only	<0.01	<0.01	<0.01	0.04	
	air+sludge	0.8	0.85	0.13	1.6	

d) Site-specific PEC/PNEC ratio for soil estimated for production and, production + on-site processing with no sludge application (APA, 2000).

Site	PEC_{soil} mg/kg dw	$PEC/PNEC_{soil}$ mg/kg dw	Conclusion
Production			
P1 [1)]	0.0002	<0.01	ii
P2	0.0105	0.04	ii
P3	0.0233	0.08	ii
P4	0.0003	<0.01	ii
P5	0.0054	0.02	ii
P6	0.00003	<0.01	ii
P7	$8.55 \cdot 10^{-7}$	<0.01	ii
P8	0.0148	0.05	ii
P9	0.0052	0.02	ii
P10	0.0002	<0.01	ii
P11	0.0014	<0.01	ii
P12	0.0003	<0.01	ii
P13	0.0220	0.07	ii
P14	0.0037	0.01	ii
P15	0.0010	<0.01	ii
P16	0.0005	<0.01	ii
P17	0.0008	<0.01	ii
P18	0.0008	<0.01	ii
P19	0.0449	0.15	ii
Production + Processing			
PP1	0.0003	<0.01	ii
PP2	0.0009	<0.01	ii
PP3	0.0004	<0.01	ii
PP4	0.0052	0.02	ii
PP5	0.0037	0.01	ii
PP7	0.0001	<0.01	ii

[1)] Production stopped in 1998

Risk characterisation for production

Conclusion (ii).

Risk characterisation for combined production and processing

Conclusion (ii).

Off-site processing

Table 3.64 Site-specific PEC/PNEC ratio for soil estimated for processing with and without sludge application (APA, 2000)

Site	PEC_{soil} deposition only mg/kg dw	$PEC/PNEC_{soil}$ deposition only mg/kg dw	Conclusion deposition only	PEC_{soil} sludge application mg/kg dw	$PEC/PNEC_{soil}$ sludge application mg/kg dw	Conclusion sludge application
Processing						
Pc1	0.000342	<0.01	ii	0.467	1.6	**iii**
Pc2	$8.27 \cdot 10^{-5}$	<0.01	ii	0.245	0. 8	ii
Pc3	0.0121	0.04	ii			
Pc4	$3.39 \cdot 10^{-5}$	<0.01	ii	0.039	0.1	ii
Pc5	$1.84 \cdot 10^{-5}$	<0.01	ii			
Pc6	$3.04 \cdot 10^{-6}$	<0.01	ii			

Risk characterisation for off-site processing and generic risk characterisation

Conclusion (iii) applies for processing site Pc1 if soils are amended with sludge and for the generic scenario for use as an intermediate.

Conclusion (ii) applies for processing sites Pc2, Pc3, Pc4, Pc5 and Pc6. This conclusion also applies for the generic scenario 1 (use as an intermediate) (**Table 3.62**).

Downstream uses

Table 3.65 Estimations of PEC/PNEC local soil

Scenario	Life stage	$PEClocal_{soil}$ (mg/kg)	$PEC/PNEC_{terrestrial}$ local soil
1: Intermediates	Processing	3.64	**12**
2: Basic chemicals	Formulation	1.51	**5**
	Processing	30.5	**102**
3: Mineral	Formulation (10%)	0.977	**3.3**
oil and fuel	Private use	0.0007	0.002
4: Polymers	Formulation (10%)	0.341	**1.1**
	Processing	0.0145	0.1
5: Paint, etc.	Formulation (50%)	0.482	**1.6**
	Private use	0.0002	<0.01
6: Basic chemical	Formulation	0.452	**1.5**
	Processing	13.7	**30.5**
7: Personal /	Formulation	0.061	0.2
domestic	Private use	0.013	0.04
8: Pulp, Paper and	Formulation	0.166	0.6
board	Processing	0.067	0.2
9: Textile	Processing	1.120	**3.7**
10: Other	Processing	0.080	0.3

The results in **Table 3.65** indicate that locally there may be risks for microorganisms in STPs from several downstream uses of toluene:

- industry use an an intermediate (scenario 1),
- industry use as basic chemicals (scenarios 2 and 6),
- mineral oil and fuel formulation (scenario 3),
- formulation of polymers (scenario 4),
- formulation of paints (scenario 5),
- textile processing (scenario 9).

Results of the risk characterisation for the terrestrial environment

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

This conclusion applies to processing sites with sludge application to soil (and scenario 1). This conclusion also applies to industrial use as basic chemicals (scenarios 2 and 6), mineral oil and fuel formulation (scenario 3), formulation of polymers (scenario 4), formulation of paints (scenario 5), and textile processing (scenario 9).

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

This conclusion applies to production and processing and some downstream uses.

3.3.4 Secondary poisoning

Not considered relevant.

3.3.5 Humans exposed via the environment

The human intake from indirect exposure in local and regional scenarios is presented in the table below. The estimations were performed according to EUSES. In the local assessment, all food products are derived from the vicinity of one point source, in the regional assessment, all food products are taken from the regional model environment. The local and regional environments are not actual sites or regions but standardised environments as defined in the TGD.

Table 3.66 Estimated human intake of toluene in mg/kg bw/d by route and downstream scenarios

Scenario	Drinking water	Fish	Leaf crops	Root crops	Meat	Milk	Air	Total intake mg/kg/d
Local								
1: Processing	0.0155	0.161	$2.02 \cdot 10^{-5}$	$1.68 \cdot 10^{-5}$	$1.78 \cdot 10^{-6}$	$2.35 \cdot 10^{-6}$	0.0121	0.189
2: Formulation	0.0065	0.0669	$1.37 \cdot 10^{-4}$	0.0025	$2.89 \cdot 10^{-6}$	$3.81 \cdot 10^{-6}$	0.0824	0.158
2: Processing	0.129	1.34	$8.62 \cdot 10^{-4}$	0.0497	$2.64 \cdot 10^{-5}$	$3.48 \cdot 10^{-5}$	0.517	2.03
3: Formulation	0.0042	0.0436	$8.91 \cdot 10^{-5}$	0.00163	$1.88 \cdot 10^{-6}$	$2.48 \cdot 10^{-6}$	0.053	0.103
3: Private use	0.0001	0.0009	$4.91 \cdot 10^{-6}$	$3.49 \cdot 10^{-6}$	$9.04 \cdot 10^{-8}$	$1.19 \cdot 10^{-7}$	0.0030	0.004
4: Formulation	0.0015	0.0159	$1.33 \cdot 10^{-5}$	$5.57 \cdot 10^{-4}$	$3.65 \cdot 10^{-7}$	$4.81 \cdot 10^{-7}$	0.008	0.026
4: Processing	0.0001	0.0015	$8.60 \cdot 10^{-6}$	$2.79 \cdot 10^{-5}$	$1.57 \cdot 10^{-7}$	$2.08 \cdot 10^{-7}$	0.0052	0.007
5: Formulation	0.0021	0.022	$1.84 \cdot 10^{-5}$	$7.88 \cdot 10^{-4}$	$5.06 \cdot 10^{-7}$	$6.67 \cdot 10^{-7}$	0.0111	0.036
5: Private use	0.0001	0.0009	$9.96 \cdot 10^{-7}$	$6.01 \cdot 10^{-7}$	$2.50 \cdot 10^{-8}$	$3.30 \cdot 10^{-8}$	0.0006	0.0016
6: Formulation	0.0020	0.0207	$4.18 \cdot 10^{-5}$	$7.53 \cdot 10^{-4}$	$8.83 \cdot 10^{-7}$	$1.16 \cdot 10^{-6}$	0.0251	0.0486
6: Processing	0.0581	0.601	$3.88 \cdot 10^{-4}$	0.0223	$1.19 \cdot 10^{-5}$	$1.57 \cdot 10^{-5}$	0.233	0.914
7: Formulation	0.00018	0.0188	$6.53 \cdot 10^{-6}$	$6.6 \cdot 10^{-4}$	$2.78 \cdot 10^{-7}$	$3.66 \cdot 10^{-7}$	0.0039	0.025
7: Private use	0.00016	0.0016	$1.08 \cdot 10^{-6}$	$2.13 \cdot 10^{-5}$	$3.25 \cdot 10^{-8}$	$4.29 \cdot 10^{-8}$	0.0006	0.0024
8: Formulation	0.00079	0.0082	$1.59 \cdot 10^{-5}$	$2.76 \cdot 10^{-4}$	$3.39 \cdot 10^{-7}$	$4.48 \cdot 10^{-7}$	0.010	0.0188
8: Processing	0.00028	0.0029	$3.15 \cdot 10^{-4}$	$2.80 \cdot 10^{-4}$	$5.29 \cdot 10^{-6}$	$6.98 \cdot 10^{-6}$	0.189	0.193
9: Processing	0.0017	0.0072	$1.78 \cdot 10^{-6}$	$1.81 \cdot 10^{-3}$	$1.86 \cdot 10^{-7}$	$2.45 \cdot 10^{-7}$	0.0011	0.0117
10: Processing	0.0004	0.0038	$7.22 \cdot 10^{-5}$	$1.68 \cdot 10^{-4}$	$1.24 \cdot 10^{-6}$	$1.63 \cdot 10^{-6}$	0.0433	0.0477
Regional								
	$8.92 \cdot 10^{-5}$	0.0009	$9.96 \cdot 10^{-7}$	$6.65 \cdot 10^{-6}$	$2.49 \cdot 10^{-8}$	$3.29 \cdot 10^{-8}$	0.0006	0.0016
Incl. gasoline	$8.95 \cdot 10^{-5}$	0.0009	$2.47 \cdot 10^{-6}$	$7.09 \cdot 10^{-6}$	$4.96 \cdot 10^{-8}$	$6.54 \cdot 10^{-8}$	0.0015	0.0025

The calculated margin of safety for total exposure of humans via the environment is in the range of 430 to 600,000 based on the subchronic NOAEL of 625 mg/kg bw/d.

Table 3.67 Estimated human intake of toluene in mg/kg bw/d by route and downstream scenarios and MOS

Scenario	Total intake mg/kg/d	MOS	Total intake incl.gasoline mg/kg/d	MOS incl. gasoline
Local				
1: Processing	0.189	3,307	0.189	3,307
2: Formulation	0.158	3,956	0.159	3,931
2: Processing	2.03	308	2.03	308
3: Formulation	0.103	6,068	0.104	6,010
3: Private use	0.004	156,250	0.005	125,000
4: Formulation	0.026	24,038	0.027	23,148
4: Processing	0.007	89,286	0.008	78,125
5: Formulation	0.036	17,361	0.037	16,892
5: Private use	0.0016	390,625	0.0025	250,000
6: Formulation	0.0486	12,860	0.0494	12,652
6: Processing	0.914	684	0.915	683
7: Formulation	0.0025	250,000	0.026	24,039
7: Private use	0.0024	260,417	0.0033	189,394
8: Formulation	0.0188	33,245	0.0197	31,726
8: Processing	0.193	3,238	0.194	3,222
9: Processing	0.0117	53,419	0.0126	49,603
10: Processing	0.0477	13,103	0.0486	12,860
Regional				
	0.0016	390,625	0.0025	250,000

Results of the risk characterisation for humans exposed via the environment

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

The calculated margin of safety (MOS) for total exposure of humans via the environment is above 300 for all local and regional scenarios. This is considered to be sufficiently high to provide reassurance that adverse health will not occur, and thus there is no concern for effects of toluene in humans exposed indirectly to toluene itself via the food chain: conclusion (ii).

However, there is concern for effects on humans due to the contribution of commercial product toluene to the formation of ozone and other harmful substances (cf. Section 4.1.3.4).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Toluene is produced in different petroleum conversion processes. The impure product is used as a base or blending feed stock to produce motor gasoline. Isolated toluene is primarily used in the chemical industry as an intermediate in the production of other chemicals (± 70% of total use). Other major uses of toluene are: as a basic chemical in the chemical industry, as a solvent in paint, thinners, adhesives, inks and lacquers, and as a process regulator in the polymer industry. An overview of production and use categories is presented in **Table 2.7**.

Toluene is used in several hundreds of products. Information about the concentration of toluene in different products from the Danish and Swedish Product Registers is presented in **Tables 2.5** and **2.6**.

Humans may be exposed to toluene 1) at the workplace, 2) from the use of consumer products, and 3) via the environment.

Toluene is the most frequently measured organic compound in the (Danish) working environment (Olsen and Seedorff, 1990) and the compound found in the greatest number of products (Seedorff and Olsen, 1990).

4.1.1.2 Occupational exposure

Occupational exposure is possible in industries where:

- toluene and gasoline is produced (chemical industry and mineral oil and fuel industry);
- toluene is used as a chemical agent or used as an ingredient (e.g. polymer, paint, lacquer and varnishes, pulp, paper and board, textile processing, and chemical industry).

Besides exposure during production and use of toluene in the industry, occupational exposure to toluene is possible, whenever toluene-containing products are used.

The use of toluene and products containing toluene may include:

- transfer of liquids by means of a transfer line and pumping,
- manual transfer of liquids (in drums),
- manual or automated adding to (chemical) processes,
- manual and automated filling (into packaging),
- manual and automated use of paint, varnishes and lacquers, adhesives and binding agents.

Exposure to toluene can be by inhalation of vapours and liquid aerosols, dermal exposure to vapours and liquids and via the gastrointestinal tract. Dermal exposure to vapours is considered insignificant and ingestion is disregarded.

Relevant populations potentially exposed are workers in the chemical industry, paint industry, and workers using products containing toluene (e.g. painters). More specifically those workers who may have more or less direct contact with the substance, being:

- workers involved in the production, drumming, and transferral of toluene and gasoline,
- workers using toluene as an intermediate, process regulator, or solvent in the chemical industry,
- workers producing and drumming products containing toluene (e.g. paint, lacquer and varnishes, adhesives and cleaning agents in paint industry, agriculture industry, and personal domestic/industry,
- maintenance and (specialised) cleaning workers in production facilities,
- workers using products containing toluene e.g. in printing industry and cleaning.

The exposure is assessed using the available information on substance, processes, and work tasks. Information on the process and measured data have been provided for the production of toluene, and gasoline, on use of toluene in the chemical industry, and products containing toluene in the printing industry, in paint, coatings, and cleaning agents.

More detailed information on these parameters may lead to a more accurate exposure assessment.

Occupational Exposure Limits in force in various countries are presented in **Table 4.1**.

Table 4.1 Occupational Exposure Limits in Various Countries

Country	Time weighted average		Short-term exposure limit		Reference
	mg/m³	ppm [1)]	mg/m³	ppm [1)]	
Belgium	191	50			
Denmark	95	25			Arbejdstilsynet (1996)
France	375		550		
United Kingdom	190	50	560	150	
Germany	190	50	950 (30 min.)		MAK- und BAT-Werte-Liste (1999)
The Netherlands	150	40	-	-	SZW (1999)
Norway	95	25			
Sweden	200	50	400	100	1993
EU	188	50			Hunter et al. (1997)
USA (ACGIH)	190	50	-	-	ACGIH (1999)

[1)] ppm: parts per million

Air exposures

The air exposure considered in this assessment is the concentration measured in the breathing zone of the workers. No account will be taken of personal protection equipment (PPE) in this exposure section, since the actual degree of protection depends on the type of PPE, the way the equipment is used and maintained, and therefore cannot be known. An outcome of the risk characterisation of working with toluene may in some cases be that PPE should be worn. According to information from industry the use of PPE during repair work in toluene producing facilities is obligatory (APA, 1998b).

Full-shift values are reported for job categories where the work pattern is not varying much from day-to-day. Whenever possible, short-term exposures are reported, because they may reflect exposure concentrations during performance of a single process. Exposures at processes are more likely to be comparable between companies and countries than full-shift values, because the latter are strongly influenced by the way production is organised (Olsen and Jensen, 1994; Olsen 1994; 1996). When the number of times a process is repeated per day and the time spent at the process is known, full-shift exposure can easily be calculated, for instance, by assuming exposure to background levels for the rest of the day. In the working environment, background exposure levels are commonly much lower than exposure at processes where toluene is used. Full-shift exposures, therefore, can be calculated by assuming the background exposure to be zero. Information about the duration of tasks is scarce. Except for the Dutch data on carpet laying, no data on exposure times are available.

The data sets provided by industry and others are used for evaluating exposure to toluene, provided that data are representative for the population from which they originate. Judging whether measured data are representative for a certain exposure situation is often a matter of expert judgement.

The main result of the estimations is the so-called reasonable worst-case estimate. This value intends to estimate the exposure level in a reasonable worst-case situation, i.e. in a situation with exposures in the higher ranges of the full distribution of exposure levels, but below the extremes reached. If a large number of data are available, a 90 percentile is generally used as an estimator of the reasonable worst-case value. If limited data sets are available (e.g. only measurements from one site or only small numbers of measurements or measurements with very little detail on task, working conditions etc.) the highest value is taken, or the results of modelling are preferred, or a conservative intermediate value is chosen to account for the weakness in the different data sets.

Calculation of 90 percentiles

In occupational hygiene practice, variation in concentration is very large and the probability distribution of concentrations can often be reasonably described by a lognormal distribution (Oldham, 1953). This means that the logarithms of concentrations are distributed normally. The main parameters of a lognormal distribution are the logarithms of the geometric mean (GM) and the geometric standard deviation (GSD). Sometimes parameters of a normal distribution, the arithmethic mean (AM) and standard deviations (SD), are provided of a data set.

The GM and GSD of a lognormal distribution can be estimated if the AM and SD are known with the following equations, assuming AM= μ and SD=σ: (Leidel et al., 1977).

$$GSD = \exp (\ln (1 + \sigma^2 / \mu^2))^{1/2}$$
$$GM = \mu^2 / (\mu^2 + \sigma^2)^{1/2}$$

μ: *true arithmetic mean of the lognormal distribution*
σ: *true standard deviation of lognormal distribution*

If a distribution parameter (SD or GSD) of a data set is known (provided or calculated) the 90 percentile can be calculated with the following equations (Mulhausen and Damiano, 1998):

lognormal distribution:	$Perc_{\alpha\%} = EXP (y + Z_\alpha \cdot \sigma y)$
normal distribution:	$Perc_{\alpha\%} = \mu + Z_\alpha \cdot \sigma$
90 percentile of a lognormal distribution:	$Perc_{90\%} = EXP (y + 1.3 \cdot \sigma y)$
90 percentile of a normal distribution:	$Perc_{90\%} = \mu + 1.3 \cdot \sigma$

y: *true arithmetic mean of the natural logarithms of the data*
σy: *true standard deviation of the natural logarithms of the data*
Z_α *standard normal variable for the proportion of interest*

Dermal exposure

Gloves may protect against dermal exposure to toluene, depending on the type of gloves, the qualitative and quantitative composition of the product, the way the gloves are used, and how often they are replaced. Use of gloves may even increase dermal uptake rate of toluene above uptake rate through unprotected skin, due to occlusion ("washerwoman's fingers"). Toluene has the notation "skin" in ACGIH's list of Threshold Limit Values, indicating that it can penetrate undamaged skin.

Dermal exposure time is usually short because of toluene's high volatility. However, if e.g. hands are dipped into liquid toluene or a toluene containing cleaning agent is applied by means of a piece of cloth held in the hand, then dermal absorption occurs.

Because no measured data are available on dermal exposure, toluene exposure will be estimated with the dermal model of EASE 2.0. EASE is a general purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data are limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

Potential dermal exposure is estimated with EASE based on work pattern (use pattern and contact level) and the exposed area. The amount of substance available for entering the body will be influenced by other factors such as; the use of PPE and the vapour pressure of the substance. Besides these factors the dermal absorption rate of the substance and the condition of the skin will eventually determine the amount of substance entering the body.

The knowledge on the influence of PPE on dermal exposure is limited. According to information from industry the use of PPE during repair work in toluene producing facilities is obligatory (APA, 1998b). Workers in the rotogravure industry are obliged to wear gloves, when in direct contact with toluene (ERA, 1998).

Similarly the knowledge on the influence of the vapour pressure of the substance on dermal exposure is very limited. It should be noted that the high volatility of toluene would lower the amount of toluene available for entering the body. The German Competent Authorities proposed a method to account for the vapour pressure of highly volatile substances in dermal exposure assessment (BAuA, 2000). Within this method the evaporation time of the dermal exposure estimate is calculated and compared with the dermal absorption rate of a substance. There are, however, a number of issues which need to be taken into consideration or need clarification before this model can be used in dermal exposure assessment (more extensively described in Appendix C). Among others, the equation used to calculate the evaporation time contains parameters on which very limited knowledge is available.

As evaporation from the skin to some extent will surely lower the amount of toluene available for entering the body, in the risk characterisation lower MOSs could be accepted for all dermal exposure scenarios, except spray painting, which is considered a steady state process.

Exposure scenarios

There are several industries in which toluene is used or produced. The exposure of the workers may be similar in the different industries. The industries can be clustered in similar exposure scenarios based upon the type of process and activity and the possibilities for exposure that relate to that process and activity.

For the occupational exposure assessment the exposure situations can be clustered into four scenarios based on the type of use of toluene. In the first scenario, production of toluene and use of toluene as an intermediate in the chemical industry (scenario Q) is considered. Although the production and use of gasoline is not formally a part of this risk assessment (cf. Section 0), exposure is assessed in the second scenario (R) for illustrative purposes in order to be able to compare the exposure to toluene in this scenario with other scenarios. The third scenario (S) considers the formulation of toluene containing products such as paints and the fourth scenario (T) considers the use of products containing toluene.

Occupational exposure may occur during:

Q Production and use of toluene as an intermediate, including quality control sampling and drumming, storage and handling (i.e. transfer from one container to another) cleaning, repair and maintenance of production equipment.
R Production of gasoline, sampling and analysis of quality control samples, cleaning, repair and maintenance of the equipment.
S Production of toluene containing products (semi-products as well as products for sale), including transferal of toluene, adding to the process and drumming.
T Use of toluene containing products, such as spray application, brushing, rolling and cleaning (including manual transferral and mixing of such products).

In this report, for each occupational exposure scenario the general description of exposure will be followed by measured data (if available), and results from similar substances in comparable exposure scenarios. This will be followed by suitable inhalation models. The methods of estimation for inhalation exposure will be compared using expert judgement and a choice for the best applicable estimates will be made. Dermal exposure will be described and assessed by means of EASE.

The following data (if available) are used for occupational exposure assessment:

- physico-chemical data of toluene and products containing the substance: physical appearance, vapour pressure at room temperature, percentage of toluene in products;
- data regarding methods of use, use pattern of the substance and products potentially containing toluene, and exposure control pattern in the relevant industries (from the HEDSET or other sources);
- exposure data for toluene from the HEDSET and other sources (literature, exposure databases);
- results from exposure models if applicable (EASE model); in the exposure models the above mentioned types of data are used.

The following parameters of exposure are assessed for each (sub)scenario:

- full-shift reasonable worst-case inhalation exposure level: the inhalation exposure level considered representative for a high percentile (90 to 95 percentile) of the distribution of full-shift exposure levels;

- full-shift typical inhalation exposure level: the inhalation exposure level considered representative for a median percentile (50 percentile) of the distribution of full-shift exposure levels;
- short-term inhalation exposure level: the inhalation exposure level considered representative for a high percentile (90 to 95 percentile) of the distribution of short-term exposure levels; short-term exposure is for this purpose considered to be exposure for up to one hour, with typical duration of approximately 15 minutes;
- dermal exposure level: the dermal exposure level considered representative for a high percentile (90 to 95 percentile) of the full-shift dermal exposure levels.

4.1.1.2.1 Production and use of toluene in the chemical industry (scenario Q)

This scenario includes all activities concerning the production and use of toluene as an intermediate in the chemical industry. Toluene is produced in refineries from crude oil. The production takes place in closed systems under strict control, because of risk of material loss, danger of environmental pollution and risk of explosions.

Toluene is used as an intermediate in the production of other chemicals (± 70% of total use). For instance in MDI-process plants toluene is used as an extracting agent to recover aniline out of process water that has been used for washing the MDA. Toluene is also formed during the production of chemicals e.g. in ethylene benzene/styrene plant toluene is formed by the dehydrogenation of ethyl benzene to styrene. The toluene is removed from the styrene product by distillation.

During production exposure to toluene is possible due to certain activities, such as sampling for analytical purposes, drumming, transfer activities involving the coupling and uncoupling of a road tanker or connection or disconnection of pipes, cleaning, and maintenance and repair work.

Transferal and subsequent use as an intermediate occur also in closed systems (continuous and batch wise). Transferal may involve flexible hosing, pumping for emptying drums, and coupling and uncoupling of a road tanker that may lead to some leakage of toluene. For certain activities, such as checking the level of toluene and sampling for analytical purposes, valves may have to be opened manually and some toluene will evaporate. When toluene is consumed or reacted in the process (use as raw material) exposure will be limited to the activities during transfer, filling of the reactor, sampling, and analysis and repair work.

When toluene is not consumed or reacted in the process, exposure may also occur while filling toluene into tanks or drums, as well as during cleaning and maintenance and repair work.

In the chemical industry two different types of workers can be distinguished for cleaning and maintenance of a production facility. Plant personnel will perform daily cleaning activities. For major maintenance however, professionals will perform campaign wise maintenance (a few weeks in a row) at different production facilities. Exposure levels (both by inhalation and dermal) are expected to be of the same level for these workers, duration and frequency of exposure will be different.

<u>Inhalation exposure</u>

Inhalation exposure to toluene is expected due to activities where toluene is handled and to background concentrations through evaporation of toluene from closed systems through valves and fittings that are not perfectly closed.

Because the number of people employed in refineries are limited, it is expected that the number of workers exposed during production is also limited.

Measured data

Measured data have been provided by industry on exposure to toluene during production and use of toluene as an intermediate in the chemical industry and during maintenance activities (APA, 1996; 1998c; and 1999). Most exposure data are 8-hour time weighted averages from personal sampling.

The Aromatic Producers Association (APA) provided personal measurements from 19 different companies covering all the manufactures of toluene within the EU and the major uses. The information provided on the measurements varies. For most data sets the number of measurements, type of activity, mean exposure and exposure range are given. For some data sets a parameter for distribution (the standard deviation or geometric standard deviation) is also provided.

For exposure data provided by APA in some cases a SD and/or a GSD is provided. However, it is not clear whether the distributions are indeed tested to be normal if a SD provided or lognormal if a GSD is provided. Therefore, if the distribution parameter (SD or GSD) of the data set is provided, the 90 percentile is calculated both under the assumption that the distribution is normal as well as under the assumption that the distribution is lognormal, according to the equations from Mulhausen et al. (1998) and Leidel et al. (1977) which are presented in Section 4.1.2. The data are summarised in **Table 4.2**.

Table 4.2 Personal measurements (8h-TWA) for exposure during production and use of toluene as an intermediate and basic chemical and calculated distribution parameters
(APA, 1996; 1998c; 1999)

Data provided by APA							Calculated distribution parameters					
No.	**Activities**	**n**	**AM (mg/m³)**	**SD (mg/m³)**	**GSD**	**Range (mg/m³)**	**GM**	**GSD**	**90% log nor**	**90% nor.**	**Sampling period**	**Ref.**
1D	Production	-	<1			0.03 - 24						APA (1996)
6	Production	15	0.95			0.06 - 6.2					1995	APA (1996)
8	Production	120	0.4			0.04 – 25.6					1995	APA (1996)
9	Production	4	<1			-					'92/'93	APA (1996)
10	Production	169	0.5	1.65	3.00	<0.4 – 18	0.17	4.62	1.2	2.7	1995	APA (1999)
11	Maintenance	110	30.1			0.23 – 308					'86-'94	APA (1996)
	Production		195									
12A	Production	14	-			0.004 – 36					'90-'95	APA (1996)
12B	Production	7	-			0.02 - 2.5					-	APA (1996)
13	Production	30	<3.8			-					'95	APA (1996)

Table 4.2 continued overleaf

Table 4.2 continued Personal measurements (8h-TWA) for exposure during production and use of toluene as an intermediate and basic chemical and calculated distribution parameters

Data provided by APA							Calculated distribution parameters					
No.	**Activities**	**n**	**AM (mg/m³)**	**SD (mg/m³)**	**GSD**	**Range (mg/m³)**	**GM**	**GSD**	**90% log nor**	**90% nor.**	**Sampling period**	**Ref.**
14 [3]	Production	63	2.6	6.07		0.2 – 34	1.00	3.94	5.8	10.4	1994/'95	APA (1999)
	Wastewater treatment plant operations	19	0.5	0.46		0.1- 1.4	0.41	2.10	1.1	1.1		
	Laboratory	16	0.5	0.69		0.1- 3	0.26	2.96	1.0	1.4		
	Transport tasks	21	12.8	25.84		0.1- 103	5.67	3.58	29.1	46.0		
16	Production	52	<1.9	<1.9							1995	APA (1996)
17	Production (Steam cracking)	182	0.12	0.23		0.04- 1.5	0.05	3.56	0.3	0.4		APA (1996)
18	Production	115	2.99	9.98		<0.2 – 102	0.86	4.85	6.5	15.8		APA (1996)
2	Use as an intermediate	153	0.4			0.02 – 43						APA (1996)
7A	Use as an intermediate	5,966	2.1	9.83		0 – 1,152	0.43	5.91	4.2	14.7		APA (1996) APA (1999)
16	Use as an intermediate	115	2.9			< 1.9 –100						APA (1996)
No known	Use as an intermediate	41	1			< 0.1 – 25						APA (1996)
1	Maintenance (Incl. meter proving)	10		0.4		0.1 – 6						APA (1998c)
10	Maintenance of pumps	76	0.35	0.38	1.80	<0.4 - 3.5	0.23	2.45	0.7	0.8		APA (1999)
11	Maintenance of pumps	8	4.3	-		< 0.4- 12						APA (1998c)
14	Maintenance (incl. inspection of tank roofs)	21	11.9	24		-	5.3	3.57	27.1	42.7		APA (1998c)
16 [1]	Maintenance	10	< 1.8	-		-						APA (1998c)
2 [2]	Maintenance (incl. filter changing)	2	-	-		< 1 – 17						APA (1998c)

No: number of the company
n: number of measurements
AM: personal arithmetic mean
SD: standard deviation
GSD: geometric standard deviation
90% log nor: 90 percentile of a log normal distribution
90% nor: 90 percentile of a normal distribution
[1] statistic sampling
[2] short-term measurement
[3] worst-case sampling strategy

More exposure data are provided by industry on the use of toluene in the chemical industry (Company A, 1999). Measurements were done over a sampling period of 8 hours with 3 M passive diffusion monitors. Exposure data of plant and maintenance personnel from process plants are presented in **Table 4.3**. The median (50%) of the whole data set (other scenarios included) is 0.12 mg/m^3 and the 95 percentile is 0.38 mg/m^3.

Table 4.3 Measured data for toluene exposure in the chemical industry (Company A, 1999)

Specific information	n	Range (mg/m^3)
MDI process plants	81	0.02 - 2.15
Steam cracker	70	0.02 - 0.38
Tank farm	73	0.01 - 5.38
Ethylenebenzene/ styrene plant	67	0.02- 1.11
Polystyrene production plant	10	0.19- 0.54
Total	307	0.02 - 5.38

n: number of measurements

For production of toluene, data from thirteen companies are available. Measured 8-hour time weighted averages vary from 0 to 308 mg/m^3. The data sets with the highest exposure level of 308 mg/m^3 also contain measurements of maintenance activities. However, it is not clear if the 308 mg/m^3 is a result of a personal measurement during production or maintenance activities. High-exposure levels are also measured during transport tasks; exposure ranges from 0.1-103 mg/m^3 (AM=13.0 and SD 25.8). For this data set (n=21), the calculated 90 percentiles are 29 mg/m^3 (assuming a log normal distribution) and 46 mg/m^3 (assuming a normal distribution). Calculated log normal and normal 90 percentiles of data sets from other companies are clearly lower: respectively, 1.2, 0.7, 5.8, 0.3, 6.5 (log normal) and 2.7, 0.8, 10.4, 0.4, 15.8 (normal).

For use of toluene as an intermediate, data from four companies are available. From one company extensive data are available (n=5,966). Measured 8-hour time weighted averages vary from 0 to 1,152 mg/m^3. The provided distribution parameters (AM = 2.1 mg/m^3 and SD = 9.8) of this data set are used to calculate the 90 percentiles: 4.2 mg/m^3 (log normal distribution) and 14.7 mg/m^3 (normal distribution).

Seven companies provided data on exposure during maintenance activities including maintenance of pumps, inspection of tank roofs, and filter changing. Measured 8-hour time weighted averages vary from 0 to 308 mg/m^3. The upper limit of the range may originate from measurement of one extreme situation. The arimethic mean from this data set for maintenance activities is 30.1 mg/m^3. It is not known if the working methods in this company are different but measurements from other companies show lower exposure levels. Measurements from one company (no. 14) are used to calculate 90 percentiles: 27.1 mg/m^3 (log normal distribution) and 42.7 mg/m^3 (normal distribution).

Dermal exposure

Dermal exposure to toluene during the production and use of toluene in the chemical industry is possible during sampling, drumming, coupling and uncoupling of road tankers, cleaning and maintenance and repair work.

The corresponding exposure levels are estimated with the EASE model. Potential dermal exposure during activities like drumming, sampling, filling is estimated to be 0.1-1 mg/cm^2/day (non-dispersive use with direct handling and an intermittent contact level). Potential dermal exposure during cleaning and maintenance is estimated to be 1-5 mg/cm^2/day (non-dispersive use with direct handling and an extensive contact level).

The area potentially exposed depends on the activity. It is assumed that during sampling, drumming, filling and coupling and uncoupling of road tankers the exposed area will be half of two hands. This corresponds to an exposed area of 420 cm², which results in a reasonable worst-case estimate of 42-420 mg/day.

The area potentially exposed due to cleaning and maintenance of production facilities and repair work will be higher. It is assumed that during cleaning and maintenance and repair work exposure is possible to both hands and a part of the forearms. This corresponds to an exposed area of 1,300 cm^2. It is assumed that the production equipment, before cleaning and maintenance or repair work is flushed with a solvent. After the flushing the concentration of the substance is assumed to be diminished with 90%. This results in a daily estimated dose of 130-650 mg/day.

Assuming a body weight of 70 kg and a dermal absorption of 100%, this will lead to a estimated potential internal exposure of 0.6–6 mg/kg bw/day for sampling, drumming, filling and coupling and uncoupling of road tankers and of 1.9–9.3 mg/kg bw/day for cleaning and maintenance of production facilities and repair work, respectively. Due to the high volatility of toluene actual dermal exposure will probably be lower. This has not been taking into account because of the limited knowledge in this field.

Conclusions

During production and use of toluene as an intermediate in the chemical industry, inhalation exposure may occur through sampling, drumming and filling (automated and by hand), coupling and uncoupling of road tankers, cleaning, and maintenance and repair work. Lower exposure levels will occur during the rest of the day. Exposure levels are expected to be in the same order of magnitude during production of toluene and use of toluene as an intermediate because in both industries closed systems are used and exposure is mainly possible due to non-dispersive activities such as drumming, adding, and transfer activities.

Measured exposure data from sixteen different companies of exposure during production and use of toluene in the chemical industry have been provided by industry (>7,000 measurements, APA, 1996; 1998c; 1999). The information about the activities that are performed during the measurements is rather scarce. Information is limited to measurements, which are performed during production of toluene, use of toluene as a raw material (intermediate) and maintenance activities. Exposure data from one company (no. 14) are separated in production, wastewater treatment, laboratory, and transport tasks. Because most of the data are time weighted averages for 8 hours, there is limited information on exposure levels during certain activities such as drumming or sampling, except for maintenance activities.

The measured data and the calculated distribution parameters are used to derive reasonable worst cases for exposure during production, use as an intermediate and maintenance. Because the distribution of the data sets is not known, the 90 percentile of the normal distribution is, as a conservative estimate, used to assess the reasonable worst-case exposure.

Full-shift exposure levels in the chemical industry where toluene is produced or used as an intermediate are for:

- activities during production of toluene such as coupling and uncoupling of a transfer lines, filling and drumming; a full-shift reasonable worst case of 45 mg/m^3 is derived from the calculated 90 percentile (assuming normal distribution) from measured exposure levels during transport tasks (company 14).
- use of toluene as an intermediate; a full-shift reasonable worst case of 15 mg/m^3 is derived from the 90 percentile (assuming normal distribution) of the largest data set (n=5,966, company 7A).
- maintenance activities*;* a full-shift reasonable worst-case exposure level of 45 mg/m^3 is derived from the calculated 90 percentile (assuming normal distribution) of measured exposure levels (company 14).

Reasonable worst-case short-term exposure levels are expected to be up to about the higher full-shift exposure levels measured during production of toluene (excluding the very high values): 100 mg/m^3. Typical exposure levels for process operators during production of toluene and use of toluene are expected to be lower: 3 mg/m^3, based on several arithmetic means reported by APA (1996; 1998c; 1999).

Duration of inhalation exposure due to specific activities (drumming, sampling etc.) is estimated to be 2-4 hours/day, whereas exposure to background concentrations is 6-8 hours per day.

Dermal exposure to toluene during the production and use of toluene in the chemical industry is possible during sampling, drumming and filling (automated and by hand), coupling and uncoupling of road tankers, cleaning and maintenance and repair work. Dermal exposure in the chemical industry is estimated with EASE to be up to 6 mg/kg bw/day for sampling, drumming, filling and coupling and uncoupling of road tankers and up to 9 mg/kg bw/day for cleaning and maintenance of production facilities and repair work. Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Frequency of exposure depends on work patterns, but daily exposure is possible.

Conclusions for scenario Q

The following exposure levels will be used for further risk assessment for scenario Q.

- Inhalation exposure: reasonable worst case, full shift:
  a. production activities 45 mg/m^3;
  b. use as an intermediate 15 mg/m^3;
  c. maintenance 45 mg/m^3;
- Inhalation exposure: reasonable worst case, short-term 100 mg/m^3;
- Inhalation exposure: typical, full shift: 3 mg/m^3;
- Dermal exposure: estimated reasonable worst case [1)]:
  d. production activities 6 mg/kg bw/day;
  e. use as an intermediate 6 mg/kg bw/day;
  f. maintenance 9 mg/kg bw/day;

[1)] Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

4.1.1.2.2 Production and distribution of gasoline (scenario R)

Toluene is a significant component in gasoline for cars. An average concentration of 11.4% (range: 2.7–21.0%.) of toluene was found in 48 German gasolines (DGMK, 1994). As gasoline is used in huge amounts, it is produced in many refineries all over the EU. The production is performed in closed systems under very strict control to prevent loss of materials, risk of environmental pollution, and danger of explosion.

The manufacture and distribution of gasoline involves a variety of work activities and types of jobs ranging from production and ancillary operation within the refinery and distribution depots, e.g. tank dipping, pump repairs, filter cleaning, loading of ships, rail cars and road tankers, delivery to service stations, and attendant filling of customers‘ vehicles (CONCAWE, 1997).

When occupational exposure in the production of gasoline is considered, the following job categories can be distinguished: on-site operators, off-site operators, maintenance staff, drum/barrel filler, and tank cleaners. The activities of an on-site operator which may lead to exposure include manually opening and closing of valves, inspecting liquid levels in containers, quality control sampling, dismantling, and flushing out pumps. Off-site operators generally work at the tank field handling mineral oil products. Tasks that may lead to exposure include draining and taking samples. Maintenance staff carry out regular maintenance and preventive repair work at all plants. Because of working with open systems, higher (short-term) exposure levels are expected during maintenance activities.

The activities of drum/barrel filler mainly consist of filling 200 l drums with gasoline. Tank cleaning is a specialist activity involving cleaning out sludge from bulk storage tanks which is performed by contractors. Tank cleaning is carried out under strict permit procedures to ensure safe entry into a confined, potentially contaminated space (DGMK, 1995; CONCAWE, 1997).

In the distribution of gasoline the filling of tanks/ships/trains and cars by attendants at a service station may be relevant for occupational exposure. Transfer activities such as filling and loading may involve coupling and uncoupling of transfer lines. During loading of tanks etc. the air is, normally, forced out of the tank through a ventilation duct, equipped with a charcoal filter for collecting the vapours or a vapour retour system is used. Filling of road tankers is normally a task, which is performed by the tanker drivers, as is delivery at the gasoline stations. Only in exceptional cases, staff of road tanker filling units fill road tankers themselves. The shipping and storage of gasoline are done by tank farm personnel.

Measured data

Measured data of occupational exposure to toluene during the production and transfer of gasoline have been provided by CONCAWE (1997; 2000). The data of 2000 are preferred above the data from 1997 because the measured are more recent. Measured data collected from 1993-1998 (CONCAWE, 2000) are presented instead of the data from 1983-1994 (CONCAWE, 1997). Both data sets contain measured data for the same job categories. The data set collected from 1993-1998 contains much more measurements and the exposure levels are clearly lower than exposure levels measured from 1983-1994. Personal full-shift and short-term exposure levels during production of gasoline are presented in **Table 4.4**. Company A also provided exposure data on the production of gasoline. Measurements were done over a sampling period of 8 hours with 3M passive diffusion monitors. Data are presented in **Table 4.5**.

Personal full-shift exposure levels and short-term measurements for transfer of gasoline are presented in **Table 4.6**. Personal full-shift and short-term exposure levels for attendants at a service station are also presented in **Table 4.6**.

Production of gasoline

Table 4.4 Full-shift and short-term inhalation exposure data for toluene from gasoline reported by CONCAWE member companies for occupations in European oil industry operations, 1993-1998 (CONCAWE, 2000)

Job title	Full-shift exposure data			Short-term (<1 hr) exposure data		
	n	AM (mg/m^3)	Range (mg/m^3)	n	AM (mg/m^3)	Range (mg/m^3)
Refinery On-site Operators	53	0.87	0.01 – 8.8	nd	nd	nd
Refinery Off-site Operators	291	0.80	0.008 – 21.6	47	7.42	0.49 – 32.0
Refinery Maintenance Workers	316	0.94	0.008 – 67.2	5	8.0	3.0 – 22.0
Laboratory Technicians	207	1.28	0.01 – 20.6	1	3.0	nd
Refinery miscellaneous (bund area)	8	4.53	1.5 – 18.0	nd	nd	nd

n: Number of measurements
nd: no data
AM: Arithmetic mean

Table 4.5 Full-shift exposure levels for toluene during production of gasoline (Company A, 1999)

Type of work	n	Range (mg/m^3)
Tank farm [1)]	73	0.01 - 5.4
Steam cracker [1)]	70	0.02 - 0.4

[1)] Measurements are performed with 3M passive monitors

Full-shift exposure levels are available for all job categories involved in the production of gasoline except for tank cleaning. Valuable information is provided on the activities of the different job categories in the production of gasoline. Exposure during tank cleaning is expected to be the same as for maintenance activities. Relatively high exposure levels are measured for miscellaneous activities at the refinery (AM = 4.53 mg/m^3, upper value 18 mg/m^3). It is not specified which workers perform these activities or which activities are included. Other Job categories with "higher" full-shift levels are laboratory technicians (AM = 1.28 mg/m^3, upper value 21 mg/m^3) and maintenance activities (AM = 0.94 mg/m^3, upper value 67 mg/m^3).

Distribution of gasoline

Table 4.6 Full-shift and short-term inhalation exposure data for toluene from gasoline reported by CONCAWE member companies for occupations in European oil industry operations, 1993-1998 (CONCAWE, 2000)

Job title	Full-shift exposure data			Short-term (<1 hr) exposure data		
	n	AM (mg/m^3)	Range (mg/m^3)	n	AM (mg/m^3)	Range (mg/m^3)
Road tanker drivers (top loading)	22	0.84	0.1 – 2.5	98	22.16	0.08 – 200
Road tanker drivers (bottom loading without vapour recovery)	10	0.95	0.045 – 3.4	24	8.51	0.3 – 38
Road tanker drivers (bottom loading with vapour recovery)	113	0.87	0.08 – 2.8	45	3.6	0.08 – 26.3
Road tanker drivers (other category)	56	2.41	0.08 – 28.6	9	3.39	0.2 – 10.2
Distribution terminal rack operators	39	3.5	0.001 – 36.2	nd	nd	nd
Distribution terminal supervisor or operators	94	2.03 **	0.003 – 7.7	8	14.33	1.5 – 61.0
Distribution terminal maintenance workers	44	1.75	0.007 – 11.0	1	8.0	nd
Distribution terminal miscellaneous	5	0.56	0.1 – 1.5	3	5.13	0.4 – 10.2
Rail car operators, top loading (without vapour recovery)	40	2.69	0.08 – 27.3	9	4.4	1.3 – 11.0
Rail car operators, top loading (with vapour recovery)	8	3.0	nd	nd	nd	nd
Rail car operators, off-loading	40	0.87	0.08 – 2.8	4	4.3	1.4 – 7.4
Rail car operators, miscellaneous	32	1.83	0.02 – 17.8	nd	nd	nd
Ship deck crew, open loading	41	2.80	0.08 – 58	4	3.25	3.0 – 4.0
Ship deck crew, off-loading	32	0.98	0.023 – 3.0	2	5.5	3.0 – 8.0
Ship deck crew, closed loading	2	3.51	0.82 – 6.2	nd	nd	nd
Marine jetty staff	43	1.13	0.023 – 4.0	23	5.65	0.45 – 38.0
Service station attendant (no vapour recovery)	451	0.51	0.012 – 2.8	nd	nd	nd
Service station cashiers (based in shop)	209	0.41	0.001 – 1.1	nd	nd	nd
Petrol pump maintenance worker	1	3.3	nd	6	10.9	0.86 – 30.8*
Service station miscellaneous (car wash, etc.)	3	0.20	0.001 – 0.5	nd	nd	nd
Airport operators	10	1.90	0.008 – 4.2	nd	nd	nd

nd: no data
* small spillage associated with highest result
** mean subject to confirmation due to transcription error in data set of Company A

Extended measured data are available for both full-shift exposure levels and short-term exposure levels of different job categories and different methods concerning the transferring/distribution of gasoline are available. Data are available on exposure to toluene during transfer of gasoline in

road tanks (loading and delivery) for both top and bottom loading and during transfer of gasoline by ship and train. The data can be considered to be representative for all EU as tanker and filling equipment are the same in all countries.

Full-shift exposure levels (8-hour TWA) during transfer of gasoline vary from 0-58 mg/m^3. Arithmetic means for different techniques and job-categories vary from 0.56 to 3.51 mg/m^3. No information was provided on the different activities performed by the workers during the sampling period. Short-term exposure levels (<1 hour) during transfer of gasoline vary from 0-200 mg/m^3. Arithmetic means vary from 3.3 to 22.2 mg/m^3.

Exposure levels of workers involved in the transfer of gasoline at service stations are much lower, the highest value measured is 2.8 mg/m^3. Short-term measured exposure data are not available for service station attendants. Only for maintenance workers at the petrol pump six measurements were performed (AM 10.9; range 0.86–30.8 mg/m^3).

Dermal exposure

Dermal exposure to toluene during the production and transfer of gasoline is possible during sampling, drumming, coupling and uncoupling of transfer lines, cleaning, and maintenance and repair work.

The corresponding exposure levels are estimated with the EASE model assuming a worst-case concentration of 21% toluene in gasoline. Potential dermal exposure during activities like drumming, sampling, coupling and uncoupling of transfer lines is estimated to be 0.02-0.2 mg/cm^2/day (non-dispersive use with direct handling, an intermittent contact level and 21% toluene).

Potential dermal exposure during cleaning and maintenance is estimated to be 0.2-1 mg/cm^2/day (non-dispersive use with direct handling, an extensive contact level and 21% toluene).

The area potentially exposed depends on the activity. It is assumed that during sampling, drumming, filling and coupling and uncoupling of transfer lines the exposed area will be half of two hands. This corresponds to an exposed area of 420 cm², which results in a reasonable worst-case estimate of 8.4-84 mg/day.

Attendants at a service station will be exposed at the palm of one hand. This corresponds to an exposed area of 210 cm², which results in a reasonable worst-case estimate of 4.2-42 mg/day.

The area potentially exposed due to cleaning and maintenance of production facilities and repair work will be higher. It is assumed that during cleaning, and maintenance and repair work exposure is possible to both hands and a part of the forearms. This corresponds to an exposed area of 1,300 cm^2. It is assumed that the production equipment, before cleaning and maintenance or repair work, is flushed with a solvent. After the flushing the concentration of the substance is assumed to be diminished with 90%. This results in a daily dose of 26-130 mg/day. Due to the high volatility of toluene actual dermal exposure will probably be lower. This has not been taking into account because of the limited knowledge in this field.

Assuming a body weight of 70 kg and a dermal absorption of 100% this will lead to a estimated potential internal exposure of 0.12-1.2 mg/kg bw/day for sampling, drumming, filling and coupling and uncoupling of transfer lines, of 0.06 – 0.6 mg/kg bw/day for attendants at a service stations, and of 0.4–1.9 mg/kg bw/day for cleaning and maintenance or repair work.

Conclusions

During production and distribution of gasoline inhalation exposure to toluene may occur through sampling, drumming, coupling and uncoupling of transfer lines, cleaning, and maintenance and repair work. Lower exposure levels will occur during the rest of the day. Activities related to production sites and activities related to the transfer of gasoline (except drumming) are performed by different workers.

The measured data are used to derive reasonable worst-case exposure levels for exposure during production and transfer activities. In the measured data, mean exposures and ranges are provided. Without a distribution parameter (SD or GSD) it is not possible to calculate the 90 percentile therefore the upper ranges are used to assess reasonable worst-case exposure.

The measured exposure data from CONCAWE (2000) are used to estimate the reasonable worst-case full-shift exposure level for workers in the production of gasoline. Full-shift exposure levels for maintenance workers, workers who fill drums, and barrels and tank cleaning personnel will be higher than exposure levels for on-site and off-site operators. Reasonable worst-case full-shift exposure level for maintenance personnel is estimated to be 70 mg/m^3 (the upper range of the data for maintenance workers). Reasonable worst-case full-shift exposure levels for on- and off-site operators are estimated to be 20 mg/m^3 (upper range of the data for off-site operators).

Only limited low exposure data are available for short-term exposure for maintenance activities. Therefore short-term exposure level is estimated to be twice the full-shift exposure levels 140 mg/m^3 for maintenance and tank cleaning. For operators (on- and off-site) reasonable short-term exposure level is estimated to be 30 mg/m^3 (upper range of measured data for off-site operators). Typical full-shift exposure levels are expected to be much lower: 1 mg/m^3 for workers involved in activities such as maintenance and tank cleaning and 1 mg/m^3 for operators.

To assess exposure for distribution of gasoline a distinction is made in transfer of gasoline (loading and unloading of tanks, trains, and ships) and the filling of a car by an attendant of a service station. Full-shift reasonable worst-case exposure level for transfer activities is estimated to be 50 mg/m^3. For workers who are involved in transfer of gasoline, short-term exposures are estimated to be 100 mg/m^3. Typical exposure levels for distribution of gasoline are estimated to be 2.5 mg/m^3.

Full-shift exposure levels of attendants at service stations will be much lower. Reasonable worst case is estimated to be 3 mg/m^3 (full-shift) and 6 mg/m^3 (short-term). Typical full-shift exposure levels are estimated to be 0.5 mg/m^3 (AM service station attendant). For workers performing maintenance activities at petrol pumps exposure levels will be higher.

Duration of inhalation exposure due to specific activities (drumming, sampling etc.) is estimated to be 2-4 hours/day, whereas exposure to background concentrations is 6-8 hours per day. For attendants at service stations duration of exposure is estimated to be 4-6 hours/day. Frequency of exposure depends on work patterns, but daily exposure is possible.

Dermal exposure to toluene during the production and transfer of gasoline is possible during sampling, drumming, and coupling and uncoupling of transfer lines, cleaning and maintenance and repair work. Repeated dermal exposure during the production and distribution of gasoline in the chemical industry is estimated with EASE to be up to:

- 1.2 mg/kg bw/day, for operators and transfer activities;
- 1.9 mg/kg bw/day, for maintenance and cleaning tanks;
- 0.6 mg/kg bw/day, for attendants at a service station.

Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Conclusions for scenario R

The following exposure levels are concluded for scenario R.

- Inhalation exposure: reasonable worst case, full shift:
  a. maintenance and tank cleaning 70 mg/m^3;
  b. operators at production sites 20 mg/m^3;
  c. transfer of gasoline 50 mg/m^3;
  d. attendants at service stations 3 mg/m^3.
- Inhalation exposure: reasonable worst case, short-term:
  a. maintenance and tank cleaning 140 mg/m^3;
  b. operators at production sites 30 mg/m^3;
  c. transfer of gasoline 100 mg/m^3;
  d. attendants at service stations 6 mg/m^3.
- Inhalation exposure: typical, full shift:
  a. maintenance and tank cleaning 1 mg/m^3;
  b. operators at production sites 1 mg/m^3;
  c. transfer of gasoline 2.5 mg/m^3;
  d. attendants at service stations 0.5 mg/m^3.
- Dermal exposure: estimated reasonable worst case[1)] :
  a. maintenance and tank cleaning 1.9 mg/kg bw/day;
  b. operators at production sites 1.2 mg/kg bw/day;
  c. transfer of gasoline 1.2 mg/kg bw/day;
  d. attendants at service stations 0.6 mg/kg bw/day.

1) Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

4.1.1.2.3 Production of toluene containing products (scenario S)

Toluene is used in several hundreds of products. Information about the concentration of toluene in different products from the Danish and Swedish product registers is presented in **Table 2.5** and **Table 2.6**. According to the information from the Danish and Swedish Product Registers some products may contain up to 100% toluene.

Production of toluene containing products, like adhesives, lacquers, paints and inks, process regulators, and corrosion inhibitors is performed in containers and drums of different sizes. The container sizes range from several cubic meters, e.g. production of rotogravure printing inks for magazine printing, to small batch production of special products.

Production of e.g. lacquers and adhesives is done by adding a polymer to the solvent while stirring. After the polymer is added, the stirring continues under a closed lid, usually equipped with an exhaust unit to prevent vapours to escape into the workroom.

Production of products, which contains pigments or other solids, is commonly performed in two steps. First the components of the ink or paint is mixed (predispersed). Then the predispersed suspension is pumped into, e.g. a pearlmill for dispersion. From the pearlmill, the product flows

into another container. Good work practice prescribes that both containers are equipped with lids. After dispersion the viscosity of the product is adjusted and the product is canned, usually using automatic tapping machines.

Inhalation exposure

Exposure during production of toluene containing products is expected during transferral of toluene, adding of toluene to the process, and during drumming of the products. Transferral of toluene to other chemical production systems is done by drums, tankers, or connecting transfer lines. Transferral by lines will lead to substantially lower emission compared to manual emptying of drums.

During mixing of products volatile substances may evaporate, especially if systems are only partially closed. Liquid products will be drummed while paste-like products will be packed in suitable containers. The packing of non-liquid products is expected to give less emission by evaporation and less possibility for skin contact. Therefore, only mixing and drumming of liquid products will be considered here. Liquids (lacquers, stains, inks, and cleaning agents) may be drummed in drums and cans of different sizes.

In formulating facilities, e.g. for paints and inks, technical control measures generally are not as extensive and effective as those taken in the production facilities.

Duration and frequency of exposure may be full shift and daily, although transferral of toluene at the beginning of the process and drumming may be done only during a part of the day, in which case the duration of skin exposure potential is less than full shift.

Measured data

Some exposure data from field studies found in the literature, which have been collected by industry, are presented in **Table 4.7** (APA, 1996). The exposure ranges and (arithmetic) mean levels from the production of paints, adhesives and plastics are given. Some of these studies are dated (1978; 1979). Recent exposure data are available from the production of plastics and adhesives by Kawai et al. (1994).

Measured exposure data on the production of preparations are presented in **Table 4.8**. Exposure data (n=538) of 130 companies collected from 1991-1995 are calculated to full-shift exposure levels. Exposure data are given in 50, 90, and 95 percentiles (BGAA, 1998).

Table 4.7 Exposures during production of toluene containing products (short-term measurements) (APA, 1996)

Type of product	n	AM (mg/m^3)	Range (mg/m^3)	Reference
Plastic and adhesives	294	8.8	0 – 507	Kawai et al. (1994)
Adhesive	31	38.4	0 – 100	Zerwas (1978)
Adhesive	31	< 30.7	0 – 46	Zerwas (1978)
Adhesive	22	3.1	2.9 – 346	Zerwas (1978)
Paint and adhesive	42	57.6	< 3.8 – 307	Winchester and Madjar (1986)
Adhesives	n.g.	n.g.	- 131	Patterson (1979)

n: number of measurements
AM: personal arithmetic mean
n.g: not given

Table 4.8 Exposures during production of toluene containing products (8-hour time weighted averages) (BGAA, 1998)

Type of company/work area	n	No. of companies	50%-value (mg/m^3)	90%-value (mg/m^3)	95%-value (mg/m^3)
Production of preparations	508	130	4	55	98

n: number of measurements

Short-term exposure levels during the production of paints and adhesives range from 0 to 500 mg/m^3.

The German data on full-shift exposure levels during production of preparations show a 90 percentile of 55 mg/m^3 and a 95 percentile of 98 mg/m^3 during the production of preparations. The data were gathered at dissolvers, beadmills, and a filling plant. Measurement results in the region of the 90% value (55 mg/m^3) were determined during mixing and filling. Similar exposure levels are expected during the production of other products.

Belgium provided some measured data on occupational exposure in workshops and industry over the period 1985-1996 (Belgium, COM.ECB4/032/98). A total of 26,726 air samples were analysed for organic solvents, 9,910 (37%) of the measurements contained toluene. A subset of 1,743 samples could be identified as personal air samples with a duration of 2-8 hours. Some statistics on the subset were provided: the geometric mean is 9.5 mg/m^3 (GSD = 5.0 mg/m^3), 50 and 90 percentiles are 7.3 and 87.2 mg/m^3, respectively. In 80 measurements (5%) exposure was higher than 190 mg/m^3. These levels were most frequently reported to occur during paint manufacturing (17) and printing (rotogravure printing and silkscreen printing) (13). No further details on the activities during measurements were reported.

Dermal exposure

Dermal exposure to toluene during the production of toluene containing products is possible during adding of toluene, sampling, drumming, and filling. There are no measured data available so exposure levels will be estimated with EASE.

During activities like drumming, sampling and filling potential dermal exposure is estimated with the EASE model to be 0.1-1 mg/cm^2/day (non-dispersive use with direct handling and intermittent contact).

The area potentially exposed depends on the activity. It is assumed that during sampling, drumming and filling the exposed area will be half of two hands. This corresponds to an exposed area of 420 cm^2, which results in a reasonable worst-case estimate of 42-420 mg/day. Due to the high volatility of toluene actual dermal exposure will probably be lower. This has not been taking into account because of the limited knowledge in this field.

Assuming a body weight of 70 kg and a dermal absorption of 100% this will lead to an estimated potential internal exposure of 0.6- 6 mg/kg bw/day for sampling, drumming, and filling.

Conclusions

During production of toluene containing products inhalation exposure may occur through transfers from drums or road tankers, sampling, drumming and filling. Lower exposure levels will occur during the rest of the day.

The exposure data from Kawai et al. (1994) and the BGAA database (BGAA, 1998) are used to derive reasonable worst-case exposure levels. The data from Kawai et al. are higher (range

0-500 mg/m^3) than the 90 percentile (55 mg/m^3) and the 95 percentile of 98 mg/m^3 of the BGAA database. Only limited information is available from the literature data. The Belgium data can only be used as an indication of exposure to toluene in general because no details are provided on number of measurements and exposure levels during certain activities.

To account for all available information, including the higher values in literature (range 0-500 mg/m^3) and the higher quality of data from the German database, the 95 percentile of the BGAA database is used as reasonable worst-case exposure level. For normal working conditions a short-term exposure level of 200 mg/m^3 will be used as a reasonable worst-case estimate for this scenario, based on the higher measured levels, but not using the extremes. Typical exposure levels are expected to be lower, 4 mg/m^3 (full shift, based on the median in the BGAA database).

Dermal exposure to toluene during the production of toluene containing products is possible during sampling, drumming, and filling. Repeated exposure is estimated to be up to 6 mg/kg bw/day. Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Duration of inhalation exposure during production of toluene containing product due to specific activities (transfer activities and filling of packaging, etc.) is estimated to be 2-4 hours/day, whereas exposure to background concentrations is 6-8 hours per day. Frequency of exposure is expected to be up to 200 days/year.

Conclusions for scenario S

The following exposure levels will be used for further risk assessment for scenario S.

- Inhalation exposure: reasonable worst case, full shift: 98 mg/m^3
- Inhalation exposure: reasonable worst case, short-term: 200 mg/m^3
- Inhalation exposure: typical, full shift: 4 mg/m^3
- Dermal exposure: estimated reasonable worst case (repeated dose) [1)] : 6 mg/kg bw/day

[1)] Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

4.1.1.2.4 Occupational use of toluene containing products (scenario T)

Toluene is used in a wide variety of products such as adhesives, lacquers, paints and inks, process regulators and corrosion inhibitors. According to the information from the Danish and Swedish Product Registers some products may contain up to 100% toluene (**Tables 2.5** and **2.6**).

Data on exposures during use of toluene containing products are abundant, but not available for all products, e.g. no data are available for toluene used in reprographic agents and in corrosion inhibitors. Data of appropriate quality are available on toluene used in cleaning agents, gluing adhesives, rotogravure inks, and painting (rolling, brushing, or spraying).

As representatives for the use of toluene containing products the following subscenarios are considered:

- use of cleaning agents (scenario T1);
- use of adhesives (scenario T2);
- use of paints, inks and lacquers (scenario T3);

Use of cleaning agents (scenario T1)

Toluene, sometimes in mixtures with other compounds, is commonly used for cleaning, e.g. of metal surfaces. Cleaning agents may contain up to 100% of toluene. A distinction can be made in manual and mechanical cleaning. In manual cleaning, the cleaning agent is applied by means of a piece of cloth or a brush. Small items are sometimes cleaned by dipping them into a bath containing the cleaning agent using for instance ultrasonic waves for enhanced cleaning. In mechanical cleaning, larger amounts of toluene are probably used during machine washing. During the cleaning process the machine is expected to be closed, however, exposure is possible during adding cleaning agent to the machine (adding may be manual or by transfer lines), and by evaporation of toluene from the cleaned material (inhalation), and dermal contact with the cleaned materials.

Inhalation exposure

Measured data

Personal full-shift and short-term exposure levels are available from BGAA (1998). Data on mechanical and manual degreasing were collected from 1991-1995 and presented in 50, 90, and 95 percentiles. Full-shift exposure levels (8-hour TWA) are calculated from measurements (n=401) with a duration of more than one hour and the duration of short-term exposure (n=48) were less than one hour. There is no information available on the composition of the cleaning liquids used during measurements.

Full-shift exposure levels and short-term exposure levels on cleaning are shown in **Table 4.9**.

Full-shift exposure data on mechanical cleaning were mainly gathered in the metalworking and chemical industries. For mechanical degreasing (n=61) the 90 percentile of full-shift levels is 22 mg/m^3. Measurement results in the region of the 90% value were determined at a container-cleaning plant. Data on manual cleaning were gathered in the metalworking, woodworking and in the chemical industry. For manual degreasing (n=340) the 90 percentile of full-shift levels is 62 mg/m^3. Measurement results in the region of the 90% value were determined during the cleaning of a plant e.g. of paint production. The 90 percentile for full-shift exposure levels are lower for mechanical cleaning (22 mg/m^3) than for manual cleaning (62 mg/m^3). The 50 percentile, however, is higher for mechanical cleaning (7 mg/m^3 and manual 3 mg/m^3) this shows that variation in exposure is higher for manual cleaning.

Short-term exposure measurements were mainly determined in metalworking and electrical engineering industries as well as in the whole sale trade. Short-term exposure levels are presented in **Table 4.9**, and are presented as cleaning without local exhaust ventilation (LEV) (n=30) and cleaning with LEV (n=18). The 90 percentiles for cleaning with (67 mg/m^3) and without ventilation (54 mg/m^3) do not vary much. Measurement results in the region of the 90 percentile were determined during the cleaning of tanks.

The full-shift exposure levels for manual cleaning are in the same range as short-term exposure levels. This probably indicates that workers who are involved in cleaning are performing cleaning activities for a large part of the day.

Table 4.9 Personal exposure levels (full-shift and short-term) during cleaning activities (BGAA, 1998)

Type of company/work area	Duration	n	no. of companies	50% value (mg/m³)	90% value (mg/m³)	95% value (mg/m³)
Cleaning, degreasing (mechanical)	Full shift [1)]	61	39	7	22	44
Cleaning, degreasing (manual)	Full shift [1)]	340	186	3	62	121
Cleaning, degreasing (no LEV)	Short term [2)]	30	8	20	54	109
Cleaning, degreasing (LEV)	Short term [2)]	18	15	9	67	106

1) Measurement of > 1 hour were calculated to full shift levels (8-hour time-weighted averages)
2) Measurements of < 1 hour
N: number of measurements. LEV: local exhaust ventilation present

Modelling

Mechanical cleaning activities such as degreasing of materials can be described as non-dispersive use with or without LEV. Manual cleaning is considered to be wide dispersive use. Inhalation exposure during cleaning, assuming a maximum concentration of 100% of toluene in cleaning agents, is assessed with EASE (version 2.0 for Windows) to be:

- non dispersive use with LEV: 10-20 ppm (38-77 mg/m^3);
- non dispersive use, direct handling and dilution ventilation: 100-140 ppm (380-532 mg/m^3);
- wide dispersive use, direct handling and dilution ventilation: 200-300 ppm (760-1,140 mg/m^3).

Mechanical cleaning might be performed full shift but manual cleaning will only be performed a (small) part of the day. If it is assumed that duration of manual cleaning will up to one hour per day. Full-shift exposure is estimated to be 145 mg/m^3 ((7·0 + 1·1,140)/8), if a negligible exposure level is assumed during the remainder of the day.

Dermal exposure

Dermal exposure will be higher for manual cleaning than for mechanical cleaning. For manual cleaning exposure is assessed, assuming wide-dispersive use and an extensive contact level (>10 times a day) and for mechanical cleaning non-dispersive use and an incidental contact level is assumed during adding of the cleaning agent. Potential dermal exposure during cleaning activities is estimated with EASE to be:

- manual cleaning: 5-15 mg/cm^2;
- mechanical cleaning: 0-0.1 mg/cm^2.

The area potentially exposed depends on the activity. It is assumed that during manual cleaning the exposed area will be half of two hands. This corresponds to an exposed area of 420 cm², which results in a reasonable worst-case estimate of 2,100-6,300 mg/day.

During manual adding of toluene the area exposed is assessed to be the palms of two hands. This corresponds to an exposed area of 420 cm^2, which results in a reasonable worst-case estimate of

0-42 mg/day. Due to the high volatility of toluene actual dermal exposure will probably be lower. This has not been taking into account because of the limited knowledge in this field.

Assuming a body weight of 70 kg and a dermal absorption of 100% this will lead to an estimated potential internal exposure of 30-90 mg/kg bw/day for manual cleaning and of 0-0.6 mg/kg bw/day for mechanical cleaning.

Conclusions

The 90 percentile of the full-shift exposure data from the BGAA for manual cleaning (62 mg/m^3) agrees with full-shift exposure level estimated with EASE for wide-dispersive use, direct handling with dilution ventilation (95-140 mg/m^3). The 90 percentile for mechanical cleaning (22 mg/m^3) is lower than the EASE-estimate for non-dispersive use with LEV (38-77 mg/m^3).

Because measured data from only one source are available and these exposure levels do not agree with the model results, the 95 percentiles of the measured data are used as reasonable worst-case exposure levels. For full-shift exposure levels during manual cleaning the 95 percentile of 120 mg/m^3 is used as a reasonable worst-case estimate. For mechanical cleaning a full-shift reasonable worst-case exposure level of 44 mg/m^3 is derived from the 95 percentile of the measured data.

The short-term exposure data from BGAA (**Table 4.9**) for cleaning with LEV (90 percentile of 67 mg/m^3) and without LEV (90 percentile of 54 mg/m^3) are of the same level as the full-shift levels for manual cleaning (90 percentile of 62 mg/m^3). For the short-term exposure levels no distinction is made in mechanical and manual cleaning so the levels might be from mechanical cleaning only. The short-term exposure levels from BGAA for cleaning are not used to derive a reasonable worst case because no information on the activities during measurements is provided.

Short-term exposure levels are expected to be twice as high as full-shift level 90 mg/m^3 for mechanical cleaning and 240 mg/m^3 for manual cleaning. Typical exposure levels will be different for manual and mechanical cleaning as well. The 50 percentile of the BGAA data are chosen to represent a typical exposure level of 7 mg/m^3 for mechanical cleaning and 3 mg/m^3 for manual cleaning.

Because no measured data are available for dermal exposure during cleaning activities with toluene the upper range of the EASE-estimates are used to conclude estimated reasonable worst cases of 90 mg/kg bw/day for manual cleaning and 0.6 mg/kg bw/day for mechanical cleaning. Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Conclusions for scenario T1 “Use of cleaning agents”

The following exposure levels will be used for further risk assessment for scenario T1:

- Inhalation exposure: reasonable worst case, full shift:
  - manual cleaning 120 mg/m^3;
  - mechanical cleaning 44 mg/m^3;
- Inhalation exposure: reasonable worst case, short-term:
  - manual cleaning 240 mg/m^3;
  - mechanical cleaning 90 mg/m^3;
- Inhalation exposure: typical, full shift:
  - manual cleaning 3 mg/m^3;
  - mechanical cleaning 7 mg/m^3;

- Dermal exposure: estimated reasonable worst case (repeated dose) [1]:
  - manual cleaning 90 mg/kg bw/day;
  - mechanical cleaning 0.6 mg/kg bw/day.

[1] Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Use of adhesives (scenario T2)

Toluene is used as a solvent in adhesives, which are used for applications in, among others, shoe manufacturing, floor covering work, in plastic and rubber processing, woodworking, production of upholstered furniture, and in leather processing. Most of the adhesives contain up to 50% toluene and a small number of products contain 50-80% toluene (**Table 2.5**). Inhalation and dermal exposure to toluene is possible during application of adhesives by spraying or using a spatula on a surface.

Inhalation exposure

Measured data

Personal full-shift exposure levels are available on applications of adhesives (gluing) containing toluene from Germany (BGAA, 1998), Portugal (Mayan et al., 1999), The Netherlands (TNO, 1998), Denmark (ATABAS), France (COLCHIC), and Sweden (1999). Short-term exposure data on gluing are available from BGAA (1998). Measured data are presented in **Table 4.10** and **Table 4.11**. Information on the measurements and activities performed during measurements are limited for the data from COLCHIC and ATABAS.

Most available exposure data concern the use of adhesives in carpet laying and shoe manufacturing.

Personal full-shift levels on carpet laying are available from a Dutch study (TNO, 1998) and the German database (BGAA, 1998). High exposure levels are expected during use of adhesives in carpet laying. Carpets are glued to the floor using either solvent-based adhesives or water-based adhesives. The adhesive is applied using either a special "comb": a flat piece of metal, plastic, or wood with notch at the edge to ease the flow of the adhesive or with a brush (for less viscous adhesives). The work is generally done in a kneeling position. The exposure situation is determined by the large surfaces from which toluene can evaporate and the short distance from the floor to the nose of the worker. Because the work is performed at shifting places, mechanical ventilation is often absent and replaced by open windows at least when the weather is not too cold.

Carpet laying is usually performed by specialists, i.e. the workers have more or less the same work pattern every day, but they work in different places.

In the Dutch study, information was collected on duration of activities during measurements: preparation (18%), application (14%), finishing (49%), and other e.g. coffee breaks (15%) (calculated as medians). Average duration of sampling was approximately 6 hours (range: 2.5-8.5 hours). Floors were covered in 25-200 m^2 rooms, as well as in staircases. Measurements were performed on water-based (n=50) and solvent-based adhesives (n=37). The solvent-based adhesives contained between 10 and 32.3% toluene. The water-based adhesive contained between 0 an 8% toluene (all but two between 2.5 and 5.2%). Ventilation and time spent in the tasks "finishing" and "other" explained 54% of the variation in exposure levels for "solvent-based adhesive". Total amount of toluene used, ventilation, relative humidity, and time spent in

the other tasks than "application" explained 65% of the variation in exposure levels for "Water based adhesive". No PPE was used (TNO, 1998).

The 90 percentiles of the exposure levels during application of solvent-based adhesives (195 mg/m^3) were in the same range as during application of water-based adhesives (188 mg/m^3), although the toluene content is much higher in the solvent-based adhesives. Solvent-based adhesives were used in small amounts on staircases and for the plinths, generally in small rooms, whereas the water-based products were used in larger amounts and in larger rooms. The amount of product used does explain the fact that exposure levels are (almost) the same.

The 90 percentile of the German data for carpet laying (335 mg/m^3) is higher than the Dutch data. There is no information on toluene levels in the used adhesives. According to the BGAA exposure levels in the region of the 90 percentile are determined during priming in rooms without ventilation (doors and windows closed). The 90 percentile for short-term exposure (358 mg/m^3) is a little bit higher than for full-shift exposure (335 mg/m^3). If carpet laying is performed during a large part (e.g. 6-8 hours) of the day, full-shift and short-term levels will not vary much.

Table 4.10 Toluene exposure data on the application of adhesives

Type of company/work area	N	Full-shift/ short-term	GM (mg/m^3)	GSD (mg/m^3)	50% (mg/m^3)	90% (mg/m^3)	95% (mg/m^3)	Reference Remarks
Carpet laying with solvent based glue	37	Full shift	77	2.2		195		TNO (1998)
Carpet laying with water based glue	50	Full shift	40	4.7		188		TNO (1998)
Gluing (floor-covering work without ventilation)	877	Full shift			45	335	504	BGAA (1998) 244 companies
Gluing (floor-covering work without ventilation)	376	Short term			51	358	489	BGAA (1998) 99 companies
Gluing (plastics and rubber processing) without LEV	128	Full shift			3	158	244	BGAA (1998) 53 companies
Gluing (plastics and rubber processing) with LEV	107	Full shift			3	39	66	BGAA (1998) 42 companies
Gluing (wood-working)	137	Full shift			1	104	196	BGAA (1998) 63 companies
Gluing (manufacture of upholstered furniture)	96	Full shift			1	17	40	BGAA (1998) 28 companies
Gluing (leather processing, shoe manufacture)	333	Full shift			10	152	225	BGAA (1998) 78 companies
Gluing (general)	716	Full shift	6	4.9		49	97	COLCHIC [1)] Range: 0.1 –1,337 mg/m^3 99 sites
Gluing in the shoe producing industry	198	Full shift	4.6	3.7		23	66	COLCHIC [1)] Range: 0.5 –236 mg/m^3 17 sites

Table 4.10 continued overleaf

Table 4.10 continued Toluene exposure data on the application of adhesives

Type of company/work area	N	Full-shift/ short-term	GM (mg/m^3)	GSD (mg/m^3)	50% (mg/m^3)	90% (mg/m^3)	95% (mg/m^3)	Reference Remarks
Gluing	147	Full shift	43	2.6		109		ATABAS [2)]
Gluing of textile material	4		43	1.76		89	109	Swedish data (1999) Sampling time is app. 2 h

N: number of measurements
GM: geometric mean
GSD: geometric standard deviation
[1)] The French National Occupational Exposure dataBase (1987-98). Sampling times from 60 – 480 minutes. Vincent (1998)
[2)] ATABAS The Danish exposure database (1983-1991)

The National Institute of Health from Portugal studied solvent exposure in shoe manufacturing (Mayan et al., 1999). Shoe manufacturing is a continuous process, without physical separation of the workplaces. Although mechanisation is used in shoe manufacturing, many processing steps are manual. Personal (n=1,055) and static (n=106) measurements were performed during cutting, sewing, fitting, and finishing at 580 workplaces in 100 factories. Personal measurements were carried out for representative working periods with a minimum of 90 minutes. Toluene was detected in more than 90% of the samples. Glues, adhesives, and finishing products used in the fitting and finishing departments are reported as the main source of organic solvent exposure. Geometric means of time-weighted averages and standard deviations are reported and presented in **Table 4.11**. The 90 percentile is estimated based on the Geometric Mean (GM) and Geometric Standard Deviation (GSD) assuming a normal distribution and that the arimethic mean is equal to the geometric mean. The equations used are presented in Section 4.1.2. Geometric means vary from 65.9 mg/m^3 (6 workplaces) during cutting to 221 mg/m^3 (200 workplaces) during gluing. The estimates of the 90 percentiles vary from 158 during cutting to 489 mg/m^3 during gluing. The highest exposure levels are reported for workers performing gluing, colouring, and cleaning tasks. There is no information provided which results were from personal or statistic sampling. High exposure levels are correlated with buildings were ventilation and other engineering control measures are inadequate. In 23% of the factories the engineering control measures were reported as effective, in 29% it was established that engineering controls were not effective in all areas of the factory, and in 48% of the factories engineering controls were reported as ineffective.

Table 4.11 Toluene exposure levels during use of adhesives in the shoe manufacturing industry (Mayan et al., 1999)

Workplaces	Number of workplaces	GM (mg/m^3)	SD (mg/m^3)	90 percentile normal 1) (mg/m^3)
Cutting				
cutting	6	65.9	71.8	158
presses/rollers	6	90.0	95.8	213
moulding	12	87.5	74.7	183
Sewing				
sewing	6	89.4	95.3	212
stamping	6	100.3	134.2	272

Table 4.11 continued overleaf

Table 4.11 continued Toluene exposure levels during use of adhesives in the shoe manufacturing industry

Workplaces	Number of workplaces	GM (mg/m^3)	GSD (mg/m^3)	90 percentile normal [1] (mg/m^3)
Fitting				
gluing	200	221.1	208.7	489
shaping	6	170.4	210.9	441
levelling	8	180.7	195.6	431
Finishing				
waxing	100	148.6	249.5	468
colouring	80	138.1	204.9	301
cleaning/ polishing	150	123.3	145.3	410

GM: geometric mean, GSD: geometric standard deviation
[1] Calculated assuming a normal distribution and AM=GM

Modelling

Use of adhesives can be described as: 1) no aerosol formation and non-dispersive use without LEV (application with a comb or brush during carpet laying and use in shoe industry), or 2) aerosol formation, wide dispersive use, and direct handling with or without LEV (spraying).

Inhalation exposure during use of adhesives, assuming a maximum concentration of 80% of toluene in adhesives (partial vapour pressure of 2.4 kPa (0.8·3 Kpa), is estimated with EASE (version 2.0 for Windows) to be:

- application with a comb or brush; (no aerosol forming and non dispersive use without LEV): 100-140 ppm (380-532 mg/m^3);
- spraying without LEV: (wide dispersive use, direct handling, and dilution ventilation): 500-1,000 ppm (1,900-3,800 mg/m^3).

Dermal exposure

Dermal exposure will be higher for spraying than applying of adhesives with a comb or brush.

For gluing with a comb or brush, exposure is assessed, assuming non-dispersive use and an extensive contact level (>10 times a day). For spraying, exposure is assessed, assuming wide-dispersive use and an extensive contact level (>10 times a day):

- potential dermal exposure during applying adhesives with a comb or brush is estimated with EASE to be: 1-5 mg/cm^2;
- potential dermal exposure during spraying is estimated with EASE to be: 5-15 mg/cm^2.

The area potentially exposed depends on the activity. It is assumed that during gluing with a comb or brush, the exposed area will be half of two hands (420 cm^2), which results in a reasonable worst-case estimate of 420-2,100 mg/day. During spraying, the exposed area is assumed to be two hands and a part of the forearms. This corresponds to an exposed area of 1,300 cm^2, which results in a reasonable worst-case estimate of 6,500-19,500 mg/day. Due to the high volatility of toluene, actual dermal exposure will probably be lower. This has not been taken into account because of the limited knowledge in this field.

Assuming a body weight of 70 kg and a dermal absorption of 100% this will lead to an estimated potential internal exposure of 6-30 mg/kg bw/day for gluing with a comb or brush and of 93-279 mg/kg bw/day for spraying.

Conclusions

Toluene containing adhesives are used for a wide variety of applications. High exposure levels are reported for carpet laying and use of adhesives in industry without LEV.

A large amount of measured data on use of adhesives are available from (national) exposure databases and studies. The 90 percentiles for full-shift exposure levels vary from 23 mg/m^3 (general gluing COLCHIC) to 335 mg/m^3 (carpet laying, BGAA). The conservative estimates of the 90 percentiles from the measured data by Mayan et al. (1999) on shoe manufacturing show higher exposure levels (up to 489 mg/m^3).

The EASE estimates for use of adhesives are generally higher than the measured data especially for spraying, though the 90 percentiles of the study by Mayan et al. (1999) do reasonable agree with the EASE estimates for manual application with a comb or a brush. These higher EASE estimates might be caused by the assumption that adhesives may contain up to 80% toluene. In order to assess a reasonable worst-case exposure, the highest toluene concentration in products is used.

The exposure levels for carpet laying and shoe manufacturing are higher than for other gluing activities. The 90 percentile of the German data (335 mg/m^3) and the estimates of the 90 percentiles data from the data by Mayan et al. (1999) are used to derive a reasonable worst-case exposure level for the use of adhesives of 400 mg/m^3. Reasonable worst-case short-term exposure levels are expected to be up to the higher (extreme) values for full-shift exposure 500 mg/m^3. Typical full-shift exposure levels will be lower and are estimated to be approximately 75 mg/m^3.

Because there are no measured data available for dermal exposure during use of adhesives, the upper range of the EASE-estimates for spraying toluene is used to conclude an estimated reasonable worst case of 279 mg/kg bw/day. Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Conclusions for scenario T2 "Use of adhesives"

The following exposure levels will be used for further risk assessment for scenario T2:

- Inhalation exposure: reasonable worst case, full shift: 400 mg/m^3;
- Inhalation exposure: reasonable worst case, short-term: 500 mg/m^3;
- Inhalation exposure: typical, full shift: 75 mg/m^3;
- Dermal exposure: reasonable worst case (repeated dose) [1)]: 279 mg/kg bw/day.

[1)] Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Use of paints, inks and lacquers (scenario T3)

Use of paints, inks, and lacquers can be distinguished in aerosol forming and non-aerosol forming activities. Aerosol forming activities are for example spray painting and printing. During these activities both inhalation and dermal exposure can occur. Non-aerosol forming activities are for example painting or transferring a liquid in the printing industry. Paints, inks, and lacquers may contain up to 80% toluene according to the Danish Product Register (**Table 2.5**).

Inhalation exposure

Measured data

Measured data are available on rotogravure printing, painting (rolling and brushing), spray painting, metal surface coating, and blanket varnishing.

Printing

In a large field study performed by Glöckle et al. (1996) on rotogravure printing exposure has been measured for practically all different job categories and processes in rotogravure printing. The principle of rotogravure printing is that the image consists of small cups (in old times, they were engraved) in the printing cylinder. The image is transferred to the printing, which is copper coated iron cylinder, by a photographic process and the cups are etched into the copper. When the cylinder is placed in the printing machine, it is partly dipped into the printing ink. When rotating, the surplus ink is scraped off the cylinder by a doctor blade leaving the cups filled with ink. The ink is sucked up of the cups and into the paper during printing. Rotogravure printing is performed in large numbers, printing speed is high, and the machines are large.

Personal (n=1,614) and static (n=887) measurements were done from 1993 to 1995. Results from personal measurements (90 and 50 percentile) and information on the measurements such as workplace or job performed, number of measurements and companies are presented in **Table 4.13**. Exposure levels were determined for printers controlling the print quality (main control desk), controlling the viscosity of the ink (e.g. printing press), handling the large paper rolls, and stacking and bundling the prints (delivery). When the paper breaks and the workers must remove the paper and draw new paper in the machine the printer enters the so-called "Printing unit, 1st level". Cleaning of cylinders is often done in pure toluene in special cleaning machines. Exposure is expected to be very high when the cleaning machines are emptied because of toluene dripping from the cylinder. Glöckle et al. reported that from the four main work areas in rotogravure printing, 1) printing cylinder preparation, 2) printing/proof printing, 3) finishing, and 4) other work areas, the highest exposure levels are found in the areas printing/proof printing with mean 90 percentiles of personal exposure level range from 28 mg/m^3 (binder) to 358 mg/m^3 at the printing unit. For static sampling (n= 887) 90 percentiles varied from 25 to 736 mg/m^3 (Glöckle et al., 1996).

The French National Occupational Exposure Database (COLCHIC) provided data on rotogravure printing (heliogravure printing) and serigraphy printing from 1987 to 1998. For rotogravure printing, measurements from personal sampling (n=313) during 60-480 minutes range from 0.2-1,129 mg/m^3 (GM=42 mg/m^3, GSD=8.3). The 90 percentile was reported to be 334 mg/m^3. No further detail was presented on the measurements.

Some measured data are also available on other printing activities. COLCHIC presented measurements (n=489) on serigraphy printing. The 90 percentile is 99 mg/m^3 (GM=7.1 mg/m^3, GSD=8.4). Measured data (n=94) from the Danish database ATABAS for serigraphy printing show a 90 percentile of 49 mg/m^3 (GM=7.7 mg/m^3, GSD=4.7).

The data on printing collected from 1991-1995 by BGAA (1998) are presented in **Table 4.13**. The highest 90 percentile is for manual screen printing without ventilation: 303 mg/m^3.

Two measurements were performed on screen printing by the Swedish labour inspector (data collected from 1990-1998 from NBOSH register). Sampling time was 2.5 hours and results were 94 and 157 mg/m^3. No further detail was presented on the measurements.

Belgium provided some measured data on occupational exposure in workshops and industry over the period 1985-1996 (Belgium, COM.ECB4/032/98). A total of 26,726 air samples were analysed for organic solvents, 9,910 (37%) of the measurements contained toluene. A subset of 1,743 samples could be identified as personal air samples with a duration of 2-8 hours. Some statistics on the subset were provided: the geometric mean is 9.5 mg/m^3 (GSD = 5.0 mg/m^3), 50 and 90 percentiles are 7.3 and 87.2 mg/m^3, respectively. In 80 measurements (5%) exposure was higher than 190 mg/m^3. These levels were most frequently reported to occur during paint manufacturing (17) and printing (rotogravure printing and silkscreen printing) (13). No further details on the activities during measurements were reported.

Table 4.12 Personal exposure on rotogravure printing (short-term measurements) (Glöckle et al., 1996)

Type of process	N	No. of companies	50% (mg/m^3)	90% (mg/m^3)
Bindery, general	22	6	8	34
Galvanic, coppering systems	20	9	8	74
Office of department head	24	9	9	31
Perfect binder	22	6	11	28
Post press, general	66	12	12	35
Office of head of shift	17	8	13	79
Saddle stitcher	169	12	14	53
Engraving machine	38	7	15	131
Material transport, end product	27	6	15	67
Galvanic, chroming systems	10	7	15	121
Inserting machine	43	6	20	45
Repair shop	44	10	35	163
Reel stand, reel cellar	78	12	37	123
Printing form preparation, general	33	9	37	137
Cylinder correction	12	4	40	116
Reel stand, machine level	12	4	46	183
Printing press	64	11	63	203
Delivery, log stacker, buffer roll	72	10	77	203
Proofing presses, general	14	6	77	128
Printing units	13	5	110	183
Main control desk	335	13	113	258
Delivery: pallets, bundles, stacks	84	12	118	243
Delivery	12	4	129	176
Printing units, 1st level	101	12	133	358
Cylinder washing machine	18	8	135	287
Bundle stacker	6	3	NS	NS
Folder	5	4	NS	NS

N: number of measurements. NS: no statistical calculation possible

Table 4.13 Personal exposure levels on printing (BGAA, 1998)

Type of company/work area	N	No. of companies	50%-value (mg/m^3)	90%-value (mg/m^3)	95%-value (mg/m^3)
Screen-printing, manual (construction industry) - without technical measures (ventilation) - with technical measures (ventilation)	25 18	8 3	15 10	303 36	351 54
Screen-printing, manual (ceramics and glass industry, printing works)	66	25	1	18	156
Printing (gravure illustration printing industry) - without technical measures (ventilation) - with technical measures (ventilation)	470 849	13 14	17 86	85 232	118 284

N: number of measurements

Painting

Measured exposure data on manual painting, spray painting, metal surface coating, and blanket varnishing have been provided by BGAA (1998), COLCHIC (1998), ATABAS, and the Swedish exposure register (National Board of Occupational Safety and Health (NBOSH, 1999). Exposure data are presented in **Table 4.14**. The reported 90 percentiles full-shift exposure levels for spray painting vary from 15 mg/m^3 in metalworking (n=546, BGAA) to 68 mg/m^3 (COLCHIC). For manual painting (rolling and brushing) 90-percentile exposure levels vary from 4 mg/m^3 during brushing and rolling in the construction industry (n=285, BGAA, 1998) to 44 mg/m^3 painting of furniture/wood material (NBOSH, 1999). High 90 percentile exposure levels are reported for mechanical surface coating without ventilation in woodworking (164 mg/m^3, the plastic and rubber industry (192 mg/m^3) by BGAA, 1998) and for blanket varnishing (172 mg/m^3 (n=7), COLCHIC, 1998).

Table 4.14 Personal exposure levels on spray painting, rolling and brushing, surface coating and blanket varnishing

Type of company/work area	N	GM (mg/m^3)	GSD	50% (mg/m^3)	90% (mg/m^3)	95% (mg/m^3)	Full shift/ Short-term	Reference/ Remarks
Spray painting	602	8	5.2		68			COLCHIC
Spray painting	261	9	6.2		62			ATABAS
Spray painting of cupboards, wardrobes, kitchen fixtures	97	1	2.48		1	1.1	Short	NBOSH (1999) 19 companies 15 min
Spray-painting (metal-working, electrical engineering)	546			2	15	38	Full	BGAA (1998) 295 companies
Spray-painting (construction industry)	406			3	32	50	Full	BGAA (1998) 82 companies
Spray-painting (wood-working)	1337			5	36	54	Full	BGAA (1998) 510 companies
Painting, furniture/wood material	8	7	4,08		44	73	Full	NBOSH (1999) Range 1-48 mg/m^3 4 companies 5.5-7.5 hours

Table 4.14 continued overleaf

Table 4.14 continued Personal exposure levels on spray painting, rolling and brushing, surface coating and blanket varnishing

Type of company/work area	N	GM (mg/m³)	GSD	50% (mg/m³)	90% (mg/m³)	95% (mg/m³)	Full shift/ Short-term	Reference/ Remarks
Brush and roller application (metal-working) - without ventilation - with ventilation	 93 22			 1 1	 27 8	 44 16	Full	BGAA (1998) 71 companies
Brush and roller application (construction industry) without ventilation	285			note A	4	25	Full	BGAA (1998) 78 companies
Brush application, painting by hand (porcelain industry) without ventilation	94			3	26	33	Full	BGAA (1998) 33 companies
Blanket varnishing	162	7	10.5		172			COLCHIC
Blanket varnishing	183	15	6.8		126			ATABAS
Mechanical surface coating (plastics and rubber industry) - without ventilation - with ventilation	 121 117			 3 1	 192 39	 352 56	Full	BGAA (1998) 93 companies
Mechanical surface coating (metal-working, electrical engineering)	148			2	21	32	Full	BGAA (1998) 76 companies
Surface treatment metal	11	48	2,67		169	241	Full	NBOSH (1999) 11-167 mg/m³ 7,5 hours
Mechanical surface coating (wood-working) - without ventilation - with ventilation	 168 440			 10 7	 164 90	 218 138	Full	BGAA (1998) 198 companies

N: number of measurements; GM: geometric mean; GSD: geometric standard deviation

Modelling

Use of paint, inks and lacquers can be described as: 1) no aerosol formation and non-dispersive use without LEV (e.g. rolling and brushing and printing), 2) aerosol formation, wide-dispersive use and dilution ventilation (spray painting), 3) aerosol formation, non-dispersive use and LEV (metal surface coating and blanket varnishing).

Inhalation exposure during use of paint, inks, and lacquers assuming a maximum concentration of 80% of toluene, is estimated with EASE (version 2.0 for Windows) to be:

- rolling and brushing and printing (no aerosol forming and non dispersive use without LEV): 100-140 ppm (380-532 mg/m^3);
- metal surface coating and blanket varnishing; (aerosol forming and non dispersive use with LEV): 100-200 ppm (380-760 mg/m^3);
- spraying: (aerosol forming and wide-dispersive use, direct handling and dilution ventilation): 500-1,000 ppm (1,900-3,800 mg/m^3).

Dermal exposure

Dermal exposure can occur during spray painting, manual painting, and during transfer of liquid in the printing industry. The dermal exposure estimated by EASE during these activities is given below.

Spray painting concerns wide dispersive use, direct handling, and extensive contact. This leads to an estimated dermal exposure of 5-15 mg/cm^2/day. During the spray painting both hands and a part of the forearms could be exposed. This corresponds to an exposed area of 1,300 cm^2. This leads to an estimated exposure of 6,500-19,500 mg/day. When the contact level is intermittent the estimated exposure becomes 1,300-6,500 mg/day.

Painting concerns non-dispersive use and direct handling with extensive contact. This leads to an estimated exposure of 1-5 mg/cm^2/day. During painting only the fingers will be exposed, this corresponds to an exposed area of 400 cm^2, which leads to an estimated exposure of 400-2,000 mg/day.

In the printing industry and during mechanical coating and blanket varnishing dermal exposure is expected during transfer of a liquid. This concerns non-dispersive use and direct handling with intermittent contact, which leads to an estimated exposure of 0.1-1 mg/cm^2/day. During the transfer of a liquid only the fingers will be exposed, this corresponds to an exposed area of 400 cm^2. The resulting estimated exposure becomes 40 to 400 mg/day.

Assuming a body weight of 70 kg and a dermal absorption of 100% this will lead to an estimated potential internal exposure of 93-279 mg/kg bw/day or 19-93 mg/kg bw/day for spray painting with extensive or intermittent contact level, respectively, of 6-29 mg/kg bw/day for painting, and of 0.6-6 mg/kg bw/day for printing. Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment for these scenarios. For spray painting, evaporation is thought to have only very limited influence on the actual dermal the exposure, since spray painting is considered a steady state process.

Conclusions

A large amount of measured data are available on inhalation exposure during rotogravure printing, painting (spraying and manual) and mechanical surface coating.

The extended data from Glöckle et al. (1996) on rotogravure printing are considered to be representative for the European rotogravure industry. The variation in exposure levels is large, depending on the activities performed and the presence of effective local exhaust ventilation. High exposure levels between 250 and 360 mg/m^3 (90 percentiles) will occur during cleaning activities, close to the printing units and at the main control desk. The 90 percentiles from the French database (COLCHIC) of 334 mg/m^3 and the German data on printing with ventilation of 232 mg/m^3 (BGAA, 1998) are in line with these results. High exposure levels are also reported for manual screen printing without ventilation (303 mg/m^3) in the construction industry by BGAA. Lower exposure levels are reported for serigraphy printing by COLCHIC (90 percentile of 99 mg/m^3) and ATABAS (90 percentile of 49 mg/m^3).

For printing (specifically for rotogravure and screen-printing) a reasonable worst-case estimate for full-shift exposure levels is derived of 350 mg/m^3. Short-term exposure levels are expected to be twice this level: 700 mg/m^3. Typical full-shift exposure levels are expected to be 80 mg/m^3.

Reported exposure data are higher for mechanical surface coating and blanket varnishing than for manual painting (rolling and brushing) and spray painting.

Based on the data provided by COLCHIC, ATABAS, BGAA, and NBOSH a full-shift reasonable worst-case exposure level for painting (manual and spraying) is derived of 50 mg/m^3. Short-term exposure levels are expected to be twice this level: 100 mg/m^3. Typical exposure levels are expected to be 8 mg/m^3.

During mechanical surface coating and blanket varnishing full exposure levels will be higher 170 mg/m^3. Short-term exposure levels are estimated to be 340 mg/m^3. Typical exposure levels will be lower 10 mg/m^3.

The EASE-estimates are used to conclude estimated reasonable worst-case levels for dermal exposure. For spray painting an estimated reasonable worst case of 279 mg/bw/day is concluded, dermal exposure levels are estimated to be lower for manual painting: 29 mg/bw/day. In the printing industry and during mechanical coating and blanket varnishing, dermal exposure is estimated to be 6 mg/kg bw/day. Due to the high volatility of toluene actual dermal exposure will probably be lower, except for spray painting, which is considered a steady state process. This has not been taking into account because of the limited knowledge in this field.

Conclusions for scenario T3 "Use of paint, inks, and lacquers"

The following exposure levels will be used for further risk assessment for scenario T3.

- Inhalation exposure: reasonable worst case, full shift:
  - printing: 350 mg/m^3;
  - painting (manual and spraying): 50 mg/m^3;
  - painting (mechanical coating and blanket varnishing): 170 mg/m^3;
- Inhalation exposure: reasonable worst case, short-term:
  - printing: 700 mg/m^3;
  - painting (manual and spraying): 100 mg/m^3;
  - painting (mechanical coating and blanket varnishing): 340 mg/m^3;
- Inhalation exposure: typical, full shift:
  - printing: 80 mg/m^3;
  - painting (manual and spraying): 8 mg/m^3;
  - painting (mechanical coating and blanket varnishing): 10 mg/m^3;
- Dermal exposure: estimated reasonable worst case (repeated dose) [1)]:
  - printing: 6 mg/kg bw/day;
  - painting
    - manual: 29 mg/ kg bw/day;
    - spraying: 279 mg/ kg bw/day;
  - painting (mechanical coating and blanket varnishing): 6 mg/ kg bw/day.

1) Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

Duration of inhalation exposure during use of toluene containing product due to specific activities is estimated to be 4-6 hour/day, whereas exposure to background concentrations is 6-8 hours per day. Frequency of exposure is expected to be up to 200 days/year.

4.1.1.2.5 Conclusion on occupational exposure

See **Table 4.15**.

Table 4.15 Conclusions of the occupational exposure assessment

Scenario / subscenario	Exposure		Estimated inhalation exposure level (mg/m³)						Estimated skin exposure level
	Duration (hr/day)	Frequency (day/year)	Full shift (8-hour-time weighted average)				Short-	term	(mg/kg bw/day)[1,2]
			Typical	Method	RWC	Method	RWC	Method	RWC
Production and use as an intermediate									
a) production and use as an intermediate	6-8	200	3	measured	45	measured	100	expert judg.	6
b) use as an intermediate	6-8	200		measured	15	measured			6
c) maintenance	6-8	200		measured	45	measured			9
2. Production of gasoline									
a) maintenance and tank cleaning	2-4	200	1	measured	70	measured	140	expert judg.	1.9
b) operators at production sites	6-8	200	1	measured	20	measured	30	expert judg.	1.2
c) transfer of gasoline	6-8	200	2.5	measured	50	measured	100	expert judg.	1.2
d) attendants at service stations	4-6	200	0.5	measured	3	measured	6	expert judg.	0.6
3. Production of products (transfer, filling and drumming)	6-8	200	4	measured	98	measured	200	expert judg.	6
4. Use of toluene containing products									
a) manual cleaning	4-6	200	3	measured	120	measured	240	expert judg.	90
mechanical cleaning	4-6	200	7	measured	44	measured	90	expert judg.	0.6
b) use of adhesives	4-6	200	75	measured	400	measured	500	measured	279
c) printing	4-6	200	80	measured	350	measured	700	expert judg.	6
d) painting: manual	4-6	200	8	measured	50	measured	100	expert judg.	29
spraying	4-6	200	8	measured	50	measured	100	expert judg.	279
mechanical coating	4-6	200	10	measured	170	measured	340	expert judg.	6

RWC: Reasonable worst case;

1) Evaporation from the skin due to the high volatility of toluene has not been taken into account in the dermal exposure assessment.

2) According to the US EPA, the estimated amount of substance deposited on the skin is approximately in line with results which could be obtained using the proposed revised CEB method for screening-level assessments of dermal exposure for similar working situations (US EPA, 2001)

4.1.1.3 Consumer exposure

4.1.1.3.1 Consumer exposure scenarios

Toluene is present in various consumer products, including paints, adhesives, varnishes, and inks for pens (Danish Product Register, 1998, **Table 2.5**). The only measured data on toluene in consumer products were from glue products. Rastogi (1993) investigated 26 glue products for non-occupational use, twenty-two of which contained toluene:

Table 4.16 Toluene glues for hobby use (Rastogi, 1993)

Percent range	Number of products	%
0 – 0.042	9	40.9
0.043 – 0.05	6	27.3
1.0 – 28.5	7	31.8
Total	22	100.0

No other references were found on consumer products containing toluene.

Five scenarios are considered for consumer exposure:

U1 Gluing,
U2 Spray painting,
U3 Car maintenance,
U4 Carpet laying, and
U5 Filling gasoline at self-service gas stations.

Although the production and use of gasoline is not formally a part of this risk assessment (cf. Section 0), exposure during filling gasoline at self-service gas stations (scenario U5) is assessed. This is done for illustrative purposes in order to be able to compare the exposure to toluene in this scenario with other scenarios.

According to the safety data sheets from some Dutch paint industries toluene may also be used as solvent in polyurethane varnishes for very specific uses (boat varnishes), and as a paintbrush cleaner. However, these scenarios will not be considered in this risk assessment.

The scenarios were selected based on:

- the amount of product used,
- the concentration of toluene in the product (shown in **Table 4.16**), and
- the frequency of exposure.

Defaults used are:

- inhalation rate: 20 m^3/day (EUSES, 1997)
- consumer body weight: 70 kg
- hobby room size: 20 m^3 (Bremmer and Veen, 1999).

Amount of product used, exposure frequency and exposure duration used in the scenarios (including exposure time after use) are in agreement with the US EPA (1987) for household

solvent products, covering 90% of the people questioned for the scenarios gluing, spray painting and car maintenance.

4.1.1.3.2 Gluing (scenario U1)

Gluing scenario is estimated for hobbyists, e.g. modelling to scale (aeroplanes, ships). Rastogi (1993) determined toluene in glues: a maximum of 28.5% was found in super glues (liquid cement for plastic) used for modelling to scale.

Inhalation exposure

According to APA (1998), the amount used for this type of glues will be 0.5 g per event. This amount seems realistic for a hobbyist modelling to scale. It is assumed that the room is not ventilated and that 100% of the toluene in the glue evaporates. The concentration then will be: 500 mg glue · 28.5% · 1/(20 m^3 room volume) = 7.1 mg/m^3.

An exposure period of (30 min use + 180 min stay after use) 210 min/day (US EPA, 1987) is used. The exposure by inhalation is then: 7.1 mg/m^3 · 1/(70 kg bw) · 20 m^3/day inhaled volume · 210 min/event · 1/(1,440 min/day) = 0.30 mg/kg bw per event.

External dermal exposure

Skin is assumed to be exposed to approximately 0.5% of the used glue (Bremmer and Veen, 1999) and all toluene is assumed to be available for absorption. The exposure to toluene is then: 500 mg glue · 28,5% · 0.5% · 1/(70 kg bw) = 0.010 mg/kg bw.

Based on the frequency of use for this scenario, estimated to be once a week and the T1/2 of toluene in the body (approximately 3 days), an acute time scale is considered appropriate.

4.1.1.3.3 Spray painting (scenario U2)

Spray painting scenario is estimated for hobbyists, e.g. modelling to scale, making aeroplanes and ship models. Amateurs using compressed air will not be considered (Bremmer and Veen, 1999). According to Dutch experts (Bremmer and Veen, 1999) spray paints consists of volatile gases that are used as propellant and solvent (>80%) and less volatile substances such as the paint. The spray paints for household use are not expected to contain toluene, as toluene is not volatile enough for being a propellant. However, in order to evaluate the risk for consumers in case there indeed are spray cans containing toluene available for consumers, this scenario is included in the risk assessment.

Inhalation exposure

Toluene may be used as a solvent for the paint. As this use is for specific conditions, the scenario will be based on hobbyists painting their models. Calculations are based on amount of paint used and the concentration of toluene in the paint, that is 100 g and 20%, respectively (APA, 1998). It is assumed that the room is not ventilated and that 100% of the toluene in the paint evaporates. The concentration then will be 100,000 mg paint · 20% · 1/(20 m^3 room volume) = 1,000 mg/m^3.

An exposure period similar to gluing of (30 min use + 180 min stay after use) 210 min/day is used. The exposure is then: 1,000 mg/m^3 · 1/(70 kg bw) · 20 m^3/day inhaled volume · 210 min/event · 1/(1,440 min/day) = 41.7 mg/kg bw per event.

External dermal exposure

The skin is assumed to be exposed to approximately 0.5% of the used paint (Bremmer and Veen, 1999) and all toluene is considered to be available for absorption. The skin exposure on a painting event is then: 100,000 mg · 20% · 0. 5% · 1/(70 kg bw) = 1.43 mg/kg bw per event.

Based on the frequency of use for this scenario, estimated to be once a week and the T1/2 of toluene in the body (approximately 3 days), an acute time scale is considered appropriate.

4.1.1.3.4 Car maintenance (scenario U3)

Car polishing (scenario U3A)

This scenario is estimated for people who polish their cars with a polish that contains 2% toluene (**Table 2.5**, Danish Product Register). The amount used per event is estimated to be 10 g. The time spent on polishing is considered similar to gluing 210 minutes per day, taking place in a small garage without ventilation and closed doors. The number of polishing events is estimated to be once every 10 weeks (0.1 event per week).

Inhalation exposure

The amount of product used for polishing will be 10 g per event. It is assumed that the room will not be ventilated and that 100% of the toluene in the polish will evaporate. The concentration in the garage is calculated then 10,000 mg · 2% · 1/(20 m^3) =10 mg/m^3.

Using an exposure period of 210 min/day similar to gluing, the exposure by inhalation is then: 10 mg/m^3 · 1/(70 kg bw) · 20m^3/day inhaled · 210 min/event · 1/(1,440 min/day)= 0.42 mg/kg bw per event.

External dermal exposure

Skin is assumed to be exposed to circa 0.5% of the used polish (similar to the gluing scenario) and all toluene is assumed to be available for absorption (external exposure). The exposure to toluene is then: 10,000 mg glue · 2% · 0.5% · 1/(70 kg bw) = 0.014 mg/kg bw per event.

Based on the frequency of use for this scenario, estimated to be once a week and the T1/2 of toluene in the body (approximately 3 days) an acute time scale is considered appropriate.

Cleaning hands in solvent based cleaning agent (scenario U3B)

This scenario is estimated for people who work on their cars and clean their hands with a cleaning agent that contains toluene. The concentration is assumed to be 65% (**Table 2.5**, Danish Product Register).

Inhalation exposure

During washing the hands, the cleaning product will be diluted and flushed away with water. The inhalation exposure time will be very short and therefore this exposure route is considered negligible.

External dermal exposure

The cleaning product will be intensively in contact with the skin. It is assumed that approximately 10 grams of cleaning agent is used and that 10% remains on the skin (TGD, 1996). It is assumed that all toluene left on the skin is available for absorption. The skin will then be exposed to: 10,000 mg · 65% · 10% · 1/(70 kg bw) = 9.3 mg/kg bw per event. According to the US EPA (1987), the frequency of use of solvent-type cleaning product is 46 times per year.

Based on the frequency of use for this scenario, estimated to be once a week and the T1/2 of toluene in the body (approximately 3 days), an acute time scale is considered appropriate.

4.1.1.3.5 Carpet laying (scenario U4)

Exposure of privates laying carpets using toluene-containing glue is expected to be similar to the exposure of workers laying carpets, since professional carpet-layers sometimes work in private homes. However, for consumers the frequency of laying carpets are expected to be very low.

Inhalation exposure

Measured exposure data are available for carpet laying performed by professionals (**Table 4.11**). Based on the available 8-hour full-shift exposure data for laying carpets (90 percentiles: 188 and 195 mg/m^3, respectively (TNO, 1998)) an air concentration of 195 mg/m^3 is chosen to represent a realistic worst-case situation.

The exposure is then: 195 mg/m^3 · 20 m^3/day · 8 hour/event · 1/(24 hours/day) · 1/(70 kg bw) = 18.6 mg/kg bw per event.

External dermal exposure

Dermal exposure is for this scenario calculated using the EASE model, because of the similarity to workers exposure (cf. scenario T2).

For gluing with a comb or brush exposure is assessed, assuming non-dispersive use and an extensive contact level (>10 times a day). Potential dermal exposure is estimated with EASE to be: 1-5 mg/cm^2.

It is assumed that the exposed area will be half of two hands (420 cm^2), which results in a reasonable worst-case estimate of 6-30 mg/kg bw/ day. This estimate does not take into account the evaporation of toluene from the skin.

Based on the very low frequency of use for this scenario, an acute time scale is considered appropriate.

4.1.1.3.6 Filling gasoline at self-service gas stations (scenario U5)

Inhalation exposure

Some measured data are available for exposure during filling gasoline at self-service gas stations (**Table 4.17**). No information is given on the exposure period.

Table 4.17 Exposures to toluene at self-service gas stations

Type of work	N	AM (mg/m^3)	Range (mg/m^3)
Clayton (1983)		11	0-63
Clayton (1991)	59	7	0–44

N: number of measurements; AM: arithmetic mean

The exposure period is usually only the time it takes to fill the gasoline tank. People driving many kilometres may need to fill up their tanks 5 days a week. With a concentration of 63 mg/m^3 and an exposure period of 10 min/event, the exposure event is assumed to be: 63 $mg/m^3 \cdot 20\ m^3/day \cdot 15$ min/event $\cdot 1/(1{,}440$ min/day$) \cdot 1/(70$ kg bw$) = 0.2$ mg/kg bw/event.

With an assumed frequency of 5 events/week, the exposure per day is assumed to be: 0.2 mg/kg bw/event $\cdot$ 5 events/week $\cdot 1/(7$ days/week$) = 0.13$ mg/kg bw/day.

External dermal exposure

Dermal exposure during filling of gasoline at self service gas stations is considered negligible. Based on the frequency of use for this scenario, a chronic time scale is considered appropriate.

4.1.1.3.7 Conclusion on consumer exposure

Table 4.18 Consumer exposure model scenarios

Exposure	Scenarios					
	U1 acute	U2 acute	U3A acute	U3A acute	U4 acute	U5 [1] chronic
Air concentration (mg/m^3)	7.1	1,000	10	Negligible	195	63
Uptake via inhalation (mg/kg bw/event)	0.3	41.7	0.42	Negligible	18.6	0.13 [3]
Potential dermal exposure (mg/kg bw/event) [2]	0.01	1.43	0.014	9.3	30	Negligible

1) Included for illustrative purposes
2) Dermal exposure modelled using the EASE, because of the similarity to workers exposure
3) mg/kg bw/day

4.1.1.4 Humans exposed via the environment

Please refer to Section 3.3.5.

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

4.1.2.1 Toxico-kinetics, metabolism and distribution

Data from human exposure and animal experiments are available.

Uptake via inhalation

The major uptake of toluene vapour is through the respiratory system. A number of investigations in humans (Carlsson, 1982; Carlsson and Lindqvist, 1977; Nomiyama and Nomiyama, 1974; Åstrand 1975) have shown that at rest a three-hour exposure to toluene vapour will result in an uptake amounting to approximately 50% of the inhaled toluene.

The concentration of toluene in alveolar air and in arterial and venous blood rises quickly during the first 10-15 minutes of exposure (Carlsson, 1982; Åstrand et al., 1972). After only 10 seconds of exposure toluene can be detected in blood from brachial arteries (Åstrand et al., 1972).

Data from experimental exposure of voluntary study subjects show that physical work results in increased toluene uptake (Veulemans and Masschelein, 1978b; Carlsson, 1982). Using a 50 W workload, exposure to 300 mg/m^3 (80 ppm) toluene for 2 hours did not result in steady state of the blood concentration of toluene in 12 study subjects. The toluene uptake was 2.4 times higher than the uptake at rest. During the work, lung ventilation was increased 2.8 times. Concentrations of toluene in alveolar air and blood increased with increasing work loads (0-150 W in periods of 30 minutes) (Carlsson, 1982). The amount of toluene absorbed increased with greater amounts of body fat (Carlsson and Ljungquist, 1982).

In nine male volunteers exposed to 200 mg/m^3 (53 ppm) toluene for 2 hours during a workload of 50 W, the total uptake of toluene was 50% of that inhaled (Löf et al., 1993).

In rats, toluene uptake after inhalation is rapid. During a three-hour exposure to 575 ppm (2,155 mg/m^3) blood and brain toluene levels reached estimated asymptotic levels in 53 and 58 minutes, respectively (Benignus et al., 1981).

In dogs exposed to 370-820 mg/m^3 (100-220 ppm) toluene via inhalation for 1-2 minutes, an uptake of approximately 90% was determined. The uptake of toluene was similar in the upper and lower repiratory tract (Egle and Gochberg, 1976).

In conclusion, toluene is absorbed rapidly via inhalation and the amount absorbed depends on pulmonary ventilation.

Uptake via oral exposure

Case reports of accidents and attempted suicides, and clinical trials involving toluene administration to leukaemia patients (Braier, 1953) show that toluene is absorbed via the alimentary system in humans.

In rats, uptake of toluene via the alimentary system is slower than the respiratory uptake. Toluene concentration in blood reached maximum values two hours after an oral dose (Pyykkö et al., 1977). About 76% was recovered as hippuric acid in the urine (Knoop and Gerhrke, 1925), and approximately 18% was excreted as toluene vapour through the respiratory system (Smith et al., 1954). Absorption appears to be nearly 100%.

In rabbits, orally dosed toluene also seems to be absorbed 100% (El Masry et al., 1956; Smith et al., 1954).

In conclusion, toluene is absorbed almost completely from the gastrointestinal channel.

Uptake via dermal exposure

Liquid toluene can be absorbed through the skin. In five volunteers exposed to toluene by immersing a hand up to the wrist in liquid toluene for 30 minutes, maximum concentrations of toluene in blood (0.17 mg/l) were found 30 minutes after start of the exposure. The maximum blood toluene concentration was maintained for 10-15 minutes after exposure had ended and was a quarter of that achieved in a two-hour inhalation exposure to 100 ppm (375 mg/m^3) toluene vapour (Sato and Nakajima, 1978).

After skin exposure of 10 male volunteers to toluene vapour (2,250 mg/m^3 (600 ppm)), excluding respiratory uptake, steady state occurred after 30 minutes with a toluene concentration of 1.08 µmol/l (100 µg/l) in venous blood. The total duration of exposure was 3.5 hours. Based on average values for lung retention and lung excretion of toluene, it was estimated that the percutaneous uptake of toluene vapour amounted to approximately 1% of the respiratory uptake at the identical air concentration (Riihimäki and Pfäffli, 1978). A similar relation between lung and percutaneous uptake of toluene is given elsewhere (Piotrowski, 1967).

The capability of toluene to penetrate the skin was investigated in isolated rat skin. At steady state, a penetration of 8.5 nmol/cm^2min (0.78 µg/cm^2min) was determined (Tsuruta, 1982).

In conclusion, dermal uptake after skin exposure to liquid toluene occurs to a limited degree. Dermal exposure to toluene vapours is not likely to be an important route.

Distribution

The blood/air partition coefficient for toluene is 11.2-15.6 at 37°C (Lindqvist, 1977; Sato et al., 1972; Sato and Nakajima, 1977; Sherwood, 1976; Ulfvarson and Övrum, 1976).

The distribution of toluene in the body is among other factors dependent on the tissue/blood partition coefficients and the metabolism. In rabbits the following partition coefficients have been found: brain, heart, liver, and intestine: 2.3, muscle tissue: 1.6, adipose tissue: 74.3, bone, connective tissue, and lung tissue: 1.9 (Sato et al., 1974). In rats brain/blood ratios of 1.2 (Kishi et al., 1988) and 1.7 (Zahlsen et al., 1992) have been determined. In humans the adipose tissue/blood partition coefficient for toluene is determined to be 81-83 (Sato et al., 1974; Sherwood, 1976). This high partition coefficient suggests that toluene can be accumulated in adipose tissue. Estimation of the biological half-lives (see later) provides further evidence for this suggestion.

In mice, the distribution of toluene and its metabolites was investigated using whole body autoradiography after acute inhalation of side chain marked ^{14}C toluene (Bergman, 1979; Bergman, 1983). In adipose tissue, bone marrow, spinal nerves, spinal cord, and in the white parts of the brain, high concentrations of radioactivity occurred as judged from the photographs. In blood, liver, and kidneys, radioactivity was also found. One hour after exposure nerve tissue showed no radioactivity. In adipose tissue nearly all radioactivity had disappeared four hours after exposure, and only traces of non-volatile radioactivity could be found in the liver. After 24 hours all radioactivity had disappeared from the body.

In rats, subcutaneous injection of toluene (100 or 500 mg/kg) resulted in maximum concentrations of blood toluene after 2 hours (Benignus et al., 1984).

Toluene passes the placenta. Two hours following exposure of rats via inhalation to 1,375 or 2,700 mg/m^3 (367 or 720 ppm) for 24 hours, foetal blood had a toluene concentration of 74% of that found in the dam's blood. The amniotic liquid contained a toluene concentration of 5% of that in the dam's blood. Four and six hours after exposure, similar relative toluene concentrations were found (Ungváry, 1984; quoted from IPCS 1985).

Groups of four 11, 14 or 17 day pregnant mice were killed 0, 30, 60 and 240 minutes after having inhaled 7,500 mg/m^3 (2,000 ppm) ^{14}C-toluene for ten minutes. Radioactivity as volatile and non-volatile was measured in lung, liver, kidney, brain, cerebellum, fat, plasma, amniotic fluid, placenta, and foetus. It was shown that toluene immediately after inhalation was taken up in the foetal tissue at a concentration of about 10% of that found in the maternal lungs. At four hours after exposure the toluene radioactivity was decreased to 2% of the original value (Ghantous and Danielsson, 1986).

Toluene has been found in human breast milk. In 12 pooled samples from four urban areas in the United States, toluene was identified qualitatively in at least 7 samples (Pellizzari et al., 1982; quoted from Jensen and Slorach, 1991).

Four lactating rats received a single subcutaneous injection of 1.2 g toluene/kg on the 10th day of lactation (Da-Silva et al., 1991). Four hours after injection the concentration of toluene in blood was 2.1 mg% and in milk 10.3 mg% (see Appendix D, note 1), thus the toluene concentration in maternal milk was five times that of maternal blood.

In conclusion, toluene is distributed to various tissues, the amount depending on the tissue/blood partition coefficient, the duration and level of exposure, and the rate of elimination. Concentrations in the brain are higher than in blood. Adipose tissue may be a reservoir for toluene. Toluene easily passes the placenta and is found in the foetus in concentrations of about 75% of that found in the maternal blood. Toluene is secreted into maternal milk.

Biotransformation

Biotransformation of toluene occurs mainly by oxidation. The endoplasmatic reticulum of liver parenchymal cells is the principal site of oxidation which involves the P450 system. Analysis of blood and urine samples from workers and voluntary study subjects exposed to toluene via inhalation in concentrations ranging from 100 to 600 ppm (375-2,250 mg/m^3) indicate that of the biotransformed toluene, appr. 99% is oxidised via benzyl alcohol and benzaldehyde to benzoic acid. The remaining 1% is oxidised in the aromatic ring, forming ortho-, meta- and para-cresol (Woiwode et al., 1979; Woiwode and Drysch, 1981).

Water solubility of the biooxidation products is achieved through linkage with suitable substances (phase 2 reaction). Benzoic acid is linked to either glycine or glucuronic acid forming either hippuric acid or benzoylglucuronide. Cresols and benzyl alcohol are linked to glucuronic acid or sulphate (IPCS, 1985). At heavy toluene exposures there may not be enough glycine available for conjugation with the toluene metabolite benzoic acid to form hippuric acid. Benzoic acid may then be conjugated with glucuronic acid, and excreted as benzoyl glucuronide.

In conclusion, toluene is readily metabolised , mainly to benzoic acid.

Elimination

Toluene or its metabolites may be eliminated via the lungs, the kidneys, or the liver.

Data from experimental inhalation exposure of voluntary subjects show that the toluene concentration in expired air decreases rapidly during the first 10 to 20 minutes after cessation of exposure to toluene via inhalation (Veulemans and Masschelein, 1978a; Carlsson, 1982; Echeverria et al., 1989). Two to four hours later, very low toluene concentrations are found in expired air (Carlsson, 1982). Of the toluene absorbed, 15-20% is exhaled during the first few hours after exposure has stopped (Nomiyama and Nomiyama, 1974). The cumulative elimination of toluene via the lungs amounts to 4-8% and 7-14% after 2 and 20 hours, respectively (Carlsson, 1982).

The cumulative elimination (in per cent) of toluene via the lungs appears to increase with increasing amounts of toluene taken up (Carlsson, 1982).

The majority (80-90%) of absorbed toluene is biotransformed and excreted from the body via the kidneys. At an exposure level of 750 mg/m^3 (200 ppm), the excretion is mainly as hippuric acid. About 1% of the biotransformed toluene is excreted as glucuronides or sulphates of o-, m-, or p-cresol (IPCS, 1985).

A very small proportion, approximately 0.06% of the toluene absorbed via inhalation, is excreted unchanged in the urine in humans (Williams, 1959).

A good correlation was found between toluene exposure (air concentration multiplied by time) and concentration of hippuric acid in post exposure urine. However, a background level of hippuric acid is present in human urine, as a product of endogenous metabolism, and of metabolism of substances present in food. In the Western part of the world, at exposure levels below 100 ppm (375 mg/m^3) hippuric acid in post exposure urine cannot be used to separate an exposed person from an unexposed one because the difference between the background level and the toluene-generated level is too small (Lauwerys, 1983). However, hippuric acid background levels in urine vary geographically. In some Third World countries a low urinary hippuric acid background level is found. Thus, in these parts of the world it is possible to use this metabolite as a biological marker for toluene exposure even at exposure levels lower than 100 ppm (Chang et al., 1996; Vrca et al., 1997a; 1997b).

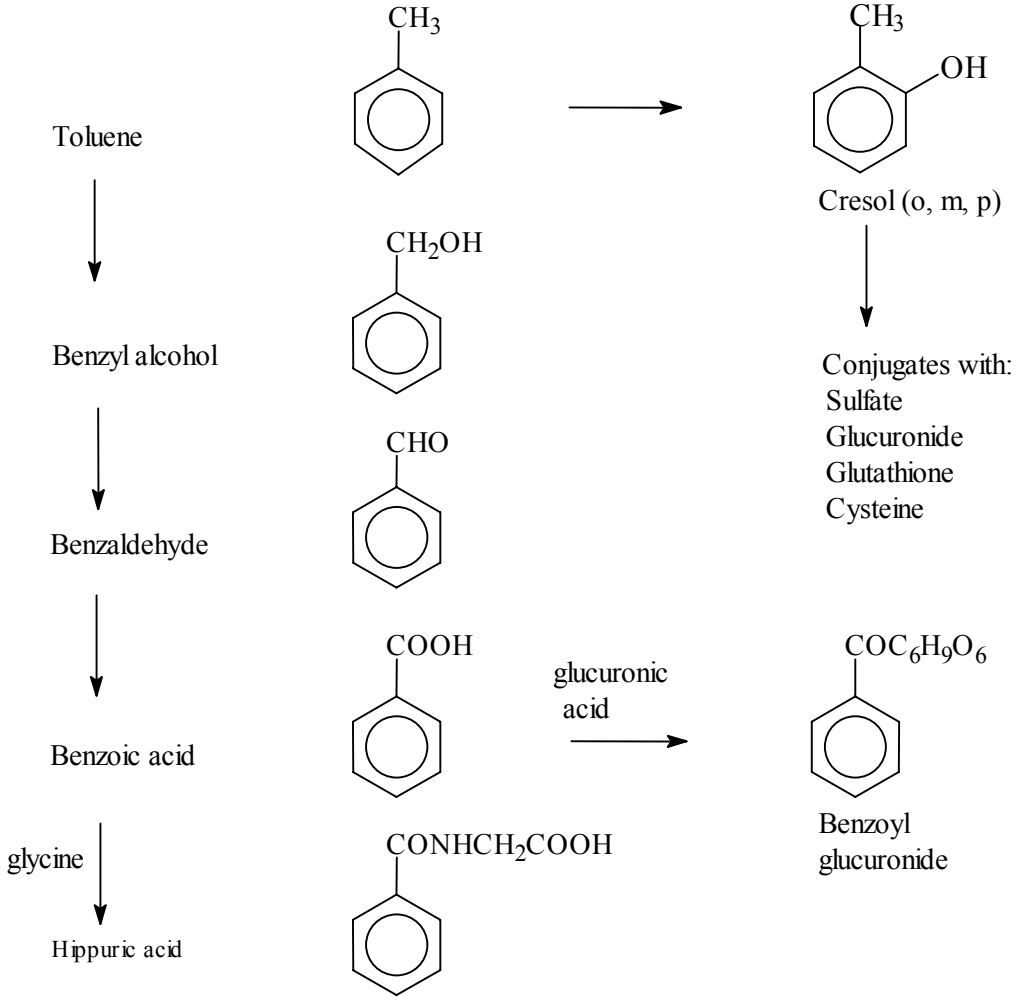
Data from rats exposed to 1,000, 1,780, or 3,000 ppm (3,750, 6,675, or 11,250 mg/m^3) of toluene via inhalation for 2 hours showed that elimination could be described by a bi-exponential function with average half-times of 6 and 90 minutes (Rees et al., 1985).

In rats a small proportion, less than 2%, of the absorbed toluene is excreted via the bile to the intestine. The substances excreted are reabsorbed in the intestine. Thus very small amounts are excreted in faeces (Abou-El-Makarem et al., 1967).

In conclusion, a proportion of around 20% of the absorbed toluene is eliminated in the expired air. The remaining 80% of the absorbed toluene is metabolised and excreted in the urine.

Figure 4.1 illustrates the metabolism of toluene in humans and animals.

Figure 4.1 Metabolism of toluene in humans and animals



Biological half-lives

Studies in humans

Two hours inhalation of 375 mg/m^3 (100 ppm) and determination of the time relations for toluene in blood and expired air after exposure gave a three-phasic half-life curve. Biological half-lives of 2 minutes, appr. 30 minutes, and appr. 3.5 hours, respectively, were calculated (Sato et al., 1974). Half-lives of 22 minutes and 175 minutes for the two last phases have been determined (Römmelt et al., 1982). In a study of workplace accidents with coma as a result of exposure to high toluene concentrations, a fourth phase with a 20-hour half-life was found. This phase is taken to represent toluene elimination from adipose tissue (Brugnone et al., 1983). Nise et al. (1989) have found elimination curves for toluene in venous blood to contain at least three exponential components with median half-lives of nine minutes, 2 hours and 90 hours. The third component reflected the decline of toluene in adipose tissue, which had a median half-life of 79 hours. The median venous blood toluene concentration was found to be 2.3 µmol/l at the end of a week last shift. After 72 hours the blood toluene concentration had fallen to 0.16 µmol/l. In another part of the same study, toluene concentrations were determined in venous blood and subcutaneous adipose tissue at 0, 63, and 135 hours. In venous blood an initial median toluene concentration of 1 µmol/l was found. After 135 hours the toluene concentration had decreased to 0.06 µmol/l. In subcutaneous adipose tissue the corresponding median toluene concentrations were 4 mg/kg fat and 1 mg/kg fat, respectively. Carlsson and Ljungquist (1982) reported that the

half-life of toluene from subcutaneous adipose tissue increased with increasing amounts of body fat. The range of values for the half-life was from 0.5 to 2.7 days.

The prolonged presence of toluene in adipose tissue with subsequent release to blood suggests that the nervous system in workers may be exposed to endogenous toluene even during periods where the worker is not externally exposed. However, toluene is not an accumulative substance as such. The tissue compartment which has the longest elimination half-time for toluene is (in all likelihood) adipose tissue. The measured T1/2 in human subcutaneous adipose tissue is about 3 days, which is short compared to substances that are highly accumulative in fat, such as PCBs (T1/2 up to several years). From the elimination half-time, the time period during which accumulation occurs (the time to reach steady-state) can be calculated by multiplying the T1/2 by 5, i.e. about 15 days (or three working weeks) for toluene. The conclusion therefore is that although there is some accumulation of toluene, it is not of great biological significance. In other words, chronic harmful effects by toluene are mechanistically explained by accumulation of effects rather than accumulation of substance.

Studies in animals

The elimination half-lives in rats exposed via inhalation for 2 hours to toluene concentrations of 1,000, 1,780, or 3,000 ppm (3,750, 6,675, or 11,250 mg/m^3) were 6 and 90 minutes for the two phases (Rees et al., 1985).

In rats, the rate of elimination from fat seems to be much higher than in humans, as only a few percent of the toluene concentration found in perirenal fat immediately after end of exposure to 100 ppm was recovered 12 hours after end of exposure (Zahlsen et al., 1992)

In summary, the elimination of toluene from adipose tissue is much faster in the rat than in humans.

Summary of toxico-kinetics, metabolism and distribution

The data for toxico-kinetics, metabolism and distribution of toluene conform with the requirements of Annex VIIA of Directive 67/548/EEC.

Toluene is absorbed almost completely from the gastrointestinal channel in animals. Approximately 50% of inhaled toluene is taken up, depending on pulmonary ventilation. Dermal uptake after skin exposure to liquid toluene occurs to a limited degree. Dermal exposure to toluene vapours is not likely to be an important route. Toluene is distributed to various tissues, the amount depending on the tissue/blood partition coefficient, the duration and level of exposure, and the rate of elimination. Concentrations in the brain are higher than in blood. Adipose tissue may be a reservoir for toluene. Toluene easily passes the placenta and is found in the foetus in concentrations of about 75% of that found in the maternal blood. Toluene is secreted into maternal milk. The half-life in human tissue may be up to three days, whereas blood toluene rapidly declines after cessation of exposure. In the rat, elimination of toluene seems to be much faster, as most toluene was eliminated from fat after 12 hours. Within a few hours after termination of exposure the blood and alveolar air contains very little toluene. A proportion (around 20%) of the absorbed toluene is eliminated in the expired air. The remaining 80% of the absorbed toluene is metabolised in the liver by the P450 system, mainly via benzyl alcohol and benzaldehyde to benzoic acid. Benzoic acid is conjugated with glycine and excreted in the urine as hippuric acid. If not enough glycine is available (high concentration of benzoic acid) benzoic acid is conjugated with glucuronic acid and excreted in the urine as

benzoylglucuronide. Small amounts of toluene undergo ring hydroxylation to form o-, m-, and p-cresol, which are excreted in the urine as sulphate or glucuronide conjugates.

There are no indications of particular species differences in the toxico-kinetics, metabolism or distribution of toluene. The elimination of toluene from adipose tissue is much faster in the rat than in humans.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

A number of acute toxicity studies on toluene have been found in the literature and in the IUCLID Data Sheet. These are summarised in **Table 4.19** given below.

Table 4.19 Acute lethality data for toluene compiled from various sources

Species	Application	LC50 (inhalation) LD50 (oral, dermal, intraperitoneal application)	Reference
Rat	Inhalation 1 hour	> 100 mg/l	Benignus (1981)
Rat	Inhalation 6 hours	22.0 - 23.5 mg/l	Bonnet et al. (1982)
Rat	Inhalation 6.5 hours	45.8 mg/l	Cameron et al. (1938)
Rat	Inhalation 4 hours	28.1 mg/l	BASF (1980)
Rat	Inhalation 4 hours	12.5 - 28.8 mg/l	Pozzani et al. (1959)
Rat	Inhalation 4 hours	33 mg/l	Carpenter et al. (1976)
Mouse	Inhalation 6 hours	24.0 - 27.9 mg/l	Bonnet et al. (1982)
Mouse	Inhalation 6 hours	26.0 mg/l	Bonnet et al. (1979)
Mouse	Inhalation 7 hours	19.9 mg/l	Svirbely et al. (1943)
Rat	Oral	7,500 mg/kg	Smyth et al. (1969)
Rat	Oral	5,900 mg/kg	Ungváry et al. (1982)
Rat	Oral	5,500 mg/kg	Kimura et al. (1971)
Rat	Oral	5,580 mg/kg	Withey and Hall (1975)
Rat	Oral	7,000 mg/kg	Wolf et al. (1956)
Rabbit	Dermal	12,400 mg/kg	Smyth et al. (19690
Rat	Intraperitoneal	1,600 mg/kg	Fodor (1972); Ikeda and Othsuji (1971); Lundberg et al. (19830
Rat	Intraperitoneal	1,330 – 1,640 mg/kg	IUCLID (1998)
Mouse	Intraperitoneal	2,159 mg/kg	Koga and Ohmiya (1978)

Doses have been converted to mg/l (inhalation) or mg/kg (oral, dermal, or intraperitoneal)

Inhalation

Six studies of acute toxicity via inhalation in the rat have been found. A varying number of hours of exposure have been used (**Table 4.19**). The study by BASF (1980) has been performed according to a test method close to the requirements of EU guideline B2 (Acute toxicity (inhalation)). Groups of 10 male and 10 female rats were exposed for 4 hours to test atmospheres of 6.08, 20.00, 23.98, 38.87, or 61.80 mg/l of toluene of 99.5% purity. The rats were observed daily for 14 days following exposure. In this study, an LC50 of 28.1 mg/l was calculated by probit analysis. This result is not contradicted by the other five studies (Benignus, 1981; Bonnet et al., 1982; Cameron et al., 1938; Pozzani et al., 1959, Carpenter et al., 1976).

In mice, similar values, ranging from 19.9 mg/l to 27.9 mg/l, have been found in three studies (Svirbely et al., 1943; Bonnet et al., 1979; Bonnet et al., 1982)

In the BASF (1980) acute inhalation toxicity study mentioned above the rats exposed to 20.00, 23.98, 38.87, or 61.80 mg/l of toluene showed watery discharge from eyes and nose, unrest, increased respiration, rocking gait, narcosis, startling movements, and hyperaemia of the ears and extremities. In the highest exposure group, salivation was observed. In the group exposed to 6.08 mg/l of toluene, no signs or symptoms were observed. All surviving rats appeared normal after 3 days following the exposure.

Toluene exposure acutely impairs cognitive function in macaque monkeys. During a 50-minute exposure to 0, 375, 750, 1,875, 3,750, 7,500, 11,250, or 16,875 mg/m^3 (0, 100, 200, 500, 1,000, 2,000, 3,000 or 4,500 ppm) toluene, increased response time and decreased precision in a matching-to-sample task were observed at 7,500 mg/m^3 and higher concentrations. During the last 18 minutes of exposure to toluene concentrations from 375 mg/m^3 to 11,250 mg/m^3, the concentration of carbon dioxide in expired air (as a composite index of the monkey's behavioural, respiratory, cardiovascular, and metabolic activities) was significantly increased. In monkeys exposed to 16,875 mg/m^3 expired CO_2 initially decreased to below air controls, while no difference relative to control was found during the second half of the exposure session (Taylor and Evans, 1985).

The behavioural effects of inhalation of toluene for 1, 2 or 4 hours in rats has been investigated. The sensitivity of unconditioned reflex and conditioned avoidance tests in evaluating behavioral toxicity was compared. Male rats were exposed by inhalation up to four hours to; 0, 800 (3,000 mg/m^3), 1,600 (6,000 mg/m^3), 3,200 (12,000 mg/m^3), or 6,400 (24,000 mg/m^3) ppm toluene. The rats were tested for behavioral changes at one-half, one, two and four hours during exposure and eighteen hours after exposure ended. In unconditioned reflex testing, the presence or absence of specific unconditioned reflexes (such as corneal, placing, grasping and righting reflexes) and simple behavior patterns including locomotor activity and coordination were observed. The conditioned reflex task consisted of shock avoidance by lever press following simultaneous light and sound stimuli. Rats began to fail unconditioned reflex tests at 800 ppm toluene. Decrements in conditioned avoidance were observed at 3,200 ppm toluene. The concentration, which affected 50% of the animals at a given time of exposure (EC50) was calculated for 16 behavioural patterns. EC50 values in the range 2,400 mg/m^3 (640 ppm) to 5,025 mg/m^3 (1,340 ppm) were determined. In general, the EC50 values were higher for 1 hour inhalation than for 4 hours inhalation (Mullin and Krivanek, 1982).

Inhalation of 5,625 mg/m^3 (1,500 ppm) toluene for 50 minutes affected the nystagmus reflex (a measure of the function of the equilibrium system) in rats (Larsby et al., 1986).

In rats receiving toluene via continuous intravenous infusion, at an infusion rate of 50 μM/kg/min for 60 minutes, the nystagmus reflex was increased when the toluene

concentration in blood reached or exceeded 0.9 mmol/l. At this blood concentration no effects were found on consciousness, respiration, or circulation (Tham et al., 1984).

Concentration-effect curves for behavioural toxicity of toluene in mice were determined for performance in an operant task (response for milk reward). The mice were tested in 8 daily test series separated by 30-minute time-out periods 5 days a week. It is not mentioned in the publication what the total number of test days was. At the end of each series, starting with the third series, the toluene concentration was cumulatively increased. At 1,125 mg/m^3 (300 ppm) and 1,875 mg/m^3 (500 ppm) no change in activity was seen. At 3,750 mg/m^3 (1,000 ppm) activity was increased. At a concentration of 9,000 mg/m^3 (2,400 ppm) activity was reduced and at 16,875 mg/m^3 (4,500 ppm) activity ceased. In conclusion, toluene at lower exposure levels was stimulatory and at higher exposure levels was depressive for response frequency in the task (Glowa and Dews, 1983).

Dose-related statistically significant increases in hypothalamic catecholamine levels and serum prolactin concentrations were seen after exposure of male rats to 0 , 300, 1,875, 5,625, and 11,250 mg/m^3 (80, 500, 1,500, and 3,000 ppm) toluene 6 hours per day for three days. According to the authors, the statistical test used did not correct for multiple comparisons of dose groups with the same control group. This means that some apparently significant differences may be due to statistical error. However, it is argued by the authors that the dose relation points to a true effect (Andersson et al., 1983).

In male rats exposed via inhalation to toluene 6 hours per day for three days, a reduced dopamine level in the forebrain was observed at 300 mg/m^3 (80 ppm). However, at the higher concentrations (1,875 mg/m^3 (500 ppm), 5,625 mg/m^3 (1,500 ppm), and 11,250 mg/m^3 (3,000 ppm)) dopamine levels did not differ from those of the controls (Fuxe et al., 1982).

Inhalation of 2,000 mg/m^3 (533 ppm) or 3,000 mg/m^3 (800 ppm) toluene, either for 24 hours or 8 hours per day for one week did not result in histopathological liver changes in mice, rats, and rabbits. Increased liver weights were observed and electron microscopy showed ultrastructural changes in the liver (increased rough endoplasmic reticulum) in all three species. The levels of the enzymes esterase, acid and alkaline phosphatase and succinate dehydrogenase were unchanged, while cytochrome P450 and cytochrome b5 concentrations were increased in the toluene-exposed groups (Ungváry et al., 1982).

Oral

Five studies of acute toxicity after oral exposure in the rat have been found. Withey and Hall, 1975, performed a study using a method which resembles that of EU guideline B1 (Acute toxicity (oral)). Groups of 20 male Sprague-Dawley Cobb rats, were fasted overnight and dosed by intubation with either 4.00, 4.56, 5.20, 5.93, or 6.76 g/kg of toluene (purity not stated). The rats were observed three times daily for at least 7 days after dosing. The LD50, calculated by probit analysis, was 5.58 g/kg. The oral LD50 values reported in the other four studies (Wolf et al., 1956; Smyth et al., 1969; Kimura et al., 1971; Ungváry et al., 1982) ranging from 5.5 to 7.5 g/kg are in accordance with this.

Dermal

A single report of acute dermal toxicity in the rabbit has been found, stating an LD50 value of 14.1 ml/kg, corresponding to 12.4 g/kg (density 0.876). The test method was not described (Smyth et al., 1969).

Intraperitoneal

The acute toxicity of toluene after intraperitoneal administration has been reported by a number of authors. The LD50 values range from 1.3 to 1.64 g/kg in the rat. In mice a value of 2.15 g/kg has been determined (**Table 4.19**).

In summary, acute effects in animals exposed via inhalation include mucous membrane irritation, unrest, increased respiration, ataxia, impaired cognitive function, disturbance of the equilibrium system, changed response frequency in operant task test, neurochemical changes. In addition, levels of liver enzymes involved in metabolism of toluene were found to be increased.

4.1.2.2.2 Studies in humans

The acute effects in voluntary human experimental subjects of toluene inhalation exposure have been examined in a number of studies.

The results achieved by 16 students in a number of performance tests were not influenced by six hours inhalation of toluene in concentrations up to 375 mg/m^3 (100 ppm). At 375 mg/m^3 headache, dizziness, and feeling of intoxication were more often reported by the study subjects than at the lower concentrations (0 mg/m^3, 37.5 mg/m^3 (10 ppm), or 150 mg/m^3 (40 ppm)) (Andersen et al., 1983).

A one-hour inhalation of toluene (472-588 mg/m^3 (126-157 ppm)) was found to affect nystagmus reflexes (visual suppression) in 15 volunteers (Hydén et al., 1983).

For 12 volunteers inhaling 300 mg/m^3 (80 ppm) toluene for 4.5 hours, the results in 4 performance tests carried out after 2 and 3.5 hours of exposure were not significantly different from the results obtained from the same persons during exposure to clean air. Subjective complaints of headache and irritation were more frequent at toluene exposure, during which a small decrease in the pulse at rest was observed (Iregren et al., 1986).

Among 8 male post-graduate students exposed to 80 ppm (300 mg/m^3) toluene via inhalation for four hours no difference in results in four choice reaction time, four choice errors, simple reaction time, visual search, visual analogues and stressalyser could be found compared to the results obtained by the same subjects exposed to clean air for four hours (Cherry et al., 1983).

For 20 volunteers inhaling 98 ppm toluene (368 mg/m^3)for 4 hours results in the psychomotor tests finger tapping, reaction time, pursuit-rotor test and Purdue hand precision test did not differ from control values obtained by the same 20 volunteers (Winneke et al., 1976).

Following inhalation exposure to 375 mg/m^3 (100 ppm) toluene for 6.5 hours, 43 printers with 9 to 25 years occupational toluene exposure did not show significantly different results in 10 performance tests compared with an equally sized group not previously exposed to toluene matched for sex, age, education and smoking habits. The toluene exposure was found to decrease manual dexterity, colour discrimination, and accuracy in visual perception in both groups. Furthermore the toluene exposure caused discomfort with complaints of low air quality, strong odour, fatigue, sleepiness, a feeling of intoxication, and irritation of the eyes, nose and throat (Bælum et al., 1985).

Forty-two college students inhaled 0, 281 mg/m^3 (75 ppm) or 562 mg/m^3 (150 ppm) toluene for seven hours on each of three days. The students carried out a number of performance tests prior to exposure, and after three and seven hours of exposure. On each day students served as their own control. Toluene exposure resulted in significantly worse results in digit span, pattern

memory, pattern recognition, symbol digit, and one hole test. The number of symptoms recorded was found to increase with increasing toluene exposure for headache and mucosal irritation. The symptoms were reported at the end of each day by subjects in response to the question "What are your reactions over the past four hours?". No details regarding the severity of headache and irritation are given in the publication. A dose response relationship was found in the number of times subjects slept increasing from 7% at 0 ppm, 14% at 281 mg/m^3 (75 ppm), to 22% at 562 mg/m^3 (150 ppm) (Echeverria et al., 1989).

A random population sample of 32 male and 39 female subjects were allocated into three groups, one exposed to clean air, one exposed to constant toluene at a concentration of 100 ppm (375 mg/m^3), and one exposed to varying concentrations of toluene (Fourteen 30-minute episodes during the exposure period, each episode starting with an increasing concentration reaching a peak of 300 ppm (1,125 mg/m^3) after 5 min and then decreasing to a stable period of about 15 min at 50 ppm (188 mg/m^3), giving a TWA of 100 ppm for the whole exposure period). An exposure period comprised a single day (7 hours). Toluene caused throat and respiratory irritation, headache and dizziness. In performance tests only minimal effects were found, with a tendency towards lower score and more errors but fewer false reactions in the primary task of the vigilance test. The effects were not statistically significant ($p<0.1$). There was no difference between constant exposure and peak exposure (Bælum et al., 1990).

In summary, the above-mentioned exposure chamber studies headache, dizziness, feeling of intoxication, irritation and sleepiness were recorded to occur with significantly increased frequency at exposure levels from 562 mg/m^3 (150 ppm) down to 281 mg/m^3 (75 ppm). At 150 mg/m^3 (40 ppm) and below the effects have not been recorded to occur with increased frequency. For these subjective symptoms a lowest observed adverse effect concentration (LOAEC) of 281 mg/m^3 (75 ppm) and a no observed adverse effect concentration (NOAEC) of 150 mg/m^3 (40 ppm) can be established.

With respect to function in performance tests, inhalation of 281 mg/m^3 (75 ppm) and 562 mg/m^3 (150 ppm) for 7 hours have resulted in significantly worse results in a number of performance tests, indicating a LOAEC of 281 mg/m^3 (75 ppm) for function in performance tests while a NOAEC cannot be established.

4.1.2.2.3 Summary of acute toxicity

The acute toxicity of toluene has been tested in a manner conforming with the data requirements of Annex VIIA of Directive 67/548/EEC.

Toluene has low acute toxicity via inhalation and the oral route. In rats, an LC50 of 28.1 mg/l/4h, and an oral LD50 of 5.58 g/kg have been reported. A dermal LD50 of 12.4 g/kg has been determined in the rabbit, however, the method used and quality of the data are unknown. As the acute toxicity via inhalation and the oral route is low, and toluene is absorbed well via these routes, it was considered that a dermal acute toxicity study would not contribute further to the hazard identification. Via the intraperitoneal route LD50s of approximately 2 g/kg for rats and mice have been found.

No classification for acute toxicity is proposed.

Toluene is classified with R67 (Vapours may cause drowsiness and dizziness) since data from experimental exposure of human volunteers show that dizziness and sleepiness are experienced at air levels substantially below the level of 20 mg/l/4h mentioned in the criteria for R67 (for

toluene this equals to 5,300 ppm). In rats exposed to 20 mg/l/4h in the BASF (1980) study rocking gait and narcosis were observed. For classification, see Section 1.

A LOAEC of 281 mg/m^3 (75 ppm) (Echeverria et al., 1989) and a NOAEC of 150 mg/m^3 (40 ppm) (Andersen et al., 1983) for the occurrence in humans of headache, dizziness, feeling of intoxication, irritation and sleepiness will be taken forward to the risk characterisation. For function in performance tests a LOAEC of 281 mg/m^3 (75 ppm) will be taken forward to the risk characterisation (Echeverria et al., 1989). Furthermore, in the absence on human dermal acute toxicity data, the dermal LD50 of 12.4 g/kg will be taken forward to the risk characterisation for acute toxicity by dermal exposure.

4.1.2.3 Irritation

Animal and human data regarding the irritative properties of toluene have been found.

4.1.2.3.1 Skin

Only animal data have been found.

Studies in animals

A skin irritation study performed by a method conforming to Annex V, method B2 (acute toxicity (skin irritation)) has been conducted (Exxon, 1988). A volume of 0.5 ml toluene was applied to the clipped dorsal intact skin of seven New Zealand White rabbits and kept under a semi-occlusive dressing for 4 hours. After exposure, the skin was rinsed with water. The observation period was 7 days. The rabbits were examined 45 minutes, 24, 48 and 72 hours following patch removal, and on day 7. Observations were scored according to the Draize method. The mean scores at each observation are presented in **Table 4.20**.

Table 4.20 Mean scores for skin irritation (Exxon, 1988)

	45 min	24 h	48 h	72 h	7 days	Mean (24, 48, and 72h scores)
Erythema	0.14	1.14	1.86	2.43	2.43	1.81
Oedema	1.00	0.71	1.14	1.43	0.86	1.10

The incidence and severity of irritation increased as the study progressed, and by 72 hours all animals exhibited erythema, ranging from very slight to severe, and slight oedema. On day 7, erythema ranged from well-defined to severe for all animals, and oedema ranged from very slight to slight for 5 animals. The mean score for erythema was 2.43 at 72 hours and on day 7. Toluene was considered moderately skin irritating in the report.

In conclusion, toluene caused significant inflammation of the skin as a mean erythema score exceeding 2 was observed which persisted for more than 24 hours. In addition, the inflammation persisted in all test animals at the end of the observation time (individual scores for erythema on day 7 were 2, 2, 2, 4, 2, 3, and 2). Toluene is classified as a skin irritant (R38 Irritating to skin). For classification, see Section 1.

Guillot et al. (1982) tested skin irritancy of toluene by four different methods, including the OECD guideline 404 method. Six male New Zealand White rabbits were simultaneously

subjected to three different test methods using occlusive application. The three methods differed with respect to whether skin was scarified or not prior to application, and in observation time points. A second group of six rabbits was used for a semi-occlusive test. The same scoring system was used to measure results from all four methods. Toluene was found slightly irritating by the OECD guideline method, and moderately irritating with the other methods. The test was evaluated by use of a national French scoring system, and therefore the results cannot readily be interpreted.

In a study performed as a preliminary test to a guinea pig maximisation test, toluene solutions of various concentrations were tested for irritancy (NOTOX, 1996). The solutions were injected intradermally and applied epidermally. Two guinea pigs were exposed epidermally only. The two guinea pigs were each exposed to two different concentrations (100 and 50%). The solutions were applied in a volume of 0.5 ml per animal to the clipped flank and covered with a patch. After 24 hours the patch was removed. Skin reactions were observed and graded according to the Draize score system at 24 h, 48 h, and 5 days after exposure. At 24 hours both animals exhibited eschar (injuries in depth) formation at one edge of the treated area in response to the 100% solution. At 48 hours this reaction was still present, and additionally a well-defined erythema (score 2) had developed. At the observation made after 5 days, a thick layer of scales and slight superficial fissuring of the skin was observed in the area treated with the 100% solution. The 50% solution was non-irritating.

Studies in humans

No data have been found. Textbooks state that it is well known that toluene has a degreasing effect on the skin. After repeated exposures, toxic contact dermatitis may develop (Browning, 1965; Gerarde, 1960).

4.1.2.3.2 Eye

The eye irritating properties of toluene has been investigated in several animal studies, and in humans.

Studies in animals

The ocular irritation potential of toluene was evaluated in a study performed according to OECD Guideline 405, and of GLP quality (Exxon, 1995). Ocular instillation of 0.1 ml toluene into the right eye of 6 New Zealand White rabbits (4 males and 2 females) elicited conjunctival irritation in all animals. Redness, chemosis, and discharge were observed in all six animals at the 1-hour observation. At the 24 and/or 48 hours observations, redness, chemosis, and/or discharge persisted in the majority of the animals. Irritation decreased as the study progressed and only redness was observed in four animals at the 72 hours observation. All animals were free of ocular irritation on day 7, and the study was subsequently terminated. Iridial responses were observed in three animals at the 1-hour observation. Corneal responses were not observed during the study. Clinical signs were not observed in any animal and all animals survived to study termination. The mean ocular irritation scores for each observation interval are shown in **Table 4.21**.

Table 4.21 Mean ocular irritation scores (Exxon, 1995)

	1 h	24 h	48 h	72 h	7 days	Mean (24, 48, and 72 h scores)
Redness	3.00	2.17	1.50	0.67	0.00	1.47
Chemosis	3.33	0.83	0.33	0.00	0.00	0.39
Iris	0.50	0.00	0.00	0.00	0.00	0.00
Opacity	0.00	0.00	0.00	0.00	0.00	0.00

In conclusion, toluene was found to cause slight eye irritation. Ocular lesions (redness, chemosis) occurred within 72 hours after exposure and persisted for at least 24 hours. However, the mean score (24 hours 48 hours and 72 hours together) for redness of the conjunctivae and chemosis did not exceed values of 2.5 and 2, respectively, which are the limits for classification with R36 (Irritating to eyes). Therefore, no classification for eye irritation was proposed.

Sugai et al. (1990) carried out an eye irritation study of toluene in rabbits. Toluene in a volume of 0.1 ml was instilled into the conjunctival sac of the left eye of three female Japanese white rabbits, with the right eye serving as control. The eyes were examined at 1, 4, 24, 48, 72, 96 hours, and 7, 14 and 21 days. Lesions were graded according to the Draize score. Toluene was judged to be a moderate to severe irritant with corneal involvement or irritation that persisted for more than 24 hours but recovered within 21 days after treatment.

Guillot et al. (1982b) conducted eye irritation tests in rabbits. 0.1 ml of toluene was instilled into the lower conjunctival sac of one eye in six male rabbits, with the other eye serving as control. Several tests were performed. In the first, eyes were not rinsed following instillation. The rabbits were observed for 7 days. Eye lesions were scored according to a numerical system. Toluene was found to be irritating to the eye. In the subsequent tests, similar instillations were performed in other groups of 6 rabbits, this time with rinsing after 4 or 30 seconds. Rinsing did not change the irritating properties of toluene instillation.

Studies in humans

Two studies have been found, where eye irritation in toluene-exposed humans has been reported. The exposure was not direct exposure of the eye to liquid toluene, but to vapours in ambient air.

Sixteen young healthy subjects were exposed to toluene in various concentrations (0, 10 (37.5 mg/m^3), 40 (150 mg/m^3), or 100 ppm (375 mg/m^3)) for six hours. A balanced Latin square design was used with respect to the sequence of exposure levels experienced by the subjects. A subjective estimate of eye irritation was made by asking the subjects to place a mark on a continuous scale with end points defined by a verbal description. Exposure to 375 mg/m^3 (100 ppm) resulted in complaints of irritation in the eyes and the nose, while exposure to 150 mg/m^3 (40 ppm) or 37.5 mg/m^3 (10 ppm) toluene did not result in irritation. In general the irritation was described as slight and was felt just after the exposure began and continued throughout the exposure day (Andersen et al., 1983).

In another study 42 young, healthy subjects were exposed for 7 hours to air or to toluene in concentrations of 281 mg/m^3 (75 ppm) or 562 mg/m^3 (150 ppm). Each subject was tested at different concentrations on each of three days using a Latin square design. At the lower toluene concentration a slight increase in the number of subjects experiencing eye irritation was reported, while almost half of the subjects experienced eye irritation at the higher concentration. No details regarding the severity of eye irritation was given in the publication (Echeverria et al., 1989).

4.1.2.3.3 Respiratory tract

Only animal data have been found.

The respiratory rate depression of toluene has been investigated in several studies. In mice, RD50 values of 12,590 mg/m^3 (3,357 ppm) (Muller and Greff, 1984), 12,650 mg/m^3 (3,373 ppm) (De Ceaurriz et al., 1981), and 19,875 mg/m^3 (5,300 ppm) (Nielsen and Alarie, 1982) have been determined. These results suggest that toluene can cause irritation to the respiratory tract at these very high concentrations. The irritative effect of lower toluene concentrations has not been examined. The usefulness of the respiratory depression test has not been established.

No classification for respiratory irritation was proposed.

4.1.2.3.4 Summary of irritation

The irritating properties of toluene have been tested in a manner conforming to the data requirements of Annex VIIA of Directive 67/548/EEC.

The results of the animal studies show that toluene is irritating to the skin in rabbits, mice, and guinea pigs. According to textbooks, it is well known that toluene has a degreasing effect on the skin of humans. One study in rabbits (Exxon, 1988) has been performed according to a method of EU guideline standard. The Exxon study will therefore be used for the risk assessment. Based on this study it was agreed to classify toluene as a skin irritant with R38 (Irritating to skin). For classification, see Section 1.

The results of three animal studies show that toluene has a potential to cause eye irritation. One of the studies (Exxon, 1995) has explicitly been performed according to the OECD guideline 405. The other two studies appear to have been performed using similar methodology, however, the problem of interpreting the scoring system used in those two studies means that the Exxon study will be used for the risk assessment. Toluene was slightly irritating in the Exxon study, however not enough to warrant classification according to the EU classification criteria. No classification for eye irritation is proposed.

The animal data for skin and eye irritation do not provide information on dose-response relations.

Toluene can cause irritation to the respiratory tract in animals. This has only been observed at very high concentrations. The irritative effect of lower toluene concentrations has not been examined. No classification for respiratory irritation was proposed.

In conclusion, toluene is irritating to skin and to eyes in animals. The degree of irritation produced is only severe enough to warrant classification with respect to skin. Toluene-induced skin irritation is long-lasting. Although there are no reports of human eye contact to liquid toluene, reports of human eye irritation in response to vapour indicate that the findings from animal studies are relevant for humans. Human eye irritation starts somewhere between a toluene vapour concentration of 150 mg/m^3 (40 ppm) and 375 mg/m^3 (100 ppm). A LOAEC of 375 mg/m^3 (100 ppm) and a NOAEC of 150 mg/m^3 (40 ppm) for the occurrence in humans of eye irritation will be taken forward to the risk characterisation.

4.1.2.4 Corrosivity

See Section 4.1.2.3 (Irritation) for data. Toluene is not corrosive.

4.1.2.5 Sensitisation

Only animal data are available.

4.1.2.5.1 Skin

A well conducted study of the skin sensitising potential of toluene exists.

A guinea pig maximisation test in accordance with EU guideline B6 (Skin sensitisation), of GLP quality, has been carried out (NOTOX, 1996). Thirty female SPF albino guinea pigs of the Himalayan strain were used in the study. Twenty guinea pigs were intradermally injected with a 10% concentration (this concentration was previously determined to produce moderate irritation without necrosis) and epidermally exposed to the undiluted test substance. Ten control guinea pigs were similarly treated, but with vehicle (corn oil) only. Two weeks later all animals were challenged with 50% (maximum non-irritant concentration) and 25% test solution, and vehicle. A single guinea pig showed a grade 1 reaction (discrete or patchy erythema) in response to the 50% solution. No other skin reactions were observed. It was concluded that toluene was not a skin sensitiser in this study.

4.1.2.5.2 Respiratory tract

No description was found of allergic effects on the airways caused by toluene exposure.

4.1.2.5.3 Summary of sensitisation

The sensitising potential of toluene has been tested in a manner conforming with the data requirements of Annex VIIA of Directive 67/548/EEC.

No human data are available. In a well-conducted guinea pig maximisation study no evidence of skin sensitisation was found, suggesting that toluene is not a skin sensitiser in humans. No data have been found with regard to respiratory sensitisation. There are no indications that toluene is a respiratory allergen.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 General toxicity

Studies in animals

The toxicity of toluene after repeated doses has been investigated in a number of studies. There are no data for the dermal route. Toluene toxicity via inhalation has been investigated in the rat (exposure duration of 2 years, 15 months, 26 weeks, 15 weeks, 90 days) and in the mouse

(exposure duration of 2 years,14 weeks). Two oral studies of 90 days' duration have been conducted, one in rats, and one in mice.

Inhalation

Rats, 90 days

Groups of 30 rats, equally divided by sex, were exposed to 0, 30, 100, 300, or 1,000 ppm of toluene (0, 112.5, 375, 1,125, 3,750 mg/m^3) for 6 hours/day, 5 days/week, for 13 weeks (Rhudy et al., 1978). No effects on body weights or food consumption were found. Haematology, clinical chemistry and urinalysis results from control animals and the highest exposure group on days 5, 45, and 89 did not reveal effects of toluen. No toluene-related gross or histopathological changes were found. Liver weights were significantly lower in all exposed groups except in the highest. The authors concluded that exposure to 1,000 ppm (3,750 mg/m^3) did not cause adverse effects.

The results of this study are published as an abstract only and the basis for the conclusions therefore cannot be evaluated. The study will not be used for the risk assessment.

Rats, 15 weeks

In a study conducted by NTP (United States National Toxicology Program) as a prerequisite for a carcinogenicity study, groups of ten male and ten female F344/N rats were exposed via inhalation to 0, 100, 625, 1,250, 2,500, or 3,000 ppm (0, 375, 2,344, 4,688, 9,375, or 11,250 mg/m^3) toluene 6.5 hours/day for 5 days/week for 15 weeks (Huff, 1990). The study was of GLP quality. The rats were observed for clinical signs daily, and weighed once per week. All animals were necropsied. Morphology was examined for a number of tissues in the control group, 2,500, and 3,000 ppm group. Eight male rats of the 3,000 ppm group died during week 2. The mean body weights of rats exposed to 2,500 or 3,000 ppm were 15-25% lower than that of controls, which was statistically significant. Clinical signs included dyspnea in all exposed groups, except males exposed at 3,000 ppm and females exposed at 1,250 ppm, and ataxia in rats exposed at 3,000 or 2,500 ppm. The relative kidney weight was statistically significantly increased at 1,250 ppm and higher in both sexes (males 3-21% increase relative to control; females 6-12% increase). Males at 1,250 ppm and higher also showed a statistically significantly increased relative liver weight (9-33%) while females at 2,500 ppm and higher showed this effect (16-21% increase). Relative weight of the brain (males 13-31% increase, females 10% increase), heart (males 11-15% increase, females 6-10% increase), and lung (males 15-18% increase, females 9% increase) were statistically significantly increased in both sexes at 2,500 and 3,000 ppm. In male rats, relative testes weight was statistically significantly increased at 2,500 and 3,000 ppm (15-24%). None of the differences in the results of the haematological or serum analyses were considered to be biologically meaningful by the author. Plasma cholinesterase activity decreased as exposure concentration increased (by 54% in females at 3,000 ppm), and the leukocyte count was decreased for female rats at 1,250 ppm or higher (12-18% relative to control). No compound-related effects were seen on sperm or on oestrous cycle. The toxic lesions seen in animals exposed by gavage were not observed in animals exposed by inhalation.

Overall, a NOAEC of 625 ppm toluene (2,344 mg/m^3) for 15 weeks inhalation exposure of rats can be derived from this well-conducted study. At 1,250 ppm (4,688 mg/m^3) and above, a 12-18% decrease in leukocyte count in females was found, which is considered an adverse effect. Also, at and above 1,250 ppm relative weight increases in a number of organs were detected.

Rats, 8, 17, 26 weeks

Three groups of 15 male and 15 female Sprague-Dawley rats (90 rats in all) were exposed 6 hours/day, 5 days/week for 8, 17 or 26 weeks to toluene concentrations of 0, 100 (375 mg/m^3), or 1,500 ppm (5,625 mg/m^3) (Bio/dynamics Inc., 1980). Selected animals were removed following 8 (3 rats/sex/toluene-exposed group), 17 (5 rats/sex/group), and 26 weeks of exposure (4 rats/sex/group) for neurohistopathological examination. All remaining rats were killed after a two-week post-exposure recovery period (3 rats/sex/toluene-exposed group, 9 control rats) and subjected to neurohistopathological examination. The higher toluene concentration was initially 2,000 ppm, but since the rats showed signs of central nervous system depression (ataxia, body tremors. prostration) during week 2 of exposure, the dose was lowered to 1,500 ppm. Haematology, clinical chemistry, and urinalysis parameters were evaluated in 10 rats/sex/group after 13 weeks, and in 5 rats/sex/group after 26 weeks of exposure. During exposure, an increase in the occurrence of dry rales and staining of the ano-genital fur was noted in the 1,500 ppm group relative to the control group. Male rats exposed to 1,500 ppm had significantly increased body weights during the latter part of the study. At 13 weeks, the 100 ppm females showed significantly increased haemoglobin and haematocrit values, and at 26 weeks this group had significantly decreased clotting time. Also at 26 weeks, increased serum glutamic pyruvic transaminase value was found in the 100 ppm female rats. Blood glucose was decreased at both sampling times in all exposed rats; this was significant only in females exposed to 1,500 ppm at 26 weeks. One male and one female rat of the 100 ppm group had very high (4-5 times increase) serum glutamic pyruvic transaminase values at week 26. Mild proteinuria was observed in all groups at both sampling times, most markedly in males exposed to 1,500 ppm at 13 weeks. No toluene-related neuropathological changes were found.

Although this study appears well-conducted, its usefulness for the risk assessment is low because of the limited design. The dose levels are far apart, animals were not subjected to full necropsy, and the number of animals available for comparison decreased during the study. At 100 ppm (375 mg/m^3), only minor effects were apparent on haematological, clinical chemical and urinalysis parameters.

Rats, 6-month exposure

Groups of 36 male Wistar rats were exposed to toluene in concentrations of 0, 500 ppm, or 1,500 ppm (0, 1,875, or 5,625 mg/m^3) for 6 hours/day, 5 days/week, for 6 months (Ladefoged et al., 1991). The rats were sacrificed 4 months after the end of exposure. At sacrifice, no differences with respect to body weight or relative weight of liver, testes, heart, or adrenals were found. Statistically significant increases were found in relative weight of spleen (500 ppm), brain (500 ppm), and kidney (1,500 ppm). As the increases were not dose-related they may be incidental findings and will therefore not be used for the risk characterisation. The design did not allow observation of reversible toxicity. The study will be described further in the section dealing with neurotoxicity.

Rats, 2-year exposure

Groups of 120 male and 120 female Fisher F344 rats were exposed via inhalation to toluene 6.5 hours per day, 5 days/week for up to 24 months in concentrations of 0, 112, 375 or 1,125 mg/m^3 (0, 30, 100, 300 ppm) (Gibson and Hardisty, 1983). Clinical observation did not reveal any substance related changes. The body weights of male rats in all toluene-exposed groups were higher than in control males throughout the study. A similar effect was noted for the females but the effect disappeared during the final weeks of the study. In haematology, blood

chemistry and urinalysis, female rats exposed to 100 and 300 ppm had at 24 months slightly but significantly reduced haematocrits and for the 300 ppm group only, the mean corpuscular haemoglobin concentration was slightly, but significantly, increased. No gross pathological or histopathological changes related to toluene exposure were seen, and no increase of tumour frequency in the male and female F344 rats was seen.

In this study, small effects on haematological findings were seen at both exposure levels. The exposure levels are low compared with the concentrations used by other investigators of long-term toluene toxicity. Since no definite signs of toxicity were found at the highest dose level, and since this is not discussed by the authors, this study is regarded as inconclusive with regard to identification of toluene-induced toxic effects, as the exposure concentrations may have been inadequate. Although the study does not identify the hazardous properties, it is still useful in the sense that 300 ppm was a clear NOAEC.

Rats, 15-month and 2-year exposure

Groups of 60 male and 60 female F344N rats were exposed by inhalation to 0, 600, or 1,200 ppm toluene (0, 2,250, 4,500 mg/m^3) 6.5 hours/day 5 days/week for two years in a GLP study (Huff, 1990). At 15 months, 10 male and 10 female rats at each dose level were terminated.

15-month exposure: No effects of toluene exposure were found on body weight or absolute and relative weight of kidney, liver or brain, except in females at 600 ppm, where the absolute liver weight was increased. The severity of nephropathy was slightly increased in exposed female rats. Results of haematological analyses did not suggest any compound-related effects. In the nasal cavity, mild to moderate degeneration of the olfactory and respiratory epithelium was more obvious in toluene-exposed rats (male: control, 5/10; 600 ppm, 10/10; 1,200 ppm 10/10; female: control 2/10; 600 ppm, 10/10; 1,200 ppm, 9/10) and goblet cell hyperplasia was somewhat increased (male: 3/10; 8/10; 5/10; female: 2/10; 5/10; 6/10), whereas other lesions were seen in a few exposed rats (Necrosis: three males and four females; metaplasia: one male and three females), and the incidences and severity of chronic inflammation were greater in exposed females than in controls (control, 5/10; 600 ppm, 9/10; 1,200 ppm, 8/10). Hyperplasia of the alveolar and bronchiolar epithelium was found in two males and three females in the 1,200 ppm group and in one control female. No other non-neoplastic or any neoplastic lesions were observed which were considered to be related to toluene exposure. The effects in the nasal cavity were considered mild toxic effects by the author. In this study, the lowest exposure level (600 ppm) caused toxic effects in the nasal epithelium. In addition, absolute liver weight was increased in females. However, relative liver weight was unaffected, and the effect was not dose-related and may therefore be considered an incidental finding.

2-year exposure: Mean body weights of male rats exposed to 1,200 ppm were 4-8% lower than those of controls from week 72 and to the end of the study. Mean body weights of female rats exposed to 1,200 ppm were 4-7% lower than those of controls from week 92 to the end of study. The initial mean body weight of the 1,200 ppm animals were 9% greater than those of controls. No compound related clinical signs were recorded, and no significant differences in survival were observed between any groups of either sex. In the nose, erosion of the olfactory epithelium and degeneration of the respiratory epithelium were significantly increased in exposed rats (erosion of olfactory epithelium - male: control, 0/50; 600 ppm, 5/50; 1,200 ppm, 8/49; female: 2/49; 11/59; 10/50; degeneration of the respiratory epithelium - male: 15/50; 37/50; 31/49; female: 29/49; 45/50; 39/50). Inflammation of the nasal mucosa and respiratory metaplasia of the olfactory epithelium were observed at significantly ($P < 0.05$) increased incidences in exposed female rats (inflammation of the nasal mucosa: 27/49; 42/59; 39/50; metaplasia of the olfactory epithelium: 0/49; 2/50; 6/50). The lesions were for the most part of mild severity. In the

forestomach ulcers were marginally increased in exposed male rats (control, 4/50; 600 ppm, 7/50; 1,200 ppm, 9/49). The severity of nephropathy was increased with exposure concentration in both sexes. Significantly more of the rats exposed to 1,200 ppm exhibited nephropathy of marked severity compared with controls. There were no substance-related increases in any tumour types.

In this study, effects similar to those found in the 15-month study described above, were found. At the lowest exposure level, 600 ppm, changes in the nasal cavity were found. In addition, effects in the forestomach and kidney were found. At the highest exposure level, a small, not statistically significant, decrease in body weight was found. There was no dose level without toxic effects, and consequently a LOAEC of 600 ppm can be derived from this study.

Mice, 14-week exposure

In a GLP study conducted by NTP (United States National Toxicology Program) as a prerequisite for a carcinogenicity study, groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 100, 625, 1,250, 2,500, or 3,000 ppm (0, 375, 2,344, 4,688, 9,375, or 11,250 mg/m^3) toluene 6.5 hours/day five days/week for 14 weeks (Huff, 1990). Five male and all ten female mice at 3,000 ppm died during the first two weeks; in addition a male at 3,000 ppm, seven female mice at 2,500 ppm, one female at 1,250 ppm, one male at 1,250 ppm and one female at 625 ppm died before the termination of the study. Final mean body weight of all exposed groups were 7-13% lower than those of controls (not statistically significant). Dyspnea was observed primarily at 3,000 and 2,500 ppm. The relative liver weights (males 45-50% increase relative to control, females 17-54% increase) for mice exposed to 625 ppm or higher, the relative lung weights for female mice exposed to 100 ppm or higher (9-12% increase), and the relative kidney weights (7-11% increase) for female mice exposed to 1,250 ppm or higher were statistically significantly greater than those of controls. None of the differences in the results of the haematological or serum chemical analyses were considered to be biologically meaningful. Centrilobular hepatocellular hypertrophy was observed in 10/10 male mice at 2,500 ppm and 4/6 male mice at 3,000 ppm. No effect on sperm count or motility or on oestrous cycle was seen.

In this study relative organ weights were increased beginning at the lowest dose level, 100 ppm (375 mg/m^3) for the lung. The toxicological significance of organ weight changes is questionable in the absence of histopathological findings, and therefore these findings will not be used as the basis for a LOAEC.

Mice, 15-month and 2-year exposure

Groups of 60 male and 60 female B6C3F1 mice were exposed by inhalation to 0, 120, 600, or 1,200 ppm toluene (0, 450, 2,250, or 4,500 mg/m^3) 6.5 hours/day 5 days/week for two years in a study of GLP quality (Huff, 1990). Ten female mice at each exposure level were terminated after 15 months.

15-month exposure: No toluene-induced effects were seen on body weight, absolute or relative organ weights of brain, kidney or liver. Haematological parameters were unaffected by exposure. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1,200 ppm.

2-year exposure: In female mice, body weights were slightly lower at 1,200 ppm compared with control. No significant differences in survival were observed between any groups of either sex. However, survival in all groups of male mice was low. This might be attributed to a high

occurrence of inflammatory lesions of the urinary and genital systems in all groups. The data regarding tumour incidence will be discussed in Section 4.1.2.8 (Carcinogenicity).

In these studies no toxicologically important effects were observed.

Summary of general toxicity in animals after inhalation exposure

Data from studies in rats and mice have been found. The 2-year study by Gibson and Hardisty showed no toxicity at 300 ppm (1,125 mg/m^3), which was the highest dose level of that study. In the well-reported 15-week NTP rat study, 625 ppm (2,344 mg/m^3) did not cause adverse effects. At higher exposure levels (1,250 ppm (4,688 mg/m^3) and above), a 12-18% decrease in leukocyte count was found, along with relative organ weight increases. In the 15-month and 2-year rat studies by NTP the main findings were erosion of the olfactory epithelium and degeneration of the respiratory epithelium in the nose at all exposure levels (600 and 1,200 ppm (2,250 and 4,500 mg/m^3)). A marginal increase in the incidence of forestomach ulcers in male rats at both exposure levels was found, and an increase in nephropathy at the highest dose level, 1,200 ppm (4,500 mg/m^3). In the 14-week NTP mouse study relative organ weights were increased beginning at the lowest dose level, 100 ppm (375 mg/m^3) for the lung. The toxicological significance of organ weight changes is questionable in the absence of histopathological findings, however, with increasing exposure concentration more organs became affected, and at 1,250 ppm (4,688 mg/m^3) two deaths were observed. In the 15-month and 2-year NTP mouse studies no toxicologically important effects were observed.

A clear inhalation NOAEC of 1,125 mg/m^3 (300 ppm) has been identified in the Gibson and Hardisty 2-year study. In the NTP studies a NOAEC of 625 ppm (2,344 mg/m^3) was identified in the 15-week study, while 600 ppm (2,250 mg/m^3) was a LOAEC for changes in the nasal cavity, forestomach and kidney in the 15-month and 2-year study. The toxicity of lower concentrations administered for 2 years was not examined by NTP. The exposure duration of the 2-year studies is considered the most relevant for evaluation of effects of long-term exposure in man. The 300 ppm (1,125 mg/m^3) NOAEC of Gibson and Hardisty does not appear unrealistically low compared with the 600 ppm LOAEC of NTP and will be taken forward to the risk characterisation.

Oral exposure

Two studies of repeated oral exposure have been found, one in rats, and one in mice. Both studies are of GLP quality.

Rats

Groups of 10 male and 10 female F344N rats received 0, 312, 625, 1,250, 2,500, or 5,000 mg toluene/kg in corn oil by gavage for 13 weeks (Huff, 1990). In the 5,000 mg/kg group all rats died within the first week. In the 2,500 mg/kg group 8 males and one female died before termination of the study. The final mean body weight of males that received 2,500 mg/kg was 19% lower than that of vehicle controls. Clinical signs included prostration, hypoactivity, ataxia, piloerection, lacrimation, and excessive salivation in the 5,000 and 2,500 mg/kg groups.

Absolute and relative kidney weight was increased in males at 625 mg/kg and higher, and in females at 1,250 mg/kg and higher (relative kidney weight by 6-46% in males, by 8-18% in females).

The increase in absolute and relative liver weights for female rats that received 2,500 or 1,250 mg/kg (22-62% relative liver weight increase) and for males that received 1,250 or 625 mg/kg (8-78% relative liver weight increase) were statistically significantly relative to those of vehicle controls. The absolute and relative heart weights for female rats that received 2,500 or 1,250 mg/kg, and the relative heart weight for males receiving 2,500 mg/kg were statistically significantly increased compared with vehicle controls. Absolute, but not relative brain weight was reduced in both sexes at 2,500 mg/kg. None of the differences observed in the results of the haematological and serum chemical analyses or urinalyses was considered to be biologically meaningful. Neuropathological changes in the brain, consisting of neuronal cell necrosis in the dentate gyrus and Ammons horn of the hippocampus, was seen in male and female rats that received 2,500 or 1,250 mg/kg. In addition to the hippocampal lesions, necrosis and/or mineralisation were present in the granular layer of the cerebellar cortex. Haemorrhage was present in the mucosa, submucosa, or muscularis of the urinary bladder of males and females of the two highest dose groups.

In this study a dose of 312 mg/kg/kg did not cause any effects. A toluene dose of 625 mg/kg caused increased absolute and relative liver and kidney weight (up to 46% increase in relative kidney weight, up to 78% increase in relative liver weight). Although no histopathological data are given in the report for the liver, presumably no abnormal findings were present. There was no evidence of an increase in hyaline droplets in the proximal tubules of the kidneys of exposed rats. Therefore, the increased relative weights of liver and kidney are interpreted as toxicologically non-significant signs of metabolic activity related to exposure. Consequently, the dose level 625 mg/kg is considered to be the NOAEL. At doses of and above 1,250 mg/kg, neurone necrosis in the brain was found, which is clearly an adverse effect.

Mice

Groups of 10 male and 10 female B6C3F1 mice received 0, 312, 625, 1,250, 2,500 or 5,000 mg toluene/kg in corn oil by gavage for 13 weeks (Huff, 1990). All mice that received 5,000 mg/kg died during the first week, 4 male and 4 female rats that received 2,500 mg/kg and one female mouse that received 1,250 mg/kg died before termination of the study. The final body weight of males that received 2,500 mg/kg was 16% lower than that of vehicle controls. Clinical signs included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, hypoactivity, and ataxia in mice at 2,500 and 5,000 mg/kg. Relative liver weights were statistically significantly increased for male mice that received 1,250 or 2,500 mg/kg (by 10-26%). In female mice absolute and relative liver weight was increased at 312 mg/kg, and relative liver weight was increased at all doses above this (by 7-29%). Relative brain and testis weight, and absolute kidney weight was increased in male mice at 5,000 mg/kg. Myocardial degeneration was found in several mice from this group. None of the differences in the results of haematological or serum clinical analyses or urinalyses were considered biologically meaningful.

In this study toluene caused increased absolute and relative liver weight in female mice even at the lowest dose level, 312 mg/kg. However, no accompanying histopathology is mentioned in the report, and these findings are therefore interpreted as signs of metabolic activity. The NOAEL was therefore considered to be 625 mg/kg. At 1,250 mg/kg, one death occurred in the 9th week of the study, and absolute and relative liver weights were increased in both sexes.

Summary of general toxicity in animals after oral exposure

An oral NOAEL of 625 mg/kg after 13 weeks of exposure has been determined in both rats and mice in well performed studies (Huff, 1990). In rats, neuronal death in the hippocampus was

found in both sexes at dose levels above the NOAEL. In mice, one death occurred at the dose level above the NOAEL.

Studies in humans

No studies examining general toxicity in humans have been found.

4.1.2.6.2 Specific organ toxicity

Studies in animals

Liver

In rats exposed via inhalation to 1,000 mg/m^3 (267 ppm), 1,500 mg/m^3 (400 ppm), 3,000 mg/m^3 (800 ppm), 3,500 mg/m^3 (933 ppm) or 6,000 mg/m^3 (1,600 ppm) toluene 8 hours/day for up to 6 months, reversible dose-dependent increases in relative weight of the liver, succinate dehydrogenase activity, and concentration of cytochrome P450 and b_5, and a decrease in glycogen content were found. Histology showed hypertrophy of the centrolobular zones in the groups exposed to high concentrations of toluene. Electron microscopy revealed proliferation of smooth endoplasmic reticulum and dilatation of the rough endoplasmic reticulum cisternae in the cells of the centrolobular zone in all toluene-exposed groups. A dose-relation was found. The authors interpreted the changes as non-specific signs of compensation, and concluded that no chronic hepatic disease had developed in repsonse to toluene exposure (Ungváry et al., 1980).

Kidney

No animal studies specifically examining kidney effects have been found. Non-specific toxic effects on the kidney have been found in general toxicity studies and are described in Section 4.1.2.6.1.

Nervous system

Groups of 7 male rat pups were exposed to 0, 100, or 500 ppm (0, 375, or 1,875 mg/m^3) toluene for 12 hours/day on postnatal days 1 through 28 (Slomianka et al., 1990). On postnatal day 28, the rats were sacrificed and their brains processed for histological and volumetric study of the hippocampus. The layers of Ammon's horn and the subiculum were not affected by 500 ppm toluene exposure. Within the area dentata, the volume of the granule layer was 6% smaller in animals exposed to 100 ppm toluene and 13% smaller in animals exposed to 500 ppm toluene. The volumes of the hilus and the commissural-associational zone of the dentate molecular layer were smaller (12% and 19%) in animals exposed to 500 ppm toluene compared to controls. Argyrophilic cells were found in the granule layer of all animals exposed to 500 ppm toluene, and the granule cell layer appeared qualitatively normal in animals exposed to 100 ppm toluene.

This study used two control groups, one for each of the exposed groups, and a significantly lower baseline was observed in the 100 ppm study. Therefore, the significant differences observed at 100 ppm are not considered useful. However, the magnitude of the toluene-induced reductions in volume in the hippocampal regions observed at 500 ppm exceeds the magnitude of the shift in baseline values in the two control groups and therefore this finding is considered relevant. Thus, the study indicates that inhalation of 500 ppm toluene for 28 days after birth

causes volumetric changes in certain areas of the hippocampus which is generally considered a common and sensitive target of CNS toxicants. A NOAEC cannot be set based on this study.

Groups of 12 male rat pups were exposed to 0 or 500 ppm (1,875 mg/m^3) toluene 12 hours/day from postnatal day 1 to 28, when half of the rats were sacrificed (Slomianka et al., 1990, described above). The other half were allowed an exposure-free period until sacrifice on postnatal day 120 (Slomianka et al., 1992). At day 120, no differences were apparent in the volumes of the dentata components of control and experimental animals.

The findings of this study indicate that the effects identified in the 1990 study may be transient.

The two Slomianka et al. studies (1990, 1992) will be discussed in Section 4.1.2.9.5 (Developmental toxicity studies in animals).

Groups of six rats were exposed to 0 or 1,500 ppm (5,625 mg/m^3) toluene via inhalation for 6 hours/day, 5 days/week for 6 months. This exposure period was followed by a four-month exposure-free period prior to sacrifice. The total number of neurones in each of the five subdivisions of the hippocampus was estimated with an optical fractionator. A statistically significant neuron loss of 16% was found in the regio inferior (CA3 and CA2) of the exposed rats (Korbo et al., 1996).

Groups of 36 rats were exposed to 0, 500, or 1,500 ppm (0, 1,875, or 5,625 mg/m^3) toluene via inhalation 6 hours/day, 5 days/week for 6 months followed by an exposure-free period of 2 months prior to testing and sacrifice (Ladefoged et al., 1991). The animals were tested in behavioural tests for learning and memory (Morris water maze, radial arm maze, passive avoidance test), and their diurnal motor activity was measured throughout the study. After sacrifice, organs were weighed and processed histologically. The brain of 12 animals in each group was dissected into the seven regions cerebellum, hemisphere, hippocampus, hypothalamus, pons, thalamus, and medulla oblongata. The regions were weighed, homogenised and the concentrations of noradrenaline, dopamine and 5-hydroxytryptamine were determined. No neurobehavioural or gross pathological changes were found except for the weight of hippocampus, which was dose-dependently reduced, statistically significantly at 1,500 ppm. The morphometric measurements did not reveal any significant loss of neuronal cells of the neocortex. An increase in perikaryonal volume and nuclear volume was found at 500 ppm. Noradrenaline, dopamine and 5-hydroxytryptamine levels were significantly changed in various brain regions at 500 and 1,500 ppm. This study shows reduction in the weight of the hippocampus, and changes in neurotransmitters related to toluene exposure. These effects were considered irreversible effects of toluene exposure by the authors.

In two separate experiments, groups of 14 (first experiment) or 16 (second experiment) male Sprague-Dawley rats were exposed to 0 or 80 ppm (300 mg/m^3) toluene via inhalation 6 hours/day, 5 days/week, for 4 weeks (von Euler et al., 1993; 1994). Three days after end of exposure, groups of 10 (first experiment) or 12 animals (second experiment) were trained for 4 days in the Morris water maze (acquisition learning). Seven days after the last acquisition trial, retention of learning was tested. It was found that escape latency and swim length was increased for the exposed rats during the third and fourth training days. The escape latency at the retention test was longer for the toluene-exposed rats. Swim speed was similar in the two groups, showing that the rats swimming ability was unaffected by toluene, while swim distance was longer in the toluene-exposed rats. Testing of apomorphine-induced locomotor activity 17 days after the last exposure showed increased motor activity in the toluene exposed rats compared with the control group. Dopamine receptor (D_2) agonist binding parameters were changed in brains from 2 rats in each group (first experiment) or 4 rats (second experiment), suggesting a possible increase in the

number of dopamine receptors, and a decrease in D_2 agonist affinity. Serum levels of prolactin from blood obtained 17 days after the last exposure were increased in the toluene-exposed rats.

This study indicates that toluene affects cognitive function in rats. The increased response to apomorphine may be related to an increase in the number of D_2 receptors.

Groups of 8 male Wistar rats were exposed to 0, 100, 300, or 1,000 ppm (0, 375, 1,125, 3,750 mg/m^3) toluene 8 hours/day six days/week for 16 weeks (Huang et al., 1992). At termination of the exposure body weight, whole brain weight, and weights of cerebrum, cerebellum, and brainstem were determined before the different parts of the brain were homogenised for determination of the neuronal marker proteins γ-enolase and calbindin-D28k; and the glial cell marker proteins α-enolase, creatine kinase-B, and β-S100 protein. There were no dose-dependent changes in body weight, whole brain weight, or weights of various brain parts. The content of neuronal marker proteins did not differ for γ-enolase in cerebrum, brainstem, and spinal cord. In the cerebellum γ-enolase showed a dose-dependent increase in concentration significant from the 100 ppm group and above. Calbindin-D28k was not changed in cerebrum, cerebellum, and brainstem, but in the spinal cord a significant decrease of this protein was seen at 1,000 ppm. The glial cell marker α-enolase were not changed in cerebrum, brainstem and spinal cord, but in the cerebellum this protein showed a significant dose-related increase from 100 ppm. The concentration of creatine kinase B in the cerebellum increased in dose-related way, the increase being statistically significant from 100 ppm, whereas for the other parts of the brain no dose-related changes were seen. For β-S100 protein again in the cerebellum a dose-related increase was found, the increase being statistically significant from 300 ppm, and in brainstem and spinal cord this protein was increased at 1,000 ppm.

This study shows that exposure of rats to toluene concentrations of 100 ppm and above induces neurochemical changes. These changes were interpreted by the authors as possible first steps in toluene neurotoxicity.

Auditory system

In a number of studies in rats the ototoxicity of toluene has been investigated. Assessment methods include electrophysiological as well as behavioural and morphological methods, and toluene has repeatedly been shown to cause impairment of auditory function in rats.

A description of the results is given in the following text.

Auditory impairment of toluene-exposed rats was first suspected when results of a study investigating neurobehavioural effects in groups of 11-12 male Fischer-344 rats, 21 days old, exposed to 0, 900 or 1,400 ppm (0, 3,375, or 5,250 mg/m^3) toluene, 14 hours/day, 7 days/week, for 14 weeks revealed deficiencies in learning a multisensory conditioned avoidance response task and a tone-intensity discrimination task (tone frequency in both tasks was 4 kHz) when the rats were trained several hours after each daily 14-hour exposure ended (Pryor et al., 1983a). Because of the short period from exposure to testing in this study, it was not possible to determine whether the effects were acute, pharmacological effects, or signs of long-lasting damage.

This was explored in a study where groups of 28 rats were exposed to 0 or 1,200 ppm (4,500 mg/m^3) toluene, 14 hours/day, 7 days/week, for 5 weeks (Pryor et al., 1983b). During the 5th exposure week, and again 2 months after the last exposure, the rats were tested in a multisensory conditioned avoidance response test. A striking lack of response to sound (a 20 kHz tone), but not to the other sensory stimuli was found at both test times. Testing in a tone-intensity

discrimination task (tone frequency was 4 kHz) began 4 weeks after the last exposure, showing no effect of toluene-exposure on performance. Two and a half months after the last exposure testing in a conditioned avoidance response was carried out using tone frequencies of 4, 8, 12, 16, or 20 kHz. Hearing was normal at 4 kHz, slightly impaired at 8 kHz, but at tone frequencies above 12 kHz a significant impairment in response was found. In conclusion, toluene exposure caused a long-lasting hearing deficit to high-frequency tones in rats.

The hearing loss was further characterised by measuring the auditory thresholds using the brainstem auditory-evoked response to clicks of 5 kHz and tone frequencies of 8, 12, and 16 kHz in the rats of the study by Pryor et al. (1983b) beginning about 2.5 months after the last exposure (Rebert et al., 1983). It was found that the thresholds in the toluene-exposed rats were elevated by 13 to 27 dB, while other characteristics of the response were changed in a manner consistent with sensorineural hearing loss. The electrophysiological findings support the previously demonstrated functional hearing loss.

The relationship between toluene concentration, exposure pattern, and hearing loss in rats was investigated in a series of experiments in male Fischer rats (Pryor et al., 1984). Hearing loss was measured by conditioned avoidance response to tone frequencies of 4, 8, 12, 16 or 20 kHz, and brainstem auditory-evoked response to tone pips of 4, 8, and 16 kHz. A multisensory conditioned avoidance response test was used to control for toluene-related effects on other neurobehavioural functions. Examination times relative to exposure varied from experiment to experiment. Two weeks of exposure to 1,000 ppm (3,750 mg/m^3) toluene 14 hours/day caused hearing loss. Lower concentrations (400 (1,502 mg/m^3) and 700 ppm (2,625 mg/m^3)) were without effect even after 16 weeks of exposure. Three-day exposures to 1,500 ppm (5,625 mg/m^3) for 14 hours/day or to 2,000 ppm (7,500 mg/m^3) for 8 hours/day were ototoxic. Single exposures to 4,000 ppm (15,000 mg/m^3) for 4 hours or to 2,000 ppm for 8 hours were without effect. Intermittent exposure to 3,000 ppm (11,250 mg/m^3) for 30 minutes every hour for 8 hours/day caused hearing loss within 2 weeks, but a similar exposure schedule for 4 hours/day was ineffective even after 9 weeks.

In conclusion, toluene ototoxicity is manifest only at relatively intense schedules of exposure. The toluene concentration and the duration of exposure must be above a certain level before hearing loss will occur.

There was no control for noise in all the above-mentioned studies.

A study has been performed to investigate whether noise from the inhalation system used to generate the test atmosphere could be a major contributing factor to the hearing loss (Pryor and Howd, 1986). Groups of male Fischer-344 rats received PEG-300 (control) or toluene (1.5 or 1.7 g /kg) via subcutaneous injections for 7 days, and were housed in a quiet environment. Hearing loss was measured more than 1 month after exposure by conditioned avoidance response to tone frequencies of 4, 8, 12, 16 or 20 kHz, and brainstem auditory-evoked response to tone pips of 4, 8, and 16 kHz. A multisensory conditioned avoidance response test was used to control for toluene-related effects on other neurobehavioural functions. A significant hearing loss at the frequencies 8, 12, 16, and 20 kHz was identified. At 4 kHz no hearing loss was observed.

This study shows that direct introduction of toluene into the body leads to hearing loss. Neither noise nor direct exposure of the external ear to toluene is a necessary factor for production of hearing deficits.

Groups of 8-12 male Sprague-Dawley rats were exposed to ambient air, to 1,000 ppm (3,750 mg/m^3) toluene 16 hours/day, 5 days/week, for 2 weeks, to noise 10 hours/day, 7 days/week, for 4 weeks, or to toluene followed by noise (same dose and schedule) (Johnson et

al., 1988). Toluene exposure began at age 21 days, while noise exposure began at age 35 days. The noise level for groups not exposed to noise was 40 dB(A), which was not expected to have any effect on hearing. Brainstem auditory responses to tone pulses at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz were measured immediately after exposure (at age 63 days), at 3 months of age, and at 6 months of age. Toluene alone and noise alone caused a considerable decrease in the auditory sensitivity, particularly at 12.5 kHz. The decrease in rats exposed to toluene followed by noise was greater than the summated effects of each factor alone. In addition to showing that exposure to toluene alone induces a decrease in auditory sensitivity, this study indicates a synergistic toxic effect of toluene and noise on auditory functions.

The same authors conducted a similar experiment with the same doses and the same exposure schedule (Johnson et al., 1990). However in this experiment the sequence of exposure was reversed, i.e. noise before toluene. The effect of toluene alone and noise alone was similar to the effects in the Johnson et al. (1988) study, however the hearing loss caused by the combined exposure did not exceed the sum of the effects of the equivalent single exposures. The authors concluded that the exposure sequence could determine the extent of auditory impairment.

Groups of 18 male Sprague-Dawley rats were exposed to air, n-hexane, toluene, or toluene plus n-hexane, each solvent in a concentration of 1,000 ppm (3,750 mg/m^3); for 21 hours/day, 7 days/week for 28 days (Nylén et al., 1994). The noise level was 76-78 dB SPL (Sound pressure level). Neurophysiologic recordings were made 2 days, 3 months, and one year after end of the exposure. Loss of auditory sensitivity measured by recording of click evoked auditory brain stem response was observed 2 days after exposure in the two toluene-exposed groups. At the two subsequent recordings no improvement was observed in the group exposed to pure toluene. In the group exposed to toluene plus hexane a synergistic loss of auditory sensitivity was observed at 3 months. No effect of toluene was seen on amplitudes and latencies of auditory brain stem response or on flash evoked potentials. Exposure to *n*-hexane alone caused a marked decrease in peripheral nerve conduction velocity 2 days and 3 months after exposure, while exposure to *n*-hexane together with toluene had only a small effect on this velocity.

This study confirms the observation by Pryor et al. (1983b) that repeated exposure to toluene via inhalation in a concentration of 1,000 ppm is ototoxic. Furthermore, even after one year hearing function had not recovered. The ototoxic effect of toluene exposure in rats may therefore be irreversible.

Groups of 9 male rats (DA-HAN) were exposed to toluene via inhalation, to toluene via inhalation plus ethanol in the drinking water, or to ethanol in the drinking water, or to air (Nylén et al., 1995). The toluene concentration was 1,000 ppm (3,750 mg/m^3) 21 hours/day, and the ethanol concentration was 5.7-8.0% ethanol in the drinking water. Exposure duration was 8 weeks. The noise level was 76-78 dB SPL. Electrophysiological recordings were made 1 week after the exposure. Auditory brain stem response to tones of 1.6, 3.15, 6.3, 12.5, and 20.0 kHz was significantly reduced in the toluene-exposed groups at all the studied frequencies. The largest loss was found at the middle frequency (12.5 kHz). Flash evoked potentials and nerve and muscle action potentials were not affected by toluene exposure.

This study, again, confirms the finding that repeated exposure to 1,000 ppm of toluene induces auditory impairment in the rat.

The hearing function of female rats (dams) exposed to 0 or 1,600 ppm (6,000 mg/m^3) toluene 6 hours/day in a developmental toxicity study on gestational day 7-20 was examined 4-6 weeks after the end of exposure (Hougaard et al., 1996). The auditory brain stem responses to tone

bursts at 4, 8, 16 20 and 32 kHz were measured, showing that the hearing threshold in the toluene-exposed rats was elevated at all frequencies, significant only at 16 kHz.

This is the only study where toluene-related ototoxicity in female rats has been studied, showing that the effect is not specific to males.

The morphological basis for the auditory impairment has been investigated (Johnson and Canlon, 1994a). A group of 13 male Sprague-Dawley rats inhaled 1,400 ppm (5,250 mg/m^3) toluene 16 hours/day for eight days. The noise level was below 50 dB(A). During exposure 3 rats were sacrificed on day 3 and 4 rats on day 5. After exposure 4 rats were sacrificed on day 4 and 2 rats after 6 weeks. After decapitation both cochleae were dissected out and stained for either light microscopy or scanning electron microscopy for histological examination and counting of hair cells. After three days of toluene exposure no loss of hair cells was observed but after 5 days of exposure a slight loss of outer hair cells was found in the third row. Four days after the exposure a loss of hair cells was found in all three rows of outer hair cells, mainly in the middle and upper turns of the cochlea. Six weeks post-exposure the damage on the hair cells had progressed towards the basal part of the cochlea, and a 50-100% loss of outer hair cells together with some loss of inner hair cells was seen. The auditory sensitivity of the rats was measured before exposure, after 3 and 5 days exposure, and 4 days after the end of exposure by electrophysiological methods (Johnson and Canlon, 1994b). The auditory brainstem response threshold was increased with an average loss of auditory sensitivity of about 20-40 dB compared with control rats, and the loss was greater with increasing number of days of exposure (during exposure only test at 12.5 kHz, after exposure test at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz). Lowered distortion product otoacoustic emissions were found after 5 days exposure, and at the last examination 4 days after the end of exposure (test at 3.0, 4.0, 5.0, 6.3, 8.0, 9.0, 11.4, 14.3, and 17.9 kHz). The greatest loss of auditory sensitivity was found in the middle frequency region. The authors compared the morphological findings with the functional measures and concluded that a fairly good correlation was found between the frequency regions showing loss of hair cells and the shifts in auditory thresholds.

The studies of Johnson and Canlon show that even short-term exposure to toluene causes long-lasting progressive morphological damage to cochleae in the ears of rats. The pattern of hair cell loss is different from that found in normal ageing or caused by known ototoxic chemicals, where losses in the high-frequency area occur first. The position of the morphological changes corresponded to the threshold shifts observed in distortion product otoacoustic emissions measured on the same rats.

Groups of 22-24 Long-Evans rats were exposed to 2,000 ppm (7,500 mg/m^3) toluene, to noise, or to toluene plus noise 6 hours/day, 5 days/week, for 4 weeks (Lataye and Campo, 1997). Determination of audiometric thresholds within the range 2-32 kHz was performed before exposure, the day after the last exposure, and 6 weeks after the last exposure. The auditory deficit induced by the combined exposure exceeded the summated losses caused by toluene alone and by noise alone. Following audiometry, the rats were sacrificed, and the cochleae were examined by light and scanning electron microscopy. Noise alone caused cochlear lesions characterised by injured stereocilia of outer hair cells, but without loss of cells, while toluene alone caused a massive loss of outer hair cells.

This study supports the findings regarding the morphological appearance of toluene-induced cochlear damage, characterised by loss of outer hair cells. It also demonstrates that noise alone can produce cochlear damage, and that the combination of toluene and noise may be synergistic.

Eight male Sprague-Dawley rats were dosed by gavage for eight weeks with 1.0 ml toluene/kg body weight/day, while control rats received corn oil (Sullivan et al., 1989). Brainstem auditory-evoked responses to tone bursts at 0.5, 1, 2, 4, 8, 16 and 32 kHz were recorded before exposure and 1 day after the last dose had been administered. Frequency-specific threshold elevations, corresponding to regions of the organ of Corti which had outer hair cell loss, were observed in toluene-treated rats. The greatest threshold elevations were found at 2-8 kHz. The rats were sacrificed after measurement of brainstem responses. The tissues of the inner ear were fixated and examined with phase-contrast microscopy. Losses of outer hair cells were observed in all toluene-treated rats, while inner hair cells were not damaged.

Further description of the cochlear lesions has been reported by Campo et al. (1997). Male 7-month old Long-Evans rats were exposed to toluene concentrations of 0, 1,000, 1,250, 1,500, 1,750, or 2,000 ppm (0, 3,750, 4,688, 5,625, 6,563, or 7,500 mg/m^3) 6 hours/day, 5 days/week, for 4 weeks. Auditory thresholds were recorded by audiometry before exposure, 24-32 hours after exposure, and 6 weeks after exposure. Only toluene concentrations at and above 1,500 ppm resulted in significant shifts in auditory threshold. The hearing deficit was found in the range 8-24 kHz, while no loss of hearing was found at 32 kHz. The rats were sacrificed 7-8 weeks after the end of exposure, and the cochlear tissues were examined by light and scanning electron microscopy. In the cochlea, a loss of outer hair cells and lack of intraganglionic bundles was found, which is a strong indication of primary cochlear injury. Loss of outer hair cells was detected in all exposed groups in a dose-related manner.

In a study by Brandt-Lassen et al. (2000) 120 male (12 rats in each exposure group) Wistar rats were exposed to either toluene alone (6 hours/day) or to toluene and noise in sequential combination (6+2 hours/day) for 10 consecutive days. Toluene exposures concentrations were 2,000, 1,500, 1,000, 500, or 0 ppm toluene (7,609, 5,706, 3,804, 1,902, or 0 mg/m^3) and the noise level was 96 dB SPL ("white noise" 4-20 kHz). Auditory thresholds were determined by auditory brain stem response (at 4, 8, 12.5, 16, 20, and 31.5 kHz) one week prior to exposure and again 12 days after the end of exposure.

Exposed to toluene only, the rats exposed at the 1,500 and 2,000 ppm level developed statistically significant mid-frequency hearing loss, whereas rats exposed to 0, 500, and 1,000 ppm did not exhibit signs of auditory impairment. Rats exposed to 500 ppm toluene and noise developed a small, but statistically significant threshold shift, equal to the hearing loss in rats exposed to noise only (0 ppm). At toluene concentrations of 1,000, 1,500, and 2,000 ppm a statistically significant interaction between noise and toluene was observed.

The rats exposed to toluene only were kept for 36 days after the end of the toluene exposure and then exposed to acute noise (105 dB) for 4 hours once. The effect of the acute noise exposure on the rats previously exposed to 500 or 1,000 ppm toluene was quite similar to the effect on the rats in the control group (not previously exposed to toluene). However, the rats previously exposed to 1,500 ppm toluene had increased auditory threshold shifts at all the test frequencies following the acute noise exposure in comparison to the rats in the other three exposure groups. The differences in thresholds shift between the 1,500 ppm group and the control group were statistically significant only at 4.0, 8.0, and 16.0 kHz.

The results give clear signs of synergistic interaction at a toluene concentration that in itself did not seem to cause any change in auditory thresholds. Further the results indicates that toluene may cause a long lasting increased vulnerability to noise exposure.

In a study by McWilliams et al. (2000) thirty-two pigmented guinea pigs (approximately 60 days old) received 0, 250, 500, and 1,000 ppm toluene by inhalation for 8 hr/day for 5 days. Distortion

product otoacoustic emission (DPOAE) assessment was undertaken before inhalation exposure and, again, following exposure.

A statistically significant reduced DPOAE ($2F_1$-F_2) amplitude was found immediately following the final toluene inhalation exposure in all exposed groups. After a three-day exposure-free recovery period DPOAE amplitude returned to or near control levels in all three exposed groups. The 250 ppm toluene subjects were discontinued.

Toluene exposures were resumed for control (n=6) and 500 ppm subjects (n=4) for 8 hours/day, 5 days/week for an additional 3 weeks. A greater reduction in DPOAE amplitude than that seen after 1 week was found. Again, recovery of the DPOAE amplitude was observed when the animals were screened 3 days following the 4-week exposure.

Upon completion of DPOAE assessment, cochleae were obtained from a limited number of subjects in the 500 ppm group for comparison of functional and histological data. Succinate dehydrogenase staining showed a distinct reduction in enzyme activity in the mid-frequency region of the cochlea acutely following toluene exposure. Although the auditory dysfunction progressed between one and four weeks of exposure, a permanent loss did not develop for these subjects and hair cell death was not seen.

The current study gives evidence of transient auditory system impairment in the guinea pig at a toluene concentration of 250 ppm (938 mg/m^3).

The UK Competent Authorities (CA) felt that the two studies dated as 2000 need to be available in a fully documented form, such that the magnitude, pattern and statistical significance of the results obtained can be clarified before particular weight is put on the reported findings.

Interaction with toluene on the auditory function

The studies mentioned in this section have already been described in greater details in the previous text and will therefore be very briefly discussed. Interaction with noise, with ethanol, and with n-hexane has been investigated. Although the results from animals exposed to toluene in combination with other agents are not directly useful for identification of the hazard of toluene, they add valuable information for use in the risk characterisation. The ototoxic effect of toluene may be enhanced by co-exposure to other agents and this must be taken into consideration in the evaluation of the MOS.

Noise: Rats were exposed to ambient air, to toluene alone, to noise, or to toluene followed by noise (Johnson et al., 1988). Toluene alone and noise alone caused a considerable decrease in the auditory sensitivity. The decrease in auditory sensitivity of rats exposed to toluene followed by noise was greater than the summated effects of each factor alone. With the reversed exposure scheme, i.e. noise followed by toluene the effect of the combined exposure did not exceed the sum of the equivalent single exposures (Johnson et al., 1990).

Rats were exposed to toluene, to noise, or to toluene plus noise (Lataye and Campo, 1997). The auditory deficit induced by the combined exposure exceeded the summated losses caused by toluene alone and by noise alone. The histopathological appearance of the cochlear lesions induced by noise and by toluene was different.

The Brandt-Lassen et al. (2000) study gives clear signs of synergistic interaction between toluene and noise even at a toluene concentration that in it self did not seem to cause any change in auditory thresholds. Further the results from this study indicates that toluene may cause a long lasting increased vulnerability to noise exposure.

These studies strongly indicate that a synergistic toxic effect of toluene and noise on auditory functions may exist. In the study by Johnson et al. (1988) and is part of the Brandt-Lassen et al. (2000) study, the exposure to toluene and noise was not simultaneous, while this was the case in the study by Lataye and Campo (1997). In the other part of the Brandt-Lassen et al. (2000) study the rats were exposed to toluene and noise in sequence on a daily basis.

The apparent synergistic interaction between noise and toluene has consequences for the design and interpretation of experiments where noise-generating inhalation exposure machinery is used; i.e. auditory effects must be evaluated as a function of toluene concentration and noise level.

Ethanol: Rats were exposed to ambient air, to toluene alone, to toluene plus ethanol, or to ethanol alone (Nylén et al., 1995). Auditory function was reduced in the toluene-exposed groups, but not in the group exposed to ethanol alone. Ethanol counteracted the effect of toluene on auditory sensitivity.

n-Hexane: Rats were exposed to air, to n-hexane alone, to toluene alone, or to toluene plus n-hexane (Nylén et al., 1994). Loss of auditory sensitivity was observed in the two toluene-exposed groups. In the group exposed to toluene plus hexane a synergistic loss of auditory sensitivity was observed 3 months after exposure.

Summary of specific organ toxicity in animals

In the liver of rats exposed for up to six months signs of compensatory hypertrophy were found, while no chronic hepatic disease had developed. No animal studies specifically examining kidney effects have been found. Rat studies have shown that toluene may cause a possibly transient reduction in the volume of hippocampal structures during postnatal development, neuron loss in the regio inferior of the hippocampus, irreversible reduction in the weight of the hippocampus, cognitive impairment in Morris maze at least shortly after exposure, and changes in neurotransmitters and other neurochemical parameters. The effects observed at 1,500 ppm in the Korbo et al. (1996) study (neuron loss) and the Ladefoged et al. (1991) study (hippocampal weight reduction) are considered to be irreversible and biologically important. In the Korbo et al. (1996) study 1,500 ppm was the only dose group examined. Although hippocampal weigh was not reduced at 500 ppm in the Ladefoged et al. study, an increase in perikaryonal volume and nuclear volume was found at this level, indicating that 500 ppm is not a clear NOAEC.

A large number of experiments show that toluene exposure causes a functional hearing deficit in rats, which can be measured as a lack of behavioural response to sound. The impairment is also evidenced by electrophysiological changes, and by morphological damage to the outer hair cells of the inner ear. Auditory impairment and morphological changes have been found after inhalation exposure, and also after oral and subcutaneous administration. Therefore, it can be concluded that the effect is not a local damage caused by direct penetration of toluene through the external ear. Inhalation concentrations of 1,000 to 1,400 ppm administered for 2-8 weeks have been effective. Effects on morphology of outer hair cells and auditory function have been found already after 5 days exposure to 1,400 ppm of toluene. The effect seems to be irreversible. Behavioural indices of impaired hearing have been found 2.5 months after exposure, but has not been examined beyond this time point. Electrophysiological measures have been found to be abnormal even 1 year after exposure, while morphology has not been examined beyond 7-8 weeks after exposure. In the opinion of the rapporteur the ototoxicity of toluene should be regarded as an irreversible effect.

The evidence points to long-lasting irreversible ototoxicity of toluene. It is likely that the rat must be exposed to a certain minimum concentration of toluene for a certain minimum of time

before ototoxicity will develop. The size of this minimum concentration is not known; nor has it been sufficiently documented that a certain low concentration will not cause ototoxicity after long-term exposure. The study with the longest exposure period is the study by Pryor (1984) in which 700 ppm (2,625 mg/m^3) toluene for up to 16 weeks was a NOAEC with a 14-hour daily exposure duration. In the same study, the LOAEC was 1,000 ppm (3,750 mg/m^3) (14 hours/day). At 1,000 ppm an exposure duration of only 2 weeks was associated with hearing loss. In this study auditory function was evaluated by estimation of auditory sensitivity, which is not the most sensitive method. It is known that damage to the auditory system can be present without being detected by estimation of auditory sensitivity. In the Campo et al. (1997) study loss of hair cells was detected down to 1,000 ppm, while auditory thresholds were only significantly changed at 1,500 ppm and above. In the McWilliams et al. (2000) study, hearing function was evaluated via distortion product otoacoustic emission. This revealed transient auditory system impairment at a toluene concentration of 250 ppm i.e., one fourth of the LOAEC from the Pryor et al. (1984) study determined via the brainstem auditory evoked response. Thus, it is possible that effects would have been detected at 700 ppm if more sensitive measurement methods had been employed, such as morphological examination, or auditory acuity measurement.

The rapporteur is of the opinion that there can be no doubt that toluene is ototoxic in rats, and that the effect is chronic.

Studies in humans

A number of studies have been performed.

Liver

Among 24 toluene abusers examined on the day of admission to hospital, alkaline phosphatase was elevated in 13 patients, while SGOT was elevated in 7. The elevated enzyme levels returned to normal after 2 weeks of abstinence (Fornazzari et al., 1983).

No increase in levels of the enzymes serum aspartate aminotransferase and alanine aminotransferase was found, in 59 men with occupational exposure to toluene (recorded level 375 mg/m^3) for more than one year (1-5 years, 22 men; 6-10 years, 18 men; more than 10 years, 19 men) when compared to an unexposed control group of equal size (Waldron et al., 1982).

In 47 toluene-exposed workers a significant increase in S-ALP (20% relative to referents) compared with a referent group of 46 non-exposed workers was found (Svensson et al., 1992b). The association was still significant when heavy alcohol consumers were excluded from the analysis. The exposure levels were generally below 300 mg/m^3 (80 ppm). Other liver function-related enzyme levels were unaffected. There was no association with cumulative exposure.

In summary, toluene abuse may be associated with transiently elevated liver enzyme levels. In occupational settings, one study has reported an increase in S-ALP while another study did not reveal any changes.

Kidney

Sniffing of toluene resulted in reversible kidney damage (O'Brian et al., 1971), haematuria (Massengale et al., 1963), reversible type 1 renal tubular acidosis (Bennett and Forman, 1980; Fischman and Oster, 1979; Kroeger et al., 1980; Moss et al., 1980; Patel and Benjamin, 1986; Reisin et al., 1975; Streicher et al., 1981; Taher et al., 1974; Weinstein et al., 1985; Will and

McLaren, 1981) and hypokalaemia (Kelly, 1975; Taher et al., 1974). In some cases sniffing resulted in irreversible damage of the kidneys (Russ et al., 1981).

A workplace accident with massive toluene exposure for 18 hours resulted in renal failure with oligouria probably caused by dehydration and myoglobinuria (Reisin et al., 1975).

Inhalation of 382 mg/m^3 (100 ppm) toluene for 6.5 hours in an exposure chamber resulted in unchanged excretion of albumin and beta-2-microglobulin for 43 printers with occupational exposure to toluene as compared to 43 age-matched controls without occupational exposure to toluene (Nielsen et al., 1985).

No signs of renal damage in 118 painters were found compared with a control group. The painters had an average of 9 years occupational exposure to toluene and xylenes. At the time of investigation, the exposure was approximately 94 mg/m^3 (25 ppm) as determined from metabolites in urine (Franchini et al., 1983).

In 42 printers with an occupational toluene exposure averaging 300 mg/m^3 (80 ppm) (range 100-900 mg/m^3 (30-240 ppm)) compared with 48 unexposed controls, no changes in glomerular filtration rate, renal concentrating ability, beta-2-microglobulin excretion, and excretion of erythrocytes and leukocytes were found (Askergren, 1982).

In conclusion, massive toluene exposure through abuse or workplace accidents has been associated with kidney damage and renal failure. Three occupational studies did not show a relation between toluene exposure and kidney damage.

Blood

Among 24 solvent abusers, 8 long-term users had lymphocyte abnormalities (5 lymphopenia, 3 lymphocytosis). Three subjects (2 were women) had a normocytic-normochromic aneaemia (Fornazzari et al., 1983).

In a study including 38 female workers employed with shoe gluing and a control group of 16 women from the same plant, but not exposed to organic solvents, the values of blood density, haemoglobin content, haematocrit and number of leukocytes were not different. However, the Mommsen toxic granula in the peripheral neutrophile granulocytes developed faster in the group exposed to toluene. Mean values of hippuric acid in urine were 3.26 mg/ml in the exposed group and 0.35 mg/ml in the control group (Matsushita et al., 1975).

In summary, there are no data indicating a specific effect of toluene on human blood parameters. It cannot be excluded that the blood abnormalities found in toluene abusers may be caused by other factors.

Cardiovascular effects

In a study involving 325 printers, past toluene exposure was elucidated through a questionnaire and an interview. The mean exposure level was approximately 375 mg/m^3 (100 ppm) for twenty years preceding the investigation. The information was used to group the printers according to an exposure index. A slight increase in systolic blood pressure showed correlation with increasing toluene exposure, as judged by the exposure index. For 133 of the printers, systolic blood pressure was measured before and after an exposure-free period of six weeks. The exposure free period resulted in a significant decrease in systolic blood pressure (Mørck et al., 1985). No significant changes were observed in diastolic blood pressure.

Nervous system

A number of studies in humans have been performed.

In several experiments, voluntary subjects have inhaled a controlled toluene-containing atmosphere in exposure chambers. These studies are described in the section on acute toxicity. Epidemiological investigations of occupationally exposed subjects have been performed. In addition, a number of studies have dealt with effects in relation to the very high exposure levels involved in toluene abuse, known as "sniffing".

High-level exposure

In a number of case reports, different effects of toluene sniffing (Brozovsky and Winkler, 1965; Boor and Hurtig, 1977; Devathasan et al., 1984; King, 1982; Lewis et al., 1981; Malm and Lying-Tunell, 1980; Sasa et al., 1978; Tsushima and Towne, 1977; Watson, 1979; Weisenberger, 1977) and of workplace exposure to toluene (La Chapelle et al., 1982; Magnussen and Fossan 1983) have been described. Symptoms include cerebellar, pyramidal and cognitive dysfunction such as tremor, ataxia, and memory impairment.

In a study of hospitalised solvent abusers, 24 patients with a mean age of 23 + 4.4 years and 6.3 + 3.9 years of toluene sniffing were examined (**Table 4.22**). Present toluene consumption was 160-425 mg toluene/day (Fornazzari et al., 1983).

Table 4.22 Neurological observations in 24 chronic toluene sniffers

Observation	Number of persons	%
Tremor	11	46
Ataxia	11	46
Memory impairment	5	21
Decreased sense of smell	2	8
Optic atrophy	2	8
Hearing impairment	2	8
Spasticity and hyperreflexia	2	8
Peripheral neuropathy	2	8
Pathological reflexes	2	8

Based on the results of the neurological examination, the patients were divided into an affected group comprising 15 subjects (four or more abnormal neurological findings) and a non-affected group of 9 subjects (less than four abnormal findings in the neurological examination). In four psychological tests abnormal results were found for the affected group. For the non-affected group, abnormal score was found only in verbal IQ. In 13 subjects, cerebrospinal fluid was examined and compared with control values from other neurological patients. The oxygen content was low, Cl^- was high, and the anion gap was very low. EEG recordings in 19 subjects revealed non-specific abnormalities in 5, while the EEGs of the remaining subjects were normal. CT-scanning results from 14 subjects (7 affected, 7 unaffected) revealed significant brain atrophy when the study subjects were compared with 20 age-matched controls who were investigated for other non-solvent related neurological disorders. The neurologically affected solvent users exhibited more prominent cerebellar sulci than the non-affected, while cortical and ventricular measures were similarly affected in both groups of solvent users.

Lazar et al. (1983) studied four toluene-sniffing patients. In addition to the neurological symptoms and findings reported above, brain stem auditory evoked potential was severely affected in the three patients tested. Audiometry showed mild abnormality in one of three patients. Moderate to severe oculomotor abnormality was found in three out of the four, and moderate to severe atrophy of the cerebellum in two of the patients.

Epidemiological studies

Several cross-sectional studies have been found, in which an exposed group of workers has been compared with a matched control group. Rotogravure printing is an occupation where a relatively pure exposure to toluene is found. The studies in which the exposure was predominantly to toluene, and where an estimate of exposure levels was made, are shown in **Table 4.23**. These studies are described further in the following text.

Table 4.23 Epidemiological studies on workers exposed to toluene, in which the exposure was predominantly to toluene

Reference	Groups studied	Toluene exposure	Toluene-related effects
Iregren (1982)	34 toluene-exposed rotogravure printers, 34 solvent mixture-exposed subjects, 34 non-exposed controls	150 ppm, reduced to 50 ppm, for an average of 16.3 years. Higher concentrations occurred occasionally.	Increased simple reaction time
Cherry et al. (1984)	59 toluene exposed workers, 59 non-exposed workers	100-500 ppm for an average of 9.4 years	No effect
Juntunen et al. (1985)	43 toluene-exposed rotogravure printers, 31 occasionally solvent-exposed controls	117 ppm for appr. 26 years, estimated mean level of exposure during the last year: 78 ppm	No effect
Larsen and Leira (1988)	22 toluene-exposed rotogravure printers, 19 unexposed controls	50-80 ppm, concentrations exceeding 1,000 ppm 5 years previously. No. of years of exposure > 12.	Higher frequency of slight or moderate organic brain syndrome
Lee et al. (1988)	193 toluene-exposed female workers, 65 non-exposed workers	1->150 ppm	Increase in prevalence of subjective symptoms
Ørbæk and Nise (1989)	30 toluene-exposed rotogravure printers, 72 unexposed controls	Mean exposure levels 43 and 157 mg/m^3 (12 and 42 ppm) for a median no. of exposure years of 29 (range 4-43).	Increase in prevalence of subjective symptoms. Impairment in spatial memory
Foo et al. (1990)	30 toluene-exposed workers, 30 low-level toluene exposed controls	88 ppm for an average of 5.7 years in exposed group 13 ppm for an average of 2.5 years in the control group	Impairment in manual dexterity, verbal memory and visual cognitive ability
Muttray et al. (1995)	59 rotogravure workers	Blood conc. of toluene ranging from <0.22 to 7.37 mg/l	No effect on colour vision in 5 tests
Vrca et al. (1995)	49 printing-press workers exposed to toluene, 59 non-exposed controls	40-60 ppm for an average of 21.4 years	Changes in visual-evoked potentials
Boey et al. (1997)	29 toluene-exposed workers, unexposed controls	90.9 ppm in exposed group, 12.2 ppm in control group. Mean blood toluene level 1.25 mg/l vs. 0.16 mg/l in controls	Impairment in psychological test
Freie Universität Berlin (1996)	1,324 toluene-exposed rotogravure workers, 154 paper industry workers	80 mg/m^3, mean blood toluene level 0.3 mg/l	Impairment in short-term memory

Thirty-four rotogravure printers with 3 to 32 years occupational exposure to toluene were tested in a psychological test battery (Iregren, 1982). The printers were not exposed 3½ days prior to the psychological examination. Measurements made between 1974 and 1979 showed that the mean toluene exposure had decreased from 562 mg/m^3 (150 ppm) to around 187 mg/m^3

(50 ppm) during the period. The printers showed a significantly increased simple reaction time compared with an equal-sized, age-matched, unexposed control group. Verbal comprehension, reasoning, perceptual speed, numerical ability, memory and manual dexterity were not affected. Because an exposure-free control group could not be obtained from the same workplace as the toluene-exposed workers, the investigators had to use workers from the control group of a previous investigation as referents.

Fifty-nine men who had been exposed to toluene (375 mg/m^3 to 1,875 mg/m^3 (100-500 ppm) for an average of 9.4 years) were matched to a similar number of unexposed workers from the same plant with regard to age, race and length of employment (Cherry et al., 1984). The subjects were examined in a test battery including clinical, neuropsychological or neurophysiological measures. Premorbid function was assessed by use of the British National adult reading test. Significantly reduced results were found in the toluene-exposed workers, indicating a lower educational level in spite of careful matching. Their performance was also worse for 12 of the 17 other variables, but only significantly worse for one variable (circle errors). After adjustment for educational level, no differences were found between the groups. It was possible to rematch 34 of the toluene-exposed subjects with controls which were comparable also with respect to the reading test. When these 34 pairs were analysed, the toluene-exposed subjects again performed less well for 12 of the 17 items, but only one of these results was significantly worse (mean reaction time).

Forty-three male rotogravure printers with long-term toluene exposure (mean 21.7 years) and 31 age- and sex-matched offset printers with occasional exposure to non-toluene solvents (mean 23 years) were examined for nervous systems effects (Juntunen et al., 1985; Antti-Poika et al., 1985; Hänninen et al., 1987). The time-weighted average toluene concentrations were calculated to have a mean of 117 ppm. The control group was exposed daily to ethyl acetate, isopropyl alcohol, and to aliphatic hydrocarbons in concentrations 1.1-5.2 times the Finnish hygienic standards in 5-10 minutes episodes for a total of 10 to 60 minutes daily. The mean total daily duration of exposure of the control subjects was 30 minutes. Clinical, neurophysiological, and neuroradiological examinations and assessment of autonomic functions did not reveal any statistically significant differences between the groups. Neuropsychological tests were done after a period of 2 to 3 days without exposure and included tests for verbal and visual cognition and memory, perceptual-motor speed, and psychomotor abilities. The rotogravure printers had significantly lower scores than the referents in the two visual intelligence tests, and were also significantly, but slightly inferior in visual memory and in eye-hand coordination. The toluene-exposed group and the control group was not matched with respect to drinking habits, since 18 of the rotogravure printers were heavy drinkers of alcohol compared with only one in the control group. As it is possible that alcohol could cause neuropsychological effects similar to those observed in the toluene-exposed workers, it is not possible to conclude that the effects were indeed caused by toluene. In addition, the study suffers from having a control group which was exposed to organic solvents on a daily basis, which may have diluted the group differences.

Nineteen toluene-exposed workers, and 19 unexposed workers, with more than 12 years of employment in two rotogravure plants were matched in pairs for age and employment status. In addition 3 exposed workers without a matching control person were examined (Larsen and Leira, 1988). At the time of the investigation toluene exposure levels were 50 to 80 ppm, measured as time-weighted averages for 8 hours. Earlier measurements five years before had shown concentrations exceeding 1,000 ppm. Low concentrations of other solvents were measured in the workroom air. The subjects were examined by means of a semi-structured psychiatric interview, with the objective of identifying cases suffering from organic brain syndrome. Special attention was paid to neurasthenic symptoms and symptoms of anxiety, depression, and somatization and psychopsychiatric reactions. The assessment was made from a global clinical evaluation and

clinical testing of the individual's cognitive capability. Immediately after each interview the subject was categorised as either suffering from mild chronic encephalopathy, organic affective syndrome, or no organic brain syndrome. The examining psychiatrist had no knowledge of the toluene exposure of the individual study subjects.

The distribution of cases of organic brain syndrome differed significantly between the exposed and unexposed groups (Chi^2 test). The distribution is shown in **Table 4.24**.

Table 4.24 Distribution of cases of organic brain syndrome among 22 toluene-exposed workers, and 19 unexposed workers from two rotogravure plants

	Toluene-exposed	Controls	Total
Mild chronic encephalopathy	6	2	8
Organic affective syndrome	7	1	8
No organic brain syndrome	9	16	25
Total	22	19	41

The distribution of cases of organic brain syndrome differed significantly between the exposed and unexposed groups. In 10 of the 19 pairs, the toluene-exposed subject had a higher organic brain syndrome score than his control counterpart. The reverse was true in two pairs, and the score was equal in seven pairs. The difference was significant ($p<0.01$, matched pairs signed ranks test).

The difference could not be explained by the presence of subjects with neurotic and/or psychopathological personality traits, since the frequency of organic brain syndrome was still significantly higher in the toluene-exposed group when such subjects were excluded from the analysis (5 persons in the exposed group and 4 persons in the control group).

This study gives evidence of a higher prevalence of organic brain syndrome in the exposed workers. Although a matching unexposed control group was used, and appropriate methods of evaluation of effects were employed, it is not possible to set a LOAEC because of the limited information on present and previous exposure.

The prevalence of subjective symptoms was surveyed in 193 toluene-exposed female shoemakers and 65 non-exposed control women (Lee et al., 1988). Based on individual measurements of toluene concentration in the breathing zone, the exposed subjects were divided into four subgroups exposed to either 1-50, 51-100, 101-150 or >150 ppm. Self-completion questionnaires with a total of 67 questions were used. Analyses of prevalences of symptoms revealed a dose-dependent increase for 43 symptoms, and among the acute symptoms, 10 out of 12 were significantly increased in the exposed group. The other 56 questions related to symptoms during the past six months and of these 32 were significantly increased in the exposed group. This study gives evidence of subjective symptoms experienced by toluene-exposed workers, but an independent assessment by an external observer is lacking.

Thirty rotogravure printers exposed to toluene for 4 - 43 years (median 29 years) were examined by means of interviews and psychometric testing (Ørbæk and Nise, 1989). A group of 72 healthy men with the same mean age and without previous exposure to solvents were used as controls. In the two printing shops where the rotogravure printers were employed, mean exposure levels of 43 mg/m^3 (11 ppm) (range 4-413 mg/m^3) and 157 mg/m^3 (42 ppm) (range 23-542 mg/m^3) of toluene, respectively, were recorded. During cleaning work peak exposure occurred (760 mg/m^3 or even higher). The exposure was measured during or one working week. During this week, five workers in each shift wore personal samplers which continuously drew air from the respiratory

zone. The air was collected in glass syringes which were changed at 30-minute intervals. It was estimated from previous hygienic measurements and other written reports that higher levels of toluene exposure had been recorded up till five years before testing. Testing was carried out on Monday mornings after approximately 66 hours without exposure. The subjects, who were aware of the reasons for the study, answered a self-administered questionnaire with 60 questions about general health, nervous system symptoms and life style. Most neurasthenic complaints, including fatigue, short-term memory problems, concentration difficulties and mood lability, were recorded significantly more frequently by the printers than by the reference group, as shown in **Table 4.25**. Electrophysiologic examination has been made on the printers with more than 20 years of exposure, and on the 50 controls, showing increased frequency of changes of several sensory nerve function measurements. This suggests, that the paresthesia reported might be real, and the authors concluded that not all the self-reported symptoms were due to bias but that some proportion reflected true problems among the printers.

Table 4.25 Percentage of workers among 30 printers and 72 referents with neurasthenic complaints, recorded by a self-administered questionnaire with 60 questions about general health, nervous system symptoms and life style

	Printers %	Referents %	p (Chi² test)
Fatigue	60	2	0.0000
Recent memory failure	60	10	0.0000
Concentration difficulty	40	6	0.0005
Mood lability	27	2	0.003
Depressive feelings	20	0	0.004
Irritability	37	4	0.0004
Headache	30	0	0.02
Dizziness	13	0	0.03
Sleep disturbances	33	6	0.004
Tremor	7	6	-
Paresthesia, numbness	53	6	0.0000
Chest oppression	23	4	0.02
Cardiac palpitations	17	4	0.13
Dyspepsia	33	26	0.7
Sexual problems	20	0	0.004
Alcohol intolerance	10	8	-

A physical and neurological examination was carried out, and blood samples were taken to control for confounding from other diseases. Similar results were found in the two groups, and no disorders were found which could influence the mental functions examined.

A test battery consisting of nine psychometric tests were used, including verbal tests, logical inductive tests, a spatial memory test, perceptual tests, and psychomotor tests. In most of the psychometric tests applied, the printers showed poorer performance than the referents.

Table 4.26 shows unadjusted mean scores in psychometric tests in groups of printers and referents with subgrouping according to alcohol consumption. In some tests a higher score is indicative of a better performance (synonyms, figure classification, block design, Benton correct,

paired associates, digit symbol, cylinder board), while in other tests it is indicative of a lower performance (Benton errors, dots total time, dots time fluctuation, dots total errors, reaction time).

Table 4.26 Unadjusted mean scores in psychometric tests in groups of 30 printers and 72 referents with subgrouping according to alcohol consumption

	Printers		Referents		Factor	
					Alcohol	Toluene
Alcohol consumption	<200g/w	>200 g/w	<200 g/w	>200 g/w	p value	p value
Age	49 years	51 years	48 years	38 years	0.19	0.23
Synonyms	18.5	20.2	22.1	24.7	0.38	0.002
Figure classification	18.2	15.9	20.0	19.8	0.15	0.11
Block design	22.9	16.8	25.8	25.5	0.03	0.06
Benton visual correct	6.4	5.4	7.3	7.2	0.042	0.009
Benton visual errors	5.4	6.8	4.1	3.8	0.12	0.03
Paired associates	20.1	18.0	20.2	23.3	0.9	0.8
Digit symbol	40.1	31.6	48.0	48.3	0.035	0.011
Dots total time	419	512	409	412	0.016	0.3
Dots time fluctuation	24	34	20.5	21.5	0.024	0.054
Dots total errors	15.6	16.6	15.0	9.5	0.7	0.6
Cylinder board	79	70	79	80	0.15	0.13
Reaction time sum 1-10 min	263	311	236	240	0.10	0.25

Following adjustment for age as well as performance in the synonyms test (presumed to be a measure of pre-exposure capability) no differences in the psychometric test results were found. However, the test of synonyms shows conflicting results, and it is possible that toluene exposure could also influence performance in this test, and it may therefore be incorrect to adjust for synonyms test performance. The authors concluded that exposure to toluene at levels below 157 mg/m^3 (42 ppm), which was the mean exposure level in the printing shop with the higher toluene level, following long-term exposure induced neurasthenic problems and might reduce psychometric test performance. This level of toluene had been estimated to be present for 5 years preceding the investigation.

Although a matching unexposed control group was used, present exposure levels were measured, and appropriate methods of evaluation of effects were employed, it is not possible to set a LOAEC because of the limited information on previous exposure.

Thirty female workers exposed to 88 ppm (330 mg/m^3) (range 49-130 ppm) toluene for an average of 5-7 years, and 30 control workers matched for sex, age, and ethnicity exposed to low levels of toluene (13 ppm (49 mg/m^3) for an average of 2.5 years were examined in neurobehavioural tests (Foo et al., 1990). Testing was done in the middle of the week before work. Blood toluene levels were 1.25±0.37 mg/l in the exposed group, and 0.16±0.06 mg/l in the control group. Toluene exposure was measured via personal samplers.

In six of eight neurobehavioural performance tests, the exposed group performed significantly worse than the control group (**Table 4.27**).

Table 4.27 Mean performance of 30 toluene-exposed workers and 30 control workers in neurobehavioural tests

	Exposed	Control	p value (T test)	p value (analysis of covariance)
Benton visual retention	5.4	7.1	0.003	0.01
Visual reproduction	5.8	8.3	0.0004	0.02
Trail making test part A	55.0	33.8	0.0008	0.003
Trail making test part B	157.0	104.0	0.009	0.007
Grooved peg board dominant hand	65.6	57.1	0.0002	0.002
Grooved peg board non-dominant hand	72.0	64.7	0.002	0.03
Digit span forward	5.8	6.8	0.02	0.005
Digit span backward	4.1	5.0	0.006	0.002
Digit span total	9.9	11.8	0.007	0.002
Digit symbol written	34.9	45.9	0.0008	0.002
Digit symbol oral	38.2	50.6	0.0004	0.0003
Finger tapping dominant hand	43.2	45.1	n.s.(p>0.05)	n.s.
Finger tapping non-dominant hand	40.1	42.0	n.s.	n.s.
Simple reaction time total	79.0	74.7	n.s.	n.s.
Simple reaction time error	2.2	1.4	n.s.	n.s.

The duration of exposure was not significantly related to the performance.

In conclusion, this study showed that manual dexterity, verbal memory, and visual cognitive ability of the workers were affected by their exposure to toluene ranging from 49 to 130 ppm (time-weighted average).

The effect of toluene on colour vision was examined in 59 rotogravure workers exposed to toluene (Muttray et al., 1995). Colour vision testing was performed on Monday before shift and on Friday after shift. The colour vision test battery included 5 different tests. The concentrations of toluene in blood ranged from <0.22 to 7.37 mg/l. No effect of toluene on colour vision could be observed even in a subgroup of heavily exposed workers.

An investigation of visual evoked potentials was carried out in two groups of subjects; 49 workers employed in a printing press where the only solvent used for the last 30 years was toluene. Toluene concentrations in the working environment were 40-60 ppm. The control group consisted of 59 workers from another factory not occupationally exposed to any known neurotoxic substances (average length of employment 20.6 years, range 4-32; SD 7.7). The average length of work service in the printing press was 21.4 years (range 4-30; SD 7.4). The level of exposure was assessed by determination of the concentration of toluene in peripheral blood, the concentration of hippuric acid and ortho-cresol in urine in subgroups of subjects chosen at random from both groups. N75, P100 and N145 waves of the pattern reversal visual evoked potentials were analysed. In the group of exposed subjects, significantly greater amplitudes were found in all waves, with significantly longer latency of the P100 wave. According to the author, this may indicate increased excitability of the visual pathways (Vrca et al., 1995).

The neuropsychological functioning of 29 workers occupationally exposed to low level of toluene for a mean of 4.9 years (mean blood toluene level 1.25 μg/ml, standard deviation

0.37 μg/ml) were assessed by a test battery based on the recommendation of US National Institute of Occupational Safety and Health (Boey et al., 1997). The exposed workers performed poorer than a control group (mean blood toluene level 0.16 μg/ml, SD 0.06 μg/ml) in short-term memory, sustained attention and concentration, visual scanning, perceptual-motor speed, and finger dexterity. The control group was matched for age and ethnicity, but there was a slight difference in the number of years of education (exposed group mean 6.0 years; control group mean 8.2 years).

In a recent study 1,324 workers from the German rotogravure industry, with a group of 154 workers from the paper industry as unexposed controls, were investigated in neuropsychological tests before and after a work shift (Freie Universität Berlin, 1996). The mean toluene level in air was 80 mg/m^3 , in the blood the mean level was 0.3 μg/ml, both measures with a large variation. Short-term memory was significantly impaired in the toluene-exposed workers. However, the authors expressed concern that the control group was not truly comparable to the exposed group, since the age distribution in the two groups was not identical.

Summary of nervous system effects in humans

Toluene abusers may develop serious neurological effects such as tremor, ataxia, and memory impairment. Atrophy of the cerebellum may occur.

Several effects of exposure to occupational levels of toluene have been identified in epidemiological studies.

Long-term exposure to volatile solvents may lead to organic brain syndrome (Arlien-Søborg, 1992). Two studies address this syndrome. The study by Larsen and Leira showed a higher frequency of organic brain syndrome in subjects exposed to toluene for more than 12 years (50-80 ppm, concentrations exceeding 1,000 ppm 5 years previously). In the study by Ørbæk and Nise, toluene-exposed workers complained substantially more of neurasthenic symptoms and scored lower in psychometric tests. Mean exposure levels at the time of the investigation were 11 and 42 ppm, while 5 years previously the exposure levels had exceeded 300 mg/m^3. Both of these studies show an increased prevalence of organic brain syndrome in exposed workers compared with the control group. In both studies the length of employment was high (Larsen and Leira >12 years, Ørbæk and Nise median 29 years), while only recent exposure data were well documented. Exposure during the years preceding the investigation was not well described. In order to determine LOAECs and NOAECs, it is necessary to have well-documented exposure information covering a considerable proportion of the entire period of employment of the study subjects. This is not the case for the two studies. Therefore, neither a LOAEC nor a NOAEC can be determined for organic brain syndrome.

The UK CA held a contrary view. In the study of Orbaek and Nise, it was only the prevalence of self-reported symptoms that was clearly different between the toluene-exposed and control groups; there was no clear evidence of a consistent, statistically significant difference between the two groups in neurobehavioural test performance, the only other type of examination made. The study of Larsen and Leira focused exclusively on the distribution of “organic brain syndrome”, as diagnosed by psychiatric interview, between a toluene-exposed and a control group. Cases of the syndrome were diagnosed in both groups, but more frequently in the in the toluene-exposed group. Both groups reportedly contained a significant proportion (approximately 20%) of members diagnosed as having “neurotic and/or psychopathological personality traits”. In the opinion of the UK CA, this is very weak evidence for the existence of a toluene-induced condition. It is the view of the UK CA that it has not been clearly demonstrated that occupational exposure to toluene produces chronic nervous system toxicity.

Other studies have investigated performance in neuropsychological tests. In the Foo et al. study 88 ppm (330 mg/m^3) was an average LOAEC (range 49-130 ppm) for impaired performance in neuropsychological tests. The study by Boey et al. also indicates toluene-related impairment in psychometric tests in subjects exposed to 90.9 ppm (341 mg/m^3). These symptoms are similar to those reported in the experimental chamber studies in Section 4.1.2.2.1 and occur at similar exposure levels. The exposure duration in the chamber studies was short-term, and the neuropsychological effects are believed to be acute effects. Therefore the results of the Boey et al. study and the Foo et al. study will not be used in the risk characterisation for repeated dose toxicity.

No evidence suggesting that occupational exposure to pure toluene can cause damage to the peripheral nervous system has been found.

Auditory system toxicity

Most investigations addressing auditory toxicity of solvents in humans relate to exposure to other solvents than toluene, to mixtures of toluene and other organic solvents, or to toluene and noise.

Szulck-Kuberska et al. (1976) demonstrated loss in auditory sensitivity among workers who were exposed to trichloroethylene (TCE). Further evidence of solvent-induced hearing loss among workers has been reported for carbon disulfide and noise (Morata, 1989), styrene (Muijser et al., 1988), and mixed solvent exposure (Jacobsen et al., 1993; Bergstrom and Nystrom, 1986).

However, three studies are of particular interest for the risk assessment of toluene. In support of the risk assessment these studies have been thoroughly discussed at an expert workshop on toluene and auditory toxicity held at the Danish EPA on January 27th 2000, where 4 of the responsible authors and other experts were present. A fourth study by Abbate et al. (1993) will be included because it concerns workers claimed to be exclusively exposed to toluene.

The hearing ability of groups of workers exposed to noise, to noise and toluene, to a mixture of solvents, and of an unexposed control group were examined by pure tone audiometry and immittance audiometry (Morata et al., 1993). The four groups were randomly selected and comparable with respect to age, previous exposure to noise and chemicals, medical history (diabetes, hypertension, ear infections, and use of ototoxic medication) and exposure due to a variety of life-style factors (hunting/shooting, motor sports, amplified music, power tools, and military service). An overview of exposure is given in **Table 4.28**.

Table 4.28 Exposure to solvents and noise Morata et al. (1993)

	Unexposed (N=50)	Noise exposed (N=50)	Noise plus toluene exposed (N=51)	Organic solvent Mixture exposed (N=39)
Place of employment	Printing plant			Paint manufacturer
Noise level dB(A)	<85	88-97	88-98	<85
Solvent concentration	-	-	Toluene: 75-600 ppm *	Toluene 10-70 ppm ** Xylene 12-40 ppm ** MEK 0-32 ppm ** MBK 0-20 ppm **
Average years of employment	13	11.6	8.1	5.6

* Range of TWA concentrations as measured in 1978 (july and september), 1979, 1980, 1990.
Measurements from 1978 (september), 1979, and 1980 were done by static sampling, while those from 1978 (July) and 1990 were obtained by personal sampling (Morata, 2000). In one section of the rotogravure printing division peak exposures were in July 1978 and in March 1980 observed to be above 1,000 ppm

** Range of TWA concentrations as measured in 1990
MEK: Methyl ethyl ketone , MBK: Methyl isobutyl ketone

High-frequency bilateral hearing loss was found in 8% of the unexposed, 26% of the noise-exposed, 53% of the noise and toluene-exposed, and 7% of the solvent-exposed workers, counting individuals with unilateral or conductive hearing loss as normal hearing individuals since these types of hearing loss were not considered to be occupational origin. If the individuals with conductive or unilateral hearing loss instead were disregarded the corresponding incidences of high-frequency bilateral hearing loss would be 10, 33, 59, and 20%, respectively.

The group exposed to noise plus toluene had significantly more workers with mild high frequency hearing loss (30-40 dB) than did all the other groups ($P<0.001$, one-way ANOVA). The acoustic reflex measurements showed that the reflex decay in the toluene plus noise group was significantly higher than in the other groups ($p<0.001$).

A multiple logistic regression for occupational hearing loss was carried out on the four groups. The variables considered for inclusion in the model were exposure group, length of employment, previous exposure to noise or chemicals, and exposure to non-occupational noise. Age was not included because it was highly correlated with the length of employment and further the study population was fairly young (median age 33 years). Exposure group and length of employment were the only variables that meet the significant level criterion for inclusion in the model. The analysis revealed that the relative risk was highest in the toluene plus noise group (10.9), followed by the solvent group (5.0), the noise group (4.1) and the control group (1.1).

Though the main constituent of the exposure in the mixed solvents group was toluene (**Table 4.28**), the risk of developing high frequency hearing loss cannot solely be attributed to toluene. However, comparing the noise only group to the noise plus toluene group provides valuable information. Since the workers of these two study groups had experienced similar noise levels (88-98 dB) the increased incidence ($P<0.001$, one-way ANOVA) of workers with mild high frequency hearing loss in the noise plus toluene group indicates that occupational exposure to toluene may increase the risk of developing occupational high-frequency hearing loss in noisy environments. The level of noise exposure was relatively high, however the average tenure of the noise plus toluene group (8.1 years) can be considered low compared to lifetime employment.

In this study, the time-weighted average toluene air concentrations for the noise plus toluene exposed workers was different at the 5 sampling times (1978-1990) and also varied between the

different sections of the division employing these particular workers. The average exposure levels measured in the time from 1978 to 1980 varied from 140 to 600 ppm whereas the sampling from 1990 when the study was performed varied from 75 to 365 ppm. The quality of these measurements varied since some measurements are obtained from static sampling while others were from personal sampling. Further it is possible that dermal exposure has contributed to the overall exposure.

These uncertainties regarding the actual toluene exposure makes this study inappropriate for setting a LOAEC/NOAEC.

In another study by Morata and co-workers, a group of 124 printing workers (all male and employed for a minimum of 1 year), all of whom were exposed to various levels of noise and a mixture of toluene, ethyl acetate, and ethanol underwent pure-tone audiometry and immittance audiometry testing after having been interviewed according to a comprehensive questionnaire (Morata et al., 1997).

A personal average exposure evaluation, based on air samples from the breathing zone of each subject, was conducted for all the subjects for toluene, ethanol, and ethyl acetate. The total toluene exposure was assessed by monitoring of hippuric acid in urine samples collected immediately after each workday. Ethanol levels ranged from 0.25 to 1,240 mg/m^3, ethyl acetate from 1.1 to 2,635 mg/m^3, and toluene from 0.14 to 919 mg/m^3. Noise levels, measured via personal noise dosimeters, were in the range of 71 to 93 dB(A).

Forty-nine percent of the workers had hearing loss. Numerous variables were analysed (stepwise logistic regression) for their contribution to the development of hearing loss. Only age and hippuric acid in urine were significantly associated with hearing loss. However, the air concentration of toluene was not found to be significantly associated with hearing loss.

The odds ratio estimates for hearing loss were 1.07 times greater for each increment of one year of age (95% CI: 1.03-1.11), and 1.76 times greater for each gram of hippuric acid per gram creatinine (95% CI: 1.00-2.98). No interactions were noted for the solvents, or between toluene and noise in causing hearing loss in this study.

The validity of urinary hippuric acid as a biological marker for toluene exposure is an issue which is being discussed.

Due to its high background levels in many countries (1 to 1.5 g), hippuric acid is no longer considered as a good biological marker for occupational exposure to toluene below 50 ppm, but is still recommended as an easy-to-analyze biological marker for exposure to toluene when background non-occupational levels of toluene are low (Chang et al., 1996). Literature indicates that hippuric acid can be associated with certain food consumption, often involving the use of preservatives, or certain berries. But in many countries, berries or food with these preservatives are not as available as they are in Europe or the US. That is the case for Brazil, where the study took place (Morata, 1999). In the Morata et al. (1997) study, low hippuric acid levels were observed for the majority of the individuals in the study group, who had no or little occupational exposure to toluene (52% with 0.5 g hippuric acid per g creatinine or less and 75% with 1 g hippuric acid per g creatinine or less). Therefore, urinary hippuric acid might be suitable as a biological marker for exposure to toluene in this particular study. Furthermore the lack of correlation between the concentration of toluene in air from the breathing zone and urinary hippuric acid concentration can possibly be explained by dermal uptake due to careless handling of toluene by the involved workers.

It was the opinion of the rapporteur that this study indicates that occupational exposure to toluene in the 0-245 ppm range might increase the probability of hearing loss. However, the design of this study makes it inappropriate for determining a LOAEC/NOAEC.

The hearing ability of a cohort of male workers from the German printing industry has been studied. In the study, which is still ongoing, repeated examinations of neurobehavioural functions, symptoms, functions of sense organs and health status are performed in the workers. In January 2000, the workers had been examined twice at the time points T1 and T2 approximately one year apart. At T1, 332 workers were examined, and at T2, 278 workers were examined. The workers will be examined a total of 4 times during the 5-year study period. The following text addresses the results of the first two investigations, of which the T1 results have been published in Demes et al. (1998), with supplementary information from Seeber (1999). The T2 results were presented to the rapporteur by the investigators at the Danish EPA toluene and auditory toxicity expert workshop in January 2000 on the understanding that the data were preliminary.

Recent and historical exposure has been assessed. Recent noise was measured by personal samplers, while recent toluene exposure was measured by repeated personal air sampling. The noise level was 82-83 dB(A) ±5-6 dB(A) for all workers. The number of workers who claimed to always use personal noise protection equipment increased over the years from 4% in 1975 to 25% in 1997.

Three historical time periods were defined: 1970-75; 1976-84; and 1985-95. Based on reports including personal air sampling and expert estimates, 4 job exposure categories were derived, where a toluene exposure estimate could be made for each of the three historical time periods. This was used for calculation of lifetime weighted average exposure (LWAE) for each worker as the sum of toluene exposure encountered at various jobs during a particular historical time period in that individual´s working life.

The workers were divided into groups according to the intensity of exposure (both with respect to recent exposure and to LWAE), “high”/”low”, and further according to the duration of exposure, “short”/“long”.

Intensity of exposure is seen in **Table 4.29**.

Table 4.29 Intensity of exposure in German printing industry worker study

	T1	T2
LWAE	46.5±17.9 ppm (high) 9.6±8.6 ppm (low)	44.6±16.9 ppm (high) 9.2±7.6 ppm (low)
Recent	25.8±22.4 ppm (high) 3.1±7.3 ppm (low)	24.7±17.6 ppm (high) 3.3±4.8 ppm (low)

The duration of exposure was 6±2 years in the “short” group, and 22±7 years in the “long” group.

The workers were examined by pure tone audiometry, which was performed after a period of at least three hours without exposure to occupational noise. Subjects had not worked for more than four hours on the day of testing. The hearing ability of the ear with better hearing ability was used for analysis, using correction for age according to ISO 1999 Annex A. Workers were excluded from analysis if they fulfilled one of the exclusion criteria: hearing impairment caused by other factors than toluene and noise determined by anamnesis, such as noise traumata, history

of severe or acute ear infections, history of surgery on middle or inner ear, otoscopically visible changes of the ear canal or the tympanic membrane, suspicion of conductive hearing loss or wax deposits, or one-sided hearing impairment. At T1, this left 231 (of 332), and at T2 188 (of 278) workers to be included in the statistical analysis.

At T1 the study cohort included 332 workers, while 278 remained at T2, a reduction of 54 subjects (16%). The reduction in the study cohort is approximately evenly distributed between the "low" and "high" groups and between the "long" and "short" groups.

The age-corrected audiometry data were analysed at T1 and T2 by analysis of variance and by logistic regressions for hearing loss.

At T1, the variance analysis did not show an effect of intensity of exposure (neither LWAE nor recent exposure). However, duration of work (6 versus 22 years) was significantly associated with an increased hearing threshold, described as a mild hearing loss at T1 (P=0.001). There was no interaction between duration and intensity.

At T2, the variance analysis did not show an effect of intensity of exposure (neither LWAE nor recent exposure). Nor was duration of work significantly associated with an increased hearing threshold. However, a statistically significant interaction of duration of work and intensity of exposure was found (P=0.037).

The outcome variable for the multiple logistic regression analyses was whether high-frequency hearing loss was present or not. "No hearing loss" included subjects with normal hearing as well as subjects with unilateral or conductive hearing loss. This analysis revealed a significant effect of age (OR=1.19) at T2.

The preliminary conclusion by the investigators is that no association between toluene exposure intensity and age-corrected auditory thresholds could be found, and that the interaction between duration and intensity of exposure needed further evaluation. Duration of work in a printing plant seems to be more important for a possible hearing deficit than the level of exposure, but needs to be further investigated.

The results of the Demes et al. (1998 and 2000) study indicate a relation between duration of toluene exposure and hearing loss, while no difference was found between the groups exposed to low-intensity versus high intensity toluene. The lack of a difference between low- and high intensity exposure could possibly be explained by the very small difference in toluene exposure levels, where low intensity refers to 9 ppm (LWAE) or 3 ppm (average recent exposure) while high intensity refers to 48 ppm (LWAE) or 24 ppm (average recent exposure). Since estimates of past exposure may include a considerable element of uncertainty it is questionable whether any difference in effect could be expected for such a small difference in exposure. Therefore, the lack of association between exposure level and hearing loss observed in this study does not contradict the findings of the two studies by Morata et al. since the exposure levels in the Morata studies were much higher than in the Demes study.

In the Demes study, duration of work (6 versus 22 years) was significantly associated with an increased hearing threshold, described as a mild hearing loss at T1. At T2 a statistically significant interaction of duration of work and intensity of exposure was found. It is not known how the duration of work could cause impaired hearing, or how duration of work and intensity of exposure could interact. Since the hearing ability data were corrected for age, this factor could not explain the association.

A possible explanation for the findings at T1 and T2 could be that toluene makes the ear more vulnerable to the harmful effect of noise on hearing. This would account for the interaction between duration of work and intensity of exposure found at T2.

From 300 rotogravure workers occupationally exposed to an average of 97 ppm toluene for 12-14 years, a subgroup of 40 was selected by means of various exclusion criteria, one of which was impaired auditory function (Abbate et al., 1993). A matching control group of 40 was selected in an identical manner from a group of unexposed subjects. Although the two groups were free of any clinical sign of neuropathy, brainstem response audiometry revealed alterations in the evoked potentials in an adaptation test in the toluene-exposed group. These alterations were interpreted as subclinical signs of auditory nervous system changes. This study is not readily useful in the risk assessment, since a selected subgroup without clinical symptoms was investigated. Further, there is no information about noise exposure.

Summary of specific organ toxicity in humans

Only studies describing effects in a particular organ system have been found. These studies indicate that toluene abuse may affect liver and kidney function. Also in occupational settings, toluene effects on liver and kidney function have been reported. Neuropsychological functions may be affected during and shortly after exposure to toluene. Long-term-exposure may be related to the development of organic brain syndrome.

The Morata et al. (1993) study indicates that occupational exposure to toluene may increase the risk of developing occupational high-frequency hearing loss in noisy environments. The Morata et al. (1997) study indicates that occupational exposure to toluene in the 0-245 ppm range might increase the probability of hearing loss. However, the studies are not appropriate for determining a LOAEC/NOAEC.

The preliminary conclusion of the ongoing Demes et al. study is that no association between toluene exposure intensity and age-corrected auditory thresholds could be found, and that the interaction between duration and intensity of exposure needed further evaluation. Duration of work in a printing plant seems to be more important for a possible hearing deficit than the level of exposure, but needs to be further investigated. The lack of association between exposure level and hearing loss observed in this study does not contradict the findings of the two studies by Morata et al. since the exposure levels in the Morata studies were much higher than in the Demes study.

4.1.2.6.3 Summary of repeated dose toxicity

The subchronic and chronic toxicity of toluene has been tested in a manner conforming to the data requirements of Annex VIIA of Directive 67/548/EEC.

Useful human and animal data are available. The toxicity of toluene after repeated doses has been investigated in a number of studies. There are no data for the dermal route, but in view of the lower absorption via this route compared with inhalation or oral exposure it is not felt that such a study is needed. Toluene toxicity via inhalation has been investigated in the rat (exposure duration of 2 years, 15 months, 26 weeks, 15 weeks, 90 days) and in the mouse (exposure duration of 2 years, 14 weeks). Two oral studies of 90-day duration have been conducted, one in rats, and one in mice. There are no indications for species differences based on the data available.

In the rat a NOAEL for general systemic toxicity of 625 mg/kg/day for repeated oral exposure was identified in a 90-day study. At higher levels (1,250 mg/kg and above) neurone necrosis and organ weight increases were found.

Also in the rat, a NOAEC for general systemic toxicity of 625 ppm (2,344 mg/m^3) for repeated exposure via inhalation was identified in a 15-week study. At higher exposure level (1,250 ppm (4,688 mg/m^3)) a 12-18% decrease in leukocyte count in females, and relative organ weight increases were found. In a two-year study a NOAEC of 300 ppm (1,125 mg/m^3) was found, this was the highest dose level. In another two-year study, the lowest dose tested, 600 ppm (2,250 mg/m^3) was a LOAEC for increased occurrence of nasal toxicity and forestomach ulcers in males.

The two-year inhalation NOAEC of 300 ppm (1,125 mg/m^3) will be taken forward to the risk characterisation.

Toluene has been shown to affect the central nervous system and the inner ear.

Long-term high-level exposure to toluene (abuse) has caused serious damage to the brain including severe neurological abnormalities and brain atrophy.

Exposure to lower toluene concentrations in occupational settings causes less obvious effects. An increased frequency of organic brain syndrome was found in subjects exposed to toluene concentrations of 50-80 ppm (190-300 mg/m^3) during the 5 years preceding the investigation, before that the concentration was higher than 1,000 ppm (3,800 mg/m^3). Exposed workers (100-200 ppm (380-760 mg/m^3) for >10 years) complained substantially more of neurasthenic symptoms and scored lower in psychometric tests. It is believed that long-term exposure (>10 years) is required before organic brain syndrome may develop (Arlien-Søborg, 1992). In order to determine LOAECs and NOAECs, it is necessary to have well-documented exposure information covering a considerable proportion of the entire period of employment of the study subjects. This is not the case for the two studies where evidence of toluene-related organic brain syndrome was found. In the Ørbæk and Nise study the median number of exposure years was 29. Mean exposure levels (TWA) were 43 and 157 mg/m^3 (measured with personal sampling during one week at the time of the investigation), and 5 years previously the exposure levels had exceeded 300 mg/m^3.

In the study by Larsen and Leira, measurements done at the time of investigation showed toluene exposures at 50 to 80 ppm (8-hour TWA). Measurements done by the trade union 5 years before had shown toluene concentrations in excess of 1,000 ppm. The study subjects were workers with a working history of >12 years at one of the rotogravure plants.

These exposure data are not sufficient for LOAEC or NOAEC determination for organic brain syndrome.

No evidence suggesting that occupational exposure to pure toluene can cause damage to the peripheral nervous system has been found, however, peripheral nerve function has not been examined in many studies.

In animals several effects on the central nervous system have been found. Neuronal cell necrosis in the dentate gyrus and Ammons horn of the hippocampus was seen in both male and female rats that received 1,250 or 2,500 mg/kg in a 90-day study. Also necrosis and/or mineralisation were present in the granular layer of the cerebellar cortex. A reduced number of neurones in the hippocampus and a reduced hippocampal weight in rats exposed to 1,500 ppm (5,700 mg/m^3) of toluene via inhalation for 6 months have been found. In very young rats exposed to toluene via

inhalation on postnatal day 1-28 reduced volume of certain hippocampal structures was found at 100 and 500 ppm (380 and 1,900 mg/m^3). At day 120, no differences were apparent in the volumes of the dentata components of control and experimental animals, indicating that the effects may be transient.

Changes in brain neurochemistry in rats have been described. Long-term exposure has been shown to cause effects on brain neurochemistry at 500 ppm (1,900 mg/m^3) still present six months after the last exposure indicating possibly irreversible changes. The effect of toluene on neurochemistry has not been investigated in a systematic fashion and the changes cannot readily be interpreted in functional terms. However, persistent changes in brain neurochemistry as found in the long-term study do indicate interference by toluene with central nervous system homeostasis and may be signs of adverse effects.

In relation to the evaluation and interpretation of data related to the occurrence of the organic brain syndrome (i.e. Ørbæk and Nise, 1989; Larsen and Leira, 1988 and Slomianka et al., 1990), the UK CA is of the opinion that there is not enough evidence to substantiate this effect.

The ototoxicity of toluene in the rat is well documented by behavioural, electrophysiological, and morphological techniques. Impaired hearing function in this species has been caused by exposure concentration levels of 1,000-1,400 ppm (3,800-5,320 mg/m^3) for 2-8 weeks. In one study, an exposure level of 700 ppm (2,660 mg/m^3) was determined as a no-effect concentration for auditory toxicity. Therefore a NOAEL of 700 ppm (2,660 mg/m^3 will be taken forward to the risk characterisation. However, the method used for the evaluation of the hearing function in the study by Pryor et al. (1984) is relatively insensitive. It is known that toluene-induced damage to the auditory system can be present without being detected by estimation of auditory sensitivity (Campo et al., 1997). Furthermore, transient auditory system impairment has been revealed at a much lower toluene concentration when using distortion product otoacoustic emission to evaluate auditory function (McWilliams, 2000). There are also strong indications from several studies of an interaction between toluene and noise with respect to effects on auditory functions in rats.

These considerations should be considered when evaluating the MOS.

Auditory toxicity has also been studied in humans. The Morata studies indicate that occupational exposure to toluene at high concentrations may increase the risk of developing mild high-frequency hearing loss, especially in noisy environments. However, the studies are not appropriate for determining a LOAEC/NOAEC.

The preliminary conclusion of the ongoing Demes et al. study investigating effects in relation to low exposure levels, is that no association between toluene exposure intensity and age-corrected auditory thresholds could be found, but that the observed interaction between duration and intensity of exposure needed further evaluation.

Toluene is classified with R48/20 (Danger of serious damage to health by prolonged exposure through inhalation), since several types of serious toxic effects after inhalation has been observed (discussed above). Toluene-induced chronic impairment of auditory function has been demonstrated in a number of animal studies. This has been substantiated by morphological evidence of cell loss in the rat cochlea. Existing data suggest that humans are sensitive to this effect at exposure levels which may be encountered in the working environment. Toluene causes irreversible changes, including neuron loss, in the central nervous system of animals. In humans severe central nervous system effects including brain atrophy have been found at very high exposure levels. Neuropsychological effects at working environment exposure levels have been demonstrated. The finding of nonmalignant tumours in mice is supportive for R48/20, and all

serious toxic effects of toluene were considered together when classification with R48/20 was agreed. For classification, see Section 1.

4.1.2.7 Mutagenicity

Toluene has been tested for mutagenicity and DNA damaging effects *in vitro* in a large number of experiments with bacteria and mammalian cells. Moreover, toluene has been tested for various genotoxic endpoints in several *in vivo* studies, and several investigations of genotoxic effects in humans being exposed to toluene in the occupational environment have been performed.

4.1.2.7.1 Bacterial mutagenicity

There are extensive data available on the lack of mutagenicity of toluene to the standard Salmonella typhimurium test strains (TA1535, TA1537, TA1538, TA98 and TA100) and other S. typhimurium test strains in the plate incorporation assay. Toluene has a boiling point of 110.6°C , and the standard plate assay is not considered to be able to accomodate volatile substances without modifications, for example, taping of the plates or use of a dessicator. In addition, toluene has, however, been found negative in a preincubation test with the standard Salmonella typhimurium test strains, which may be considered to be adequate for the test of compounds with boiling points from 107°C to 132°C (Hughes et al., 1987). For this reason, no further testing for bacterial mutagenicity appear to be required.

Table 4.30 Bacterial mutagenicity of toluene

Test organism	Protocol	Results	Reference
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Standard plate test, 0.87-4,350 μg per plate Suspension test, dose-range not specified	- (+)	Jagannath et al. (1978)
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Standard plate test, dose-range not specified	-	Nestmann et al. (1980)
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Standard plate test, 100-2,000 μg per plate	-	Bos et al. (1981)
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Standard plate test, 10-5,000 μg per plate	-	Spanggord et al. (1982)
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Preincubation test, 10-1,000 μg per plate	-	Haworth et al. (1983)
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100, UTH8413, UTH8414	Standard plate test, 50-2,000 μg per plate	-	Connor et al. (1985)

Jagannath et al. (1978) have performed an evaluation of the mutagenicity of toluene (purity not stated) in the S. typhimurium standard plate assay (dose range 0.001 to 5.0 μl per plate) and in suspension assays (dose-range not reported) for mutagenicity in the standard S. typhimurium test strains and for gene conversion in two Saccharomyces cerevisiae D4 test strains. A 50% reduction of the cell survival was obtained with 0.03% (v/v) toluene in the bacteria and with 1.1% (v/v) toluene in the yeast strains. The standard plate assays were negative. Fluctuating results were obtained in the suspension assay, especially with TA100 without activation, but the data obtained were reported to be within the normal variation experience. The quality of the study was relatively poor.

Nestmann et al. (1980) have found toluene from Aldrich (purity not stated) negative in the standard S. typhimurium test strains with and without rat liver S-9 mix. However, the dose range used was not described, and only data on mutagenic test substances were reported. More volatile compounds than toluene were tested in a dessicator.

Bos et al. (1981) have found toluene from Merck (purity not stated) negative in the standard S. typhimurium plate test without S-9-mix and with liver S-9 from untreated or Aroclor treated rats at 100, 200, 500, 1,000, and 2,000 μg per plate. No consistent depression of the colony counts at the top dose level was observed. The study appeared to be of a good quality.

Spanggord et al. (1982) have found toluene (purity and source not stated) negative in the standard S. typhimurium plate test with and without S-9 mix (source and induction not specified) at 10-5,000 μg per plate. The colony counts were not reported

Toluene (purified quality from Fischer) has been tested in the S. typhimurium standard test strains using a preincubation procedure (Haworth et al., 1983). During a 20-min preincubation period, the test bacteria and the test substance ± S-9 mix were incubated at 37^{o}C in a culture tube. This procedure mediates a closer contact between toluene and the test bacteria than the standard S. typhimurium plate assay. Toluene was negative without activation and with liver S-9 fractions from male Sprague Dawley rats or male Syrian hamsters pretreated with Aroclor 1254. Toluene was tested at dose-levels of 10, 33.3, 100, 333.3, and 1,000 μg per plate, and depressions of the colony counts were observed at the top dose used, indicating cytotoxicity. The assays were performed as a part of a study of 250 chemicals, and when no cytotoxicity was observed the top dose used was 10,000 μg per plate. The study was of a high quality, and performed as a part of the US National Toxicology Program (NTP).

Connor et al. (1985) have tested toluene (99% pure from MCB) in TA98 and TA100 and two repair-proficient S. typhimurium strains UTH8413 and UTH8414 ± Aroclor induced rat liver S-9 mix at 50, 100, 500, 1,000, and 2,000 μg per plate in the standard plate assay. The study appeared to be of a good quality, and it was reported to be negative. However, no data on the colony counts obtained were published.

4.1.2.7.2 DNA interactions in bacteria, fungi, and fruit flies

Toluene has not been found to induce DNA repair mediated toxicity to various bacteria, gene conversion in the yeast Saccharomyces cerevisiae or genotoxic effects in Drosophila melanogaster.

Winston and Matsuhita (1975) have found that 1% (v/v) toluene (purity not stated) induced a permanent loss of initiation of DNA replication in Bacillus subtilis, but the same dose was later found to be highly cytotoxic to bacteria (Jagannath et al., 1978).

McCarrol et al. (1981 a and b) did not find that toluene (purity not stated) produced differential killing of DNA repair proficient compared to DNA repair deficient strains of Bacillus subtilis rec$^{+/-}$ (133,333 to 200,000 μg per ml of medium) or Escherichia coli (400,000 to 600,000 μg per ml of medium). The testing was performed with and without Aroclor induced rat liver S-9 mix. The doses used appear, however, to be gigantic, and much less concentrations of toluene have been reported to be completely cytolethal in other bacterial studies. No details on the cytotoxicity of toluene were given in the paper.

Nakamura et al. (1987) have tested the SOS-inducing activity of toluene (pure from Wako) in S. typhimurium TA1535/pSK 1002 using the *umu* test procedure. 100 μg/ml of medium was reported to be the highest dose tested, and the study was reported to be negative.

Jagannath et al. (1978) have performed an evaluation of the ability of toluene (purity and dose levels used not stated) to induce gene conversions in two Saccharomyces cerevisiae D4 test strains in a suspension assay. The test was negative, but the quality of the study was relatively poor.

Rodrigue-Arnaiz and Villalobos-Pietrini (1985 a and b) have administrated toluene (purity not stated) in doses of 0.5-3.0% orally with the food to Drosophila melanogaster. Toluene was not observed to induce sex-linked recessive lethal mutations or heritable translocations. Doses of 1-1.5% did, however, induce aneuploidy (sex chromosome loss and nondisjunction).

4.1.2.7.3 Genotoxicity in mammalian cells

The genotoxicity of toluene *in vitro* has been evaluated in several types of mammalian cells, including cell lines with mouse lymphomas or Syrian hamster embryo cells, primary rat hepatocytes and human lymphocytes. At non-cytotoxic doses, toluene does not appear to induce biologically significant increases in forward mutations, sister chromatid exchanges, micronuclei or DNA damage *in vitro*. Significant levels of cytotoxicity have been reached in most studies, and no further testing for genotoxic effects in mammalian cells *in vitro* appear to be required.

Jagannath et al. (1978) have performed an evaluation of the mutagenicity of toluene (purity not stated) in the L5178Y TK+/- mouse lymphoma assay at doses of 0.05, 0.1, 0.15, 0.2 and 0.3 μl/ml of medium corresponding to 44 to 260 μg/ml of medium. A more than 90% reduction of the cell survival was obtained at the top dose level, and approximately 50% survival was observed at the two dose levels below. The study was negative, as all mutant frequencies were within the expected range of the spontaneous background.

McGregor et al. (1988) have also evaluated the mutagenicity of toluene (purity not stated) in the L5178Y TK+/- mouse lymphoma assay with and without Aroclor induced rat liver S-9 mix. Toluene appeared to be highly toxic to the cells, and total lethality was induced at doses of 275 to 500 μg/ml of medium. Significant, mutagenic responses were observed in all experiments. The relative total growth of the cells was, however, reduced by more than 70% at the high dose levels, and only weak increases (<1.5 times the background) in the colony counts were obtained at less toxic dose levels. Today, such small increases in mutant frequencies are regarded to be without biological significance, and the study is interpreted as negative.

Table 4.31 Genotoxicity of toluene in mammalian cells *in vitro*

Test organism	Protocol	Results	Reference
L5178Y TK+/- Mouse lymphomas	Forward mutation 44-260 μg/ml	-	Jagannath et al. (1978)
L5178Y TK+/- Mouse lymphomas	Forward mutation 6.25-250 μg/ml	-	McGregor et al. (1988)
Human lymphocytes	SCE 15.2-1,520 μg/ml	-	Gerner-Smidt and Friedrich (1978)
Syrian hamster embryo cells	Enhancement of virus mediated cell transformation 1,000 μg/ml	-	Casto (1981)
Rat hepatocytes	DNA single strand breaks 0.03–3.0 mM	-	Sina et al. (1983)
Human fibroblasts	Nick translation assay (DNA damage and repair) 3.0 mM	-	Snyder and Matheson (1985)
Human lymphocytes	SCE 50 μM - 1 mM	-	Richer et al. (1993)
Human lymphocytes	Micronuclei 0.1-2.0 mM	-	Zarani et al. (1999)

Gerner-Smidt and Friedrich (1978) have studied the potential of toluene (purity not specified) to induce sister chromatid exchange (SCE) in cultured human lymphocytes. Doses of 15.2, 152 and 1,520 μg toluene per ml of medium did not induce either chromosomal aberrations or SCE's.

Casto (1981) has reported that 1,000 μg toluene (purity not stated) per ml of medium did not enhance adenovirus transformation of Syrian hamster embryo cells. No details of the study were given in the article, and the effect does not appear to be specific for genotoxic substances.

Sina et al. (1983) have exposed isolated rat hepatocytes to toluene (purity not specified) for 3 hours at doses of 0.03, 0.3, and 3 mM, and analyzed the cells for DNA single strand breaks by alkaline elution. A low cellular viability of <15% was found at the two lowest doses, whereas the viability was reported to be 48% with 3 mM toluene. The induction of significant DNA damage was reported, but this appeared to be due to a very low control level, and the data obtained were all in the range of the controls in experiments with other substances. For this reason, the result is interpreted as negative

Snyder and Matheson (1985) have tested toluene (purity not specified, from Eastman Chemical Co.) for DNA damage and repair in human fibroblasts using the nick translation assay. A single dose of 3 mM was tested, and the study was reported to be negative.

Richer et al. (1993) have studied induction of sister chromatid exchange by low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes *in vitro* and *in vivo*. Toluene was 40% cytotoxic at 1mM and 100% cytotoxic at 2.5 mM *in vitro*. Exposure of lymphocytes to non-cytotoxic concentrations of toluene (50 μM-1 mM) *in vitro* did not significantly increase the levels of SCE's. In addition, no significant increases of the levels of SCE's were observed after in *vivo* exposure of five human volunteers (non-smokers) to 50 ppm toluene 7 hours/day over 3 consecutive days.

Zarani et al. (1999) have studied the potential of toluene (purity and source not specified) to induce micronuclei in isolated human lymphocytes. Doses of 0.1, 0.5, 1, 2 mM toluene failed to

induce micronuclei in binucleated lymphocytes from four donors after 48 hours of exposure. The experiments were performed with and without rat liver S-9 mix.

4.1.2.7.4 Genotoxicity *in vivo* in animal and human experiments

Toluene has been tested for clastogenicity and other types of DNA interactions in several *in vivo* experiments. Positive results have been obtained in three cytogenetic studies performed in the former USSR in the 1970's. In two of the studies rats were receiving up to 1,000 mg/kg bw of toluene by subcutaneous injections, and in one study rats were exposed to atmospheres containing 610 mg/m^3 of toluene (see IARC 1989, McGregor 1994). It has, however, been implied that these significant cytogenetic responses might be due to contamination with benzene. In more recent studies, toluene has not induced biological significant increases in micronuclei and chromosomal aberrations in the bone marrow of mice and rats or DNA damage in peripheral blood cells, bone marrow, and liver of mice. In a dominant lethal assay, toluene was not considered to be mutagenic to the sperm of mice in the doses tested, as it did not cause increases in pre- or post-implantation loss of embryos. In addition, a study with human volunteers has demonstrated that exposure to 50 ppm toluene for 7 hours in 3 consecutive days did not induce increased frequencies of sister chromatid exchange in peripheral blood lymphocytes. For this reason, toluene can be considered to be non-genotoxic *in vivo*, and no further testing for genotoxic effects of toluene *in vivo* appear to be required.

Jagannath et al. (1978) have performed an evaluation of the in *vivo* clastogenicity of toluene (purity not stated) in rat bone marrow. Toluene was administrated i.p. to the animals at 0.025 cc/kg, 0.082 cc/kg and 0.247 cc/kg corresponding to 22, 71, and 215 mg/kg bw. The study was negative, as all chromosomal aberrations observed were in the range of the spontaneous background. No depression of the mitotic index was observed at any of the dose levels tested.

Brusick and Mazursky (1981) have evaluated the potential of toluene to induce dominant lethal mutations in sperm cells of CD-1 male mice. Toluene (purity not specified) was administered at 100 ppm and 400 ppm via inhalation, 6 hours per day, 5 days per week for 8 weeks to 12 males per dose level. Following treatment, the animals were mated sequentially to two females per week for each of 2 weeks. The females were killed 14 days after the midweek of mating, and the uteri were examined for living and dead implantations. Toluene was not considered to be mutagenic to the sperm in the doses tested, as it did not cause increases in pre- or post-implantation loss of embryos.

Gad-El-Karim et al. (1984) have studied the clastogenic effect of toluene (purity 99%) in the bone marrow of male and female CD-1 mice. The animals were treated with toluene by oral gavage at two dose levels (860 or 1720 mg/kg bw) and sacrified 30 hours after exposure. Toluene did not induce micronuclei or chromosomal aberrations, and it reduced the clastogenic effects of benzene, when the two substances were given in combination.

Table 4.32 Genotoxicity of toluene *in vivo*

Test object	Protocol	Results	Reference
Rats, strain not specified	Bone marrow clastogenicity 22-215 mg/kg, i.p.	-	Jagannath et al. (1978)
CD1 mice	Dominant lethal assay 100 and 400 ppm, inhalation	-	Brusick and Mazursky (1981)
CD1 mice	Bone marrow clastogenicity 860 and 1720 mg/kg, oral gavage	-	Gad-El-Karim et al. (1984)
NMRI and B6C3F1 mice	Bone marrow micronucleus tests 104-435 mg/kg , i.p.	-	Mohtashamipur et al. (1985; 1987)
Sprague Dawley rats	Bone marrow micronucleus and clastogenicity test 108.75-440 mg/kg , i.p	-	Roh et al., (1987)
Human volunteers	SCE's in blood lymphocytes 50 ppm, 7h, 3 days	-	Richer et al. (1993)
BDF1 mice	Single cell gel assay (DNA damage) 500 ppm, inhalation	-	Plappert et al. (1994)

Mohtashamipur et al. (1985 and 1987) have studied the potential of toluene (purity 99% from EGA Chemie) to induce micronuclei in the bone marrow of male NMRI and B6C3F1 mice. The animals were treated with i.p. injections of two similar doses of the test compound 24 hours apart, and sacrified 30 hours after the first injection. Dose levels of 0.12, 0.25, 0.37, and 0.50 ml/kg bw were used corresponding to 104, 218, 322, and 435 mg/kg bw. Five and three animals per treatment group were used in the first and second study, respectively. Statistical significant, but very weak increases in micronuclei were observed. However, the number of micronuclei induced was in the range of historical controls, and the observations are not considered to be biologically significant.

Roh et al. (1987) have studied the potential of toluene (purity chromatographic grade) to induce micronuclei and chromosomal aberrations in the bone marrow of male Sprague Dawley rats. The animals were treated with i.p. injections at dose levels of 108.75, 220, and 440 mg/kg bw. Five animals per treatment group were used. A statistical significant, but very weak increase in micronuclei were observed at the middle concentration. This result is not interpreted as biological significant. The number of chromosomal breaks, gaps and translocations were not significantly increased in any of the treatment groups. The total number of abnormal cells was significantly increased at the top dose, but the wording abnormal cells were not defined in the report. In addition, the study on chromosomal aberrations was not reported with sufficient details to allow an evaluation of the biologically significance of the observations and it is not regarded as valid. Simultaneous exposure to toluene and benzene reduced the effects of both substances.

Plappert et al. (1994) did not detect significant DNA damage in peripheral blood cells, bone marrow, and liver of BDF1 mice exposed to 500 ppm toluene by inhalation. DNA damage was quantified by the single cell gel assay.

4.1.2.7.5 Occupational studies of genotoxic effects

Equivocal results have been obtained in a multitude of studies with biological monitoring of various genotoxic effects in peripheral blood lymphocytes from workers exposed to toluene in the occupational environment. In several studies, the participants have been exposed to a multitude of organic solvents. Most of the studies have, however, been performed with rotogravure printing plant workers predominantly exposed to toluene, but confounding due to coexposure to ink cannot be completely excluded in any of the cases. Smoking has been estimated to increase chromosomal aberrations by 10-20% and sister chromatid exchange by 5-8% (Nordic Study Group, 1990), and a clear synergistic effect between toluene exposure and smoking has been demonstrated in two studies (Bauchinger et al., 1982; Hammer et al., 1998). The possible confounding effects of benzene and smoking were, however, not considered in the first studies, performed in the 1970's, and the validity of the studies published by Forni et al. (1971) and Funes-Cravioto et al. (1977) has been questioned on this basis (McGregor, 1994). In addition, the results reported by Pelclová et al. (1990) and Nise et al. (1991) may be questioned due to inadequate matching for smoking habits. Occasional exposure to very high toluene concentrations may, however, be the basis of the positive findings in the cytogenetic studies published by Funes-Cravioto et al. (1977) and Pelclová et al. (1990). Exposure to restricted toluene concentrations (≤200 ppm) in the occupational environment has also appearently been causing small, but significant increases in chromosomal aberrations in a study where a large number cells were scored (Bauchinger et al., 1982), and in several studies using the more sensitive biomarker sister chromatid exchange (Popp et al., 1992; Hammer et al., 1998). In a recent study applying the Comet assay, which is a non-specific and even more sensitive biomarker for DNA damage, negative results were, however, obtained (Pitarque et al., 1999).

Forni et al. (1971) did not find significant increases in structural chromosomal aberrations in peripheral blood lymphocytes from 24 rotogravure plant workers, age 29-60 years, with an average occupational exposure to 200 ppm toluene for 3 to 15 years compared to a group of 24 controls matched for age and sex. Smoking habits were not taken into account.

Funes-Cravioto et al. (1977) reported significant increases in structural chromosomal aberrations in peripheral blood lymphocytes of 14 rotogravure plant workers, age 23-54 years, with occupational exposure to 100-200 ppm toluene, with occasional rises to 500-700 ppm, for 1.5 to 26 years compared to a group of 49 controls. Smoking habits were not considered.

Mäki-Paakanen et al. (1980) did not find significant increases in structural chromosomal aberrations or sister chromatid exchanges in peripheral blood lymphocytes from 32 rotogravure plant workers, age 21-50 years, with occupational exposure to 7-112 ppm toluene for 3 to 35 years compared to a group of 15 controls matched for age and sex. Benzene contamination of toluene was below 0.05%. However, significant increases in sister chromatid exchanges were observed in both toluene exposed and unexposed smokers compared to non-smokers.

Table 4.33 Occupational studies of genotoxic effects

Subjects	Method	Result	Reference
24 rotogravure workers	Clastogenicity, pbl ~ 200 ppm	-	Forni et al. (1971)
14 rotogravure workers	Clastogenicity, pbl ~ 100-200 ppm	+	Funes-Cravioto et al. (1977)
32 rotogravure workers	Clastogenicity and SCE, pbl 7-112 ppm	-	Mäki-Paakanen et al. (1980)
16 paint industry workers	SCE, pbl ~ 11 mg/m^3	-	Haglund et al. (1980)
20 rotogravure workers	Clastogenicity and SCE, pbl ~ 200-300 ppm	+	Bauchinger et al. (1982) Schmid et al. (1985)
42 rotogravure workers	Clastogenicity, pbl 104-1,170 ppm	+	Pelclová et al. (1990)
21 rotogravure workers	Clastogenicity, Micronuclei, pbl ~ 40-400 ppm	+/-	Nise et al. (1991)
20 shoe workers	SCE and DNA strand breaks, pbl ~ 70 mg/m^3	+/-	Popp et al. (1992)
65 filling station workers	Oxidative DNA damage, urinary 8-OHdG, ~ 0.16 mg/m^3	-	Lagorio et al. (1994)
38 and 45 shoe workers	Clastogenicity and SCE, pbl ~54.66 and 93.57 mg/m^3	(+/-)	Karacic et al. (1995)
49 shoe makers	Clastogenicity, pbl ~ 0.1 mg/l in blood	-	Bogadi-Sare et al. (1997)
42 rotogravure workers	SCE, pbl ~ 236 mg/m^3	+	Hammer et al. (1998)
34 shoe workers	Comet assay, pbl ~ 96-412 mg/m^3	-	Pitarque et al. (1999)

Pbl: peripheral blood lymphocytes
SCE: sister chromatid exchange

Haglund et al. (1980) did not find significant increases in sister chromatid exchanges in peripheral blood lymphocytes from 17 male paint industry workers exposed to a mixture of solvents, mainly xylene. However, 16 participants had an average occupational exposure to 11 mg/m^3 toluene (range 1-1,257 mg/m^3). The controls were matched for age, sex and smoking habits. No significant increases in structural chromosomal aberrations in peripheral blood lymphocytes from the 5 most exposed workers (>100 mg/m^3 toluene) were observed.

Bauchinger et al. (1982) reported significant increases in structural chromosomal aberrations and sister chromatid exchanges in peripheral blood lymphocytes from 20 male rotogravure plant workers, age 32-60 years, with an average occupational exposure to 200-300 ppm toluene for more than 16 years compared to a group of 24 controls matched for age, smoking habits and social environment. The chromosomal aberrations were predominantly of the chomatid type with increased yields of breaks and exchanges, and the yield of gaps was also significantly increased. Significant increases in sister chromatid exchanges were both observed in smokers compared to non-smokers, and in toluene exposed workers compared to controls matched for smoking habits. There appeared to be a relatively strong synergistic effect between toluene exposure and smoking. An enhanced incidence of chromatid type aberrations was observed up to 2 years after cessation of exposure to toluene (Schmid et al., 1985).

Pelclová et al. (1990) did find significant increases in structural chromosomal aberrations in peripheral blood lymphocytes from 42 rotogravure plant workers, mean age 39 years, with an average occupational exposure to 104-1,170 ppm toluene for 12 years. In addition, an increased percentage of aberrant cells and chromatid breaks was observed in 28 office and technical employees of the same plant, where more than half of the group worked 2 hours daily in the rotogravure workshop. The differences between the two groups working at the plant and 32 controls working in other factories were significant. Smoking was considered, but the groups

were not sufficiently matched concerning smoking habits. Moreover, the influence of ink mist on the genotoxic effects observed could not be excluded.

Nise et al. (1991) studied the induction of micronuclei and structural chromosomal aberrations in peripheral blood lymphocytes from 21 male rotogravure printers with an average occupational exposure to 150 mg/m^3 toluene and 21 unexposed controls. Significant increases of micronuclei in the lymphocytes from exposed workers were observed after growth stimulation of the cells with pokeweed mitogen, but not after treatment with phytohemagglutinin. No significant differences in structural chromosomal aberrations were observed. The controls did, however, not appear to be matched adequately for age and smoking habits.

Popp et al. (1992) did find small, but significant increases in sister chromatid exchange and DNA damage in peripheral blood lymphocytes from 20 female workers in a shoemaking plant workers, age 29-56 years, with an average occupational exposure to 70 mg/m^3 toluene for 18 years compared to a group of 20 controls matched for age, sex and smoking habits. There was, however, no correlation between the actual toluene and benzene uptake measured by personal air monitoring and the genotoxic effects. Four months after cessation of work, DNA strand breaks decreased significantly in lymphocytes from six reinvestigated workers.

Lagorio et al. (1994) studied 65 filling station attendants from Italy for personal exposure to benzene, toluene, and xylenes, and excretion of 8-OHdG. Information about age, length of employment, smoking habits, and diagnostic exposure to x rays was collected. A poor, but significant correlation was found between urinary 8-OHdG and exposure to benzene ($r = 0.34$). No significant correlations were found between urinary 8-OHdG and exposure to toluene or xylenes.

Karacic et al. (1995) studied structural chromosome aberrations and sister chromatid exchanges (SCEs) in peripheral blood from female workers employed in the shoe-making industry in two periods: 1987 (group I; N = 38) and 1992 (group II; N = 45). In 1992, benzene had been substituted with toluene to a large extend. Occupational exposure to benzene and toluene was confirmed through their determination in the working area, blood, and phenol in pre- and post-shift urine. The cytogenetic study showed a significant increase in dicentric chromosomes in exposed groups I and II when compared to the control group. Statistically significant higher SCE frequencies were found in group I compared to the control group and also compared to group II. Between exposed group II and the controls no statistically significant difference in SCEs was found. Comparing the same 11 workers present in both periods the results showed no difference in chromosome aberrations between the two periods of examination. SCE frequencies were significantly higher in 1987 when greater benzene absorption occurred, confirmed by biomarkers of benzene exposure. The results indicate that genotoxicity may occur in workers exposed to low levels of benzene in the shoe industry.

Bogadi-Sare et al. (1997) have studied the incidence of structural chromosome aberrations and sister chromatid exchanges in peripheral blood lymphocytes of 49 female shoe-makers, mean age 38 years, mean length of occupational exposure 17 years and in a group of 27 well-matched controls. Workers were exposed to concentrations of benzene up to 15 ppm and of toluene up to 50 ppm. The presence of benzene and toluene in the workers blood samples, and the presence of phenol in pre- and post-shift urine were considered proof of occupational exposure. Chromosomal aberration analysis revealed a significant increase in dicentric incidence in the exposed group compared to the controls ($p = 0.004$). However, significant correlation between cytogenetic test results and the exposure biomarkers was not established. On the contrary, correlation between the cytogenetic test results and data on confounding factors (e.g. age and alcohol consumption), was marked.

Hammer et al. (1998) did find marked, significant increases in sister chromatid exchange in peripheral blood lymphocytes at a high confidence level from 42 rotogravure printing plant workers, age 22-60 years, with an average occupational exposure to 141 to 328 mg/m^3 (median 236 mg/m$^{3)}$ toluene (purity 99.8%) for 18.9 years compared to a group of 45 controls matched for age and sex. Measurements of hippuric acid in urine samples were used as a biomarker of the toluene exposure. The influence of smoking and alcohol consumption on sister chromatid exchange as well as on hippuric acid levels could be clearly separated from those induced by toluene, and there was a marked synergistic effect between toluene exposure and smoking, and a very clear dose-response pattern could be established concerning the effects of different smoking habits and toluene exposure. However, the influence of ink mist on the genotoxic effects observed could not be excluded.

Pitarque et al. (1999) have evaluated DNA damage in peripheral blood leukocytes of 34 female shoe workers exposed to toluene and other organic solvents and 19 controls using the Comet assay. The mean age was 38 years and the mean length of occupational exposure 12 years. Workers were exposed to concentrations of toluene from 96 mg/m^3 to 412.3 mg/m^3. As a biomarker of exposure hippuric acid was determined in urine samples collected in the end of the working day. Multiple regression analysis revealed a positive correlation (r=0.70) between air toluene levels and urinary hippuric acid. No significant differences in Comet results between exposed and non-exposed individuals were found, and the cellular distribution of Comet values in the exposed subject was similar to the controls. In addition, neither smoking, age nor glutathione S-transferase M1 genotype significantly affected the outcome of the Comet assay.

4.1.2.7.6 Summary of genotoxic effects

Toluene has been tested for mutagenicity, clastogenicity and other types of DNA interactions in a multitude of *in vitro* and *in vivo* experiments. There are extensive data available on the lack of mutagenicity of toluene to the standard Salmonella typhimurium test strains in the plate incorporation assay, and toluene has also been found negative in a well-performed preincubation test, which is more adequate for the test of compounds with a volatility comparable to toluene. For this reason, no further testing for bacterial mutagenicity appears to be required. In addition, toluene has not been found to induce DNA repair mediated toxicity to various bacteria, gene conversion in Saccharomyces cerevisiae or genotoxic effects in Drosophila melanogaster. At non-cytotoxic doses, toluene has not induced biological significant increases in forward mutations, sister chromatid exhanges, micronuclei or DNA damage *in vitro.* Significant levels of cytotoxicity have been reached in most studies, indicating the contact between toluene and the biological test objects. In recent studies, where benzene contamination can be excluded, toluene has not induced biological significant cytogenetic changes in the bone marrow of rodents or DNA damage in peripheral blood cells, bone marrow, and liver of mice. Prolonged exposure to 50 ppm toluene has also not induced increased frequencies of sister chromatid exchange in peripheral blood lymphocytes of human volunteers. In addition, toluene was not considered to be mutagenic to the sperm of mice in a dominant lethal assay. Equivocal results have been obtained in a multitude of studies with biological monitoring of various genotoxic effects in peripheral blood lymphocytes from workers exposed to toluene in the occupational environment, but confounding due to coexposure to ink, other solvents and various genotoxic substances in the environment cannot be excluded, and a clear synergistic effect between toluene exposure and smoking has been demonstrated. On balance, toluene can be considered to be non-genotoxic, and no further testing for genotoxic effects appear to be required.

4.1.2.8 Carcinogenicity

Animal and human data have been found. IARC (1989; 1999) has evaluated toluene as not classifiable as to its carcinogenicity to humans (IARC Group 3). In Section 4.1.2.8.3 (Summary of carcinogenicity) a summary of the 1999 evaluation by IARC is given and compared to the evaluation in the present risk assessment.

4.1.2.8.1 Studies in animals

The carcinogenic potential of toluene via inhalation exposure has been evaluated in a rat study, and in rats and mice by the US National Toxicology program. The carcinogenic potential of toluene via oral exposure has been evaluated in rats in one study. The carcinogenic potential of toluene after dermal application has been examined in mice.

Inhalation

Groups of 120 male and 120 female Fisher F344 rats inhaled toluene 6.5 hours per day, 5 days/week for up to 24 months in concentrations of 0, 112, 375 or 1,125 mg/m^3 (0, 30, 100, 300 ppm) (Gibson and Hardisty, 1983). The clinical observations did not reveal any substance-related changes. The body weights of male rats in all toluene-exposed groups were greater than control males throughout the study. A similar effect was noted for the females but the effect disappeared during the final weeks of the study. No gross pathological or histopathological changes related to toluene exposure were seen, and no increase of tumour frequency in the male and female F344 rats was seen.

The exposure levels in this study are low compared with the concentrations used by other investigators of long-term toluene toxicity (e.g., 625 ppm for 15 weeks did not cause general toxicity in the study by Huff (1990)). In a carcinogenicity study, the highest dose level should elicit signs of minimal toxicity in order to ensure that the test animals have been adequately exposed. In the present study no sign of slight toxicity, such as weight loss, was found at the highest dose. As this could mean that the exposure concentrations may have been inadequate, this study is considered to be inconclusive with regard to toluene-induced carcinogenic effects.

Huff (1990) carried out two-year carcinogenicity studies in rats and mice using inhalation of up to 1,200 ppm toluene for 6.5 hours/day, 5 days/week without finding evidence of carcinogenicity. In the rat study, groups of 60 male and 60 female F344N rats were exposed by inhalation to 0, 600, or 1,200 ppm toluene 6.5 hours/day 5 days/week for two years in a GLP study. No significant differences in survival were observed between any groups of either sex. There were no substance-related increases in any tumour types.

In the mouse study, groups of 60 male and 60 female B6C3F1 mice were exposed by inhalation to 0, 120, 600, or 1,200 ppm toluene 6.5 hours/day 5 days/week for two years in a study of GLP quality. In female mice, body weights were slightly lower at 1,200 ppm compared with control. No significant differences in survival were observed between any groups of either sex. However, survival in all groups of male mice was low. This might be attributed to a high occurrence of non-neoplastic inflammatory lesions of the urinary and genital systems in all groups. The incidence of adenomas of the pars distalis in the pituitary gland in female mice at 600 ppm was significantly greater than in controls. However, due to a lack of supporting hyperplasia and dose response, the finding was not considered biologically meaningful by the author. Adenomas of the pars intermedia were seen in 0/49 control, and in 1 mouse of each toluene-exposed groups of

female mice. In male mice, a single pars intermedia adenoma was found at the highest exposure level. The data are presented in **Table 4.34**.

Table 4.34 Incidence of pituitary adenomas (histologically non-malignant tumours) in the NTP mouse carcinogenicity study

	Control		120 ppm		600 ppm		1,200 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female
pars intermedia	0/59	0/49	0/58	1/48	0/58	1/49	1/56	1/46
pars distalis	0/59	12/49	2/58	19/48	1/58	21/49	0/56	15/46

Note: Exposure to toluene via inhalation

The historical incidence of neoplasms of the pars intermedia was reported as 1/370 in chamber control female B6C3F1 female mice and 3/1,528 in untreated controls.

The occurrence of a single adenoma in each of the three exposed groups of females was not considered to be related to toluene exposure by the authors because the incidences did not increase with dose and because only one neoplasm was observed in males.

In the opinion of the rapporteur it cannot be ruled out that the occurrence of adenomas in the pars intermedia may be interpreted as treatment-related, although marginal. The frequency of this tumour type in historical controls was reported as being 1/370 (0.3%). The occurrence of 1 such tumour in each female dose group, and in the highest male dose group (2%) should not be dismissed. A dose-response relationship is not necessarily to be expected for a tumour of such low frequency of occurrence. Adenomas are benign tumours and are not known to have a tendency to become malignant. In conclusion, it cannot be excluded that toluene has a tumourigenic effect, and if so the effect is marginal.

Oral exposure

Significant increases of haemolymphoreticular neoplasias and malignant tumours were seen in a group of 80 Sprague-Dawley rats given 500 mg toluene per kg body weight by gavage once daily, 4-5 days/week for 104 weeks (two years) followed by observation until natural death (Maltoni et al., 1983 and 1985). The authors concluded that toluene administered orally caused an increase in the total number of malignant tumours.

This study is not considered relevant for the risk assessment, as the report of tumour incidence data does not fulfil guideline requirements.

Skin application

The carcinogenic potential of toluene has been evaluated by IARC. The evaluation report describes that toluene has been used as vehicle control in a number of studies in mice. Eight studies were mentioned, of which 5 were noted to either include a small number of animals, a short duration, or incomplete reporting of results. In one study a group size of 50 was used, the duration of the study was 73-120 weeks, but histology was not performed. In two studies a group size of 50 was used, mean survival was 83 weeks and 77 weeks, and histology was performed. No clear increase of skin tumours attributable to toluene was noted in the eight studies (IARC, 1989).

In a study not included in the IARC report, toluene was used as vehicle in a carcinogenicity study of twelve selected petroleum refinery streams (Primate Research Institute, 1988; published

as a journal article in Broddle et al., 1996). The study was performed according to GLP and to US EPA guidelines. A total of 18 groups were tested, since three test materials were tested in two concentrations. In the toluene-treated group, pure toluene was applied topically two times per week in a volume of 50 µl, covering at least 1 cm^2, to the shaved interscapular region of the back of 50 male mice for lifetime. There was no collective final sacrifice, therefore, all animals were necropsied at different times on study, when found dead or moribund. Survival at 18 months was 86% in controls and 76% in the toluene-exposed group, and at 24 months the figures were 62% survival for controls and 52% for toluene-exposed mice. A histopathological evaluation was made on untreated and test site skin including dermal and subcutaneous tumours, and on all suspected dermal and systemic neoplasms. The results are presented in **Table 4.35**.

Table 4.35 Skin tumour incidence in untreated controls and toluene-treated group in a skin-painting study (Primate Research Institute, 1988)

Group	Site	Benign tumours	Malignant tumours	Tumour type
No treatment	Test site	0	0	-
	Non-test site	0	0	-
Toluene	Test site	0	8%	1 fibrosarcoma (2%) 3 squamous cell carcinoma (6%)
	Non-test site	4%	0	2 fibroma (4%)

The difference in tumour incidence between the two groups was not significant (p=0.055; Fisher Exact test). However the occurrence of histologically highly malignant tumours in 4 toluene-treated mice, at the test site, versus no malignancies in the control group, is a strong indication that toluene was a causative factor in tumour development. The authors concluded that toluene was "borderline significant" and ranked toluene as a "weak dermal carcinogen" in the final draft report. The control group does not seem to exhibit an atypically low tumour incidence, since the occurrence of 0% tumours at the non-test site was also reported for 11 other test materials in the study. In the toluene-treated mice, all animals exhibited mild or moderate desquamation and an average of 10-20% showed mild irritation and scabbing, increasing up to 40% in older mice. It is known that a relation may exist between skin irritation and skin carcinomas. However, in the report other compounds, which produced similar degree of skin irritation, resulted in a lower tumour incidence than toluene. Therefore, the relationship between skin irritation and tumour development may not be straightforward.

4.1.2.8.2 Studies in humans

In the IARC evaluation of toluene (IARC, 1989), four case-control studies involving several anatomical sites of cancer are mentioned. The results could not be evaluated with regard to toluene itself, because the exposure was to mixtures of solvents and not to pure toluene.

A cohort of 1,020 rotogravure printers exposed to toluene and employed for a minimum period of three months in eight plants during 1925-85 was studied (Svensson et al., 1990). Based on the measurements in the 1940es and 1950es the maximum toluene concentration was about 450 ppm, but it was only about 30 ppm in the mid 1980es. Exposure to benzene had occurred up to the beginning of the 1960es. Compared with the regional rates, total mortality did not increase during the observation period 1952-86. There was no increase in mortality from non-malignant diseases of the lungs, nervous system, or gastrointestinal and urinary tracts. There was no overall

excess of tumours in the years 1958-85. Among the specific cancers only those of the respiratory tract were significantly increased. However, statistical significance was not attained, when only subjects with an exposure period of at least five years and a latency period of at least 10 years were considered.

The results from a historical cohort study of 6,830 male workers in the German rotogravure industry have recently been published (Wiebelt and Becker, 1999). The workers were exposed to toluene from 1960 to 1992 in three work areas (printing cylinder preparation, printing/proof printing, and finishing) with different exposure levels in 11 rotogravure plants. Since the benzene content of toluene in Germany has been restricted to a maximum of 0.3% since the beginning of the 1960s the exposure to toluene was considered pure. Individual measurements of toluene exposure were not performed. The concentration of toluene in printing/proof printing was in general lower than the exposure limit of 100 ppm (200 ppm before 1985), and in the other two areas lower than 30 ppm. It is not stated how or when these toluene concentrations were determined. No further information about exposure is given in the publication.

A mortality follow-up was performed for the period of 1960-1992. If a cohort member was found to be deceased, a copy of the death certificate was obtained. However, for deaths occurring before 1987, only a fraction of death certificates could be obtained. The true number of cause-specific deaths for the time before 1987 was estimated by a method based on information on available causes of death.

Of the 6,830 workers, 225 were lost to the follow-up (3%). The number of deaths was 466. Death certificates were available for 357 deaths (77%), and unavailable for 109 deaths (23%). All causes of death were coded according to ICD-9 (9^{th} revision of the International Classification of diseases).

The standardised mortality rate for overall mortality was 91.3 based on the 466 deaths. This was explained by the authors as being possibly due to "healthy worker effect" – the phenomenon that workers who experience adverse health reactions tend to leave the occupation, and the workers still at work are those who are resistant to the effects of occupational exposure.

A significantly decreased standardised mortality rate of 67 for total mortality was seen in one of the three work areas.

Total mortality from cancer (100 deaths, 122.7 if the estimated cancer deaths were included) did not differ substantially from the expected level.

Analysis of cause-specific cancer mortality showed increased standardised mortality rates for lung cancer, liver, gall bladder, bone and articular cartilage, connective tissue, brain and leukaemia on the basis of rather small numbers of cases. The increases were not statistically significant. The authors concluded that with respect to brain cancer and leukaemia (which, by comparison with benzene, would be expected target sites) the study was inconclusive, since the number of cancers was low, and a possible increased cancer mortality rate therefore difficult to detect.

Analysis of cause-specific cancer mortality by work area revealed that in one of the work areas, printing/proof printing (with high toluene exposure levels in the past), mortality from cancers of the bone and connective tissue was significantly elevated.

The standardised mortality rate for bone cancer was 813, and for connective tissue cancer 631.

In the entire cohort, mortality from lung cancer was increased by 35% above total mortality, and by 95% in the finishing work area with low toluene exposure (not statistically significant). The

lack of a relation to exposure level means that the data do not support an association between toluene exposure and lung cancer.

In this study, indices of an increased risk for death caused by certain types of cancers in workers exposed to toluene were found.

Exposure information was very limited and based on work area. It is not described how workers were assigned to work area if a job change occurred during the employment period.

It is questionable whether death certificates are an accurate source for information about cancer in the deceased. The information in the German cancer registry has been discussed by Wagner (1985). Death certificates are filled out by family practitioners and contain information about immediate cause of death and diseases contributing to death. Death certificates are filled out shortly after a person dies, and histological verification of tumour type at this time may not be available.

However, according to Wagner (1985), nearly all German cancer patients are examined by X-ray or biopsy before death, and for 70-80% of cancer patients histological findings are available from biopsy material. Several international surveys have shown around 80% "correct" death certificates in different countries. The likelihood that cancer will be put on the death certificate as the cause of death depends on the type of tumour. Some tumours are considered more malignant than others by the physician and are therefore more likely to be judged causative for the patient´s death.

In the light of the above-mentioned factors, the information derived from death certificates is likely to underestimate the true incidence of cancer in the examined population. Furthermore, some tumour types may be under-reported, because they are not considered to be the cause of death.

The authors of the present study do not comment upon the accuracy of the death certificates in regard to cancer diagnoses, except with respect to the lack of availablity of death certificates for 23% of the deaths. The investigators used an estimation method to make up for the missing certificates.

So, although this study provides indices of an increased risk for death caused by certain types of cancers in workers exposed to toluene, the uncertainties regarding exposure and cancer diagnoses means that this study will not be directly used in the risk assessment.

4.1.2.8.3 Summary of carcinogenicity

The carcinogenic potential of toluene has been tested in a manner conforming to the data requirements of Annex VIIA of Directive 67/548/EEC.

Two inhalation studies in animals, one in rats and one in mice, both by NTP (Huff, 1990), and one study in mice using skin application, are considered relevant for the risk assessment. The inhalation exposure route in these studies is relevant for humans. The results of the rat study are negative. In the mouse study, adenomas of the pars intermedia in the pituitary gland, a very rare tumour type, were found in all toluene-exposed groups of females, and in the highest dose group of males. A single adenoma was found in each of these groups. The skin-painting study (Primate Research Institute, 1988) showed skin irritation and tumour development, the difference in tumour incidence was just below statistical significance (p=0.055). The only useful

epidemiological cancer study which has been found does not show an excess of tumours in toluene-exposed workers.

Based upon the available data it cannot be concluded that toluene is carcinogenic. It has been shown that toluene induces non-malignant tumours in the pituitary gland of mice, and skin irritation and malignant tumours in mice. However, the evidence is not strong enough to fulfil the EU criteria for classification for carcinogenicity.

Toluene has been evaluated by IARC in 1989 and 1999. Although some differences in the interpretation of animal tumour data by IARC and the present risk assessment are apparent, the overall conclusion in the risk assessment report of no classification for carcinogenicity is in accordance with the evaluation by IARC (not classifiable as to carcinogenicity to humans).

A summary of the IARC (1999) evaluation is given below:

With respect to human carcinogenicity data, eight studies were found in which toluene was mentioned as an exposure. Two were community-based case-control studies, one of which involved brain cancer and one involved several types of cancer. Of the six industry-based studies, three were analysed as cohort studies and three were configured as nested case-control studies of one or a few types of cancer. In two of the studies, that of shoe-manufacturing workers in the United States and particularly that of Swedish rotogravure printers, it was believed that toluene was the predominant exposure; in the other studies, there were probably concomitant exposures. Cancers of most sites were not significantly associated with toluene exposure in any study. Stomach cancer mortality was significantly elevated in the Swedish rotogravure printers study, it was slightly, though not significantly, elevated in two other studies, and it was not associated at all in a fourth. Rates of lung cancer were significantly elevated in the cohort of shoe manufacturers and in the Swedish cohort of rotogravure printers, but were not associated at all in two other studies. Colorectal cancer was significantly elevated in the Swedish rotogravure printers study and in the Canadian case-control study, and colon cancer was no significantly elevated in the shoe manufacturers cohort. While results on leukaemias and lymphomas generally showed no association, these were based on small numbers. Considering the multiple exposure circumstances in most studies and the weak consistency of findings, these results are not strong enough to conclude that there is an association.

With respect to animal carcinogenicity data, the two studies on inhalation exposure, one study in mice and one study in rats, showed no significant increase in the incidence of tumours. Repeated application of toluene to the skin of mice did not result in an increased incidence of skin tumours according to IARC.

Evaluation: There is inadequate evidence in humans for the carcinogenicity of toluene. There is evidence suggesting lack of carcinogenicity of toluene in experimental animals.

Overall evaluation: Toluene is not classified as a carcinogen to humans (Group 3).

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on hormones

The impact of toluene exposure on plasma concentrations of FSH, LH and testosterone was assessed in 262 male employees of two Danish photographic printing plants (Mørck et al., 1988). The exposure of each participant was quantitated using a scoring system. The average exposure

levels fell from 200 ppm to 100 ppm during the investigated exposure period. Many of the workers had regularly been exposed to peak concentrations ranging from 400 ppm to 2,600 ppm and lasting for 5-60 minutes. The potentially confounding factors: age, weight, height, alcohol consumption and tobacco smoke were included in the statistical analysis which showed that plasma FSH levels were positively correlated with the exposure score. No associations between toluene exposure and plasma levels of LH and testosterone were found. The value of this study is limited, because a control group was not used.

Twenty men from a rotogravure printing company with a mean duration of employment of 25 years (range 0.5-37) and a mean age of 48.2 years (range 30-63) were compared with 44 male industrial workers without exposure to organic solvents and a mean age of 39.0 years (range 23-63) for concentration of ten hormones in serum (Svensson et al., 1992a). With respect to the printers, the individual time weighted average toluene concentration in air was 36 ppm (range 8-111), toluene levels in the blood was 1.7 µmol/l (range 1.0-6.6) and in adipose tissue 5.7 mg/kg (range 2.5-21). There was a negative association between blood toluene and plasma levels of prolactin. The exposed group had significantly decreased concentrations of follicle stimulating hormone, luteinising hormone, and free testosterone; and an increase in the concentration of triiodothyronine compared with the control group. No correlation was found between cumulative exposure and plasma hormone concentrations. In eight printers, the levels of follicle stimulating hormone and luteinizing hormone increased during a 4-week vacation, indicating reversibility; while levels of thyroid stimulating hormone, free triiodothyronine, and free thyroxine decreased. The observed effects were rather small with most hormone levels being within the reference limits.

Forty seven men from two rotogravure-printing companies were studied for their hormone status (Svensson et al., 1992b). In company A, the 28 men had a mean duration of employment of 18.4 years (range 4-33 years). In company B the 19 men had a mean duration of employment of 14.5 years (range 3-39 years). Twenty three workers from a metal industry and 23 craftsmen from hospital workshops were used as referents. The mean age for the exposed group was 44.4 years (range 23-62 years), and for the referents it was 43.5 years (range 20-61 years). Occupational exposure to toluene was measured for each working shift over a week, and the workers were divided into exposure groups based on these data. In company A the following exposure groups were found: <5 ppm, 5-10 ppm, 10-15 ppm, and in company B the following: 20-25 ppm, 35-35 ppm, and >45 ppm. The referents had no exposure to toluene or other solvents. No statistically significant differences were found in any of the hormone concentrations between the total exposed and referent groups, however, younger members of the exposed group had significantly lower plasma LH, FSH, and testosterone levels. Increasing exposures to toluene (at the present exposure level) were significantly associated with decreasing plasma concentrations of LH and testosterone. No correlation was found between cumulative exposure and plasma hormone concentrations.

The authors of the two above-mentioned studies conclude that the results indicate that low-level toluene exposure (below the Swedish TLV; at the time of sampling 80 ppm) may affect the hypothalamus-pituitary axis. Possible explanations include a link to toluene-induced changes in neurotransmitter levels, or to dopamine-like activity of toluene or its metabolites.

In relation to the risk assessment, the rapporteur notes that the effects cannot be regarded as directly adverse, since the hormone levels were within reference limits, and the effects seemed to be reversible. The fact that the levels were within normal reference limits, however, does not imply that the effect on hormone levels is non-existing. The differences may seem small, but especially for hormones small changes may be of importance and it is considered as remarkable that two human studies show similar effects on hormone levels (i.e. lower FSH, LH and

testosterone). These findings may indicate a possible interference with endocrine mechanisms by toluene. However, limited data from an earlier Danish study investigating substantially higher toluene exposure levels do not show similar effects and, therefore clear conclusions regarding the effects of toluene on hormone levels cannot be drawn.

4.1.2.9.2 Effects on sperm morphology and oestrous cycle

In a 15-week inhalation study (Huff, 1990) sperm morphology and vaginal cytology was examined in rats exposed via inhalation to 100, 625, and 1,250 ppm toluene 6.5 hours/day, 5 days/week. No compound-related effects were found.

4.1.2.9.3 Effects on fertility

Studies in animals

A mouse dominant lethal assay has been performed (Brusick and Mazursky, 1981). The method conforms to that of EU guideline B.22 (Rodent dominant lethal test). Groups of 12 male CD-1 mice were exposed via inhalation to toluene concentrations of 0, 375 or 1,500 mg/m^3 (0, 100, or 400 ppm) 6 hours/day, 5 days/week for 8 weeks. A positive control group received a single dose of 0.3 mg/kg triethylenemelamine on day 40. Each male was mated to four unexposed virgin females. Females were killed 14 days after the midweek of mating. Toluene did not reduced fertility (or toxicity) in the highest dose group.

In a combined two-generation fertility and teratogenicity inhalation study groups of at least 10 male and 20 female Charles River CD rats were exposed to either 0, 375, 1,875, or 7,500 mg/m^3 (0, 100, 500, or 2,000 ppm) toluene 6 hours/day, 7 days/week during an 80-day pre-mating period and a 15-day mating period (API, 1985). Females were further exposed on days 1-20 of gestation and during day 5-21 of lactation.

In the P generation a slight inhibition of body weight gain was observed in males at 500 and 2,000 ppm, and minor reductions in maternal body weight were reported during gestation and lactation in the group of females exposed to 2,000 ppm.

Toluene did not affect fertility in this study.

Groups of 15 Sprague-Dawley rats were exposed to air, 600 or 2,000 ppm of toluene vapour, 6 hours/day (Ono et al., 1996). Male rats 7 weeks of age were exposed for 90 days, starting 60 days before mating. Female 10-week old rats were exposed from 14 days before mating until day 7 of gestation. The high toluene dose caused salivation and lacrimation in all females during daily exposure from the 20th day of exposure and onwards. There were no significant differences in body weight between the exposed and control females. Female rats were paired on a 1:1 basis with male rats of the same dose group. Except for one rat pair in the 600 ppm group, all pairs copulated. Only one female rat, in the 2,000 ppm group, did not become pregnant. Pregnant females were sacrificed on day 20 of gestation and the uterus was removed. No statistically significant differences were observed between exposed and unexposed dams with respect to number of corpora luteae, implantations, live fetuses, sex ratio, malformations (0 in all groups), fetal weight, or fetal deaths. In the 2,000 ppm group, foetal mortality was higher than in the control group and the number of dams with dead fetuses was increased.

Eight males from each group were sacrificed the day after the last exposure. Quantitative morphometry of the spermatogonic cycle stages was carried out. The remaining males were

sacrificed on the second day after the last exposure, and examined for spermatozoa and elemental analysis. In males exposed to 2,000 ppm kidney weight increase accompanied by basophilic changes and tubular necrosis, and thymus weight decrease indicated toxic effect of toluene. Relative and absolute epididymides weights were decreased at 2,000 ppm. No abnormalities of testes and epididymides were detected on histopathological examination. The number of spermatogenic cells counted at 3 stages was not affected by toluene exposure. The sperm count was significantly decreased (approximately 20-25%) at 2,000 ppm. Also, at 600 ppm, a decreased sperm count was found (approximately by 10%), this was not statistically significant. Sperm motility was not affected.

This study indicates that toluene causes a reduction in epididymal weight and sperm count in male rats at 2,000 ppm. That fertility was not affected is not surprising, as this parameter is relatively insensitive in the rat. In female rats exposed before mating and during the early stages of pregnancy, toluene was toxic to the embryo and foetus.

Groups of female Wistar rats (P generation) were exposed to 0 (n=38), 1,125, 2,250, 3,750, or 4,500 mg/m^3 (0, 300, 600, 1,000 or 1,200 ppm) (n=23 to 29 in exposed groups) toluene 6 hours/day on day 9 to 21 of pregnancy (Thiel and Chahoud, 1997). The adult F_1-generation was mated and the fertility was determined. Mating and pregnancy indexes were unaffected. The fertility index of F_1 rats prenatally exposed to 600 ppm was significantly increased compared with the control group, but since no concentration relation was present it was concluded that the difference had occurred by chance.

Studies in humans

In a cross-sectional study, a sample of 150 male and 90 female printing industry workers in Germany were interviewed retrospectively on reproductive experiences (Plenge-Bönig and Karmaus, 1999). Exposure categories comprised job descriptions and information on exposure measurements obtained by industrial hygienists. The fecundability ratio was estimated on the basis of time to pregnancy or periods of unprotected intercourse not leading to pregnancy (256 periods for men and 174 for women). Confounders such as age, ethnicity, smoking, parity, pelvis inflammatory diseases, and frequency of sexual intercourse were controlled for in the analyses. There was no association between occupational exposure to toluene and subfecundity in men and their partners. The exposure of the men was classified as low (<10 ppm), medium (10-30 ppm) and high (<200 ppm before 1984, <100 ppm 1984-94, <50 ppm after 1994). In women who worked in exposed areas, a significant reduction of their fecundability of about 50% was found compared with periods working in other industries. The women worked exclusively in the stacking and bookbinding process, where the overall exposure to toluene was classified as low (<10 ppm). As toluene has been exclusively used in the German printing industry since 1960, exposure to other chemicals can be excluded. Confounders known to have an influence on time to pregnancy – such as smoking and age – were found to be more often associated with exposed periods, but controlling for them did not have an effect on the results.

The finding of the study indicates that an adverse of toluene on male fecundity is unlikely but cannot be completely excluded. For women, after considering possible biases, low daily exposure to toluene seems to be associated with reduced fecundity. Other forms of exposure such as noise and stress were not examined in the study and cannot therefore be excluded as having produced part of the findings or the overall result in the women. Also, there is a potential for recall bias in this study, e.g. persons with undesirable outcome may have recall of exposure that are different from those who do not experience the outcome. This applies for men as well as women and therefore it is considered as impossible to draw clear conclusions from this study.

Rates of menstrual disorders were studied in 231 female production workers exposed to toluene (mean 88, range 50-150 ppm) and compared with a control group of 58 production workers in other departments of the same factory where little or no exposure to toluene occurred (0-25 ppm) (Ng et al., 1992a). An external community control group of 187 working class women were also studied. There was no evidence that menstrual disorders were likely to result from exposure to toluene.

Summary of effects on fertility

Toluene has in two studies not shown adverse effects on fertility in rats, and the NOAECs are 2,000 ppm (7,500 mg/m^3). However, significantly decreased sperm count and reduced epididymal weight was found in the Ono et al. (1996) study at an exposure concentration of 2,000 ppm (7,500 mg/m^3) during 6 hours/day for 90 days. Although the effects occurred in the presence of other systemic effects (increased kidney and decreased thymus weight), no data support that the effects on sperm count and epididymal weight were secondary to these other effects. The NOAEC was 600 ppm (2,250 mg/m^3). The sperm count data actually point to a dose-response relation, i.e. slightly decreased at 600 ppm and significantly decreased at 2,000 ppm.

The lower sperm count etc. has not been shown to be functionally significant in rats, i.e. no effect on fertility has been seen. It is, however, well known that the rat has a large reserve capacity concerning the number of sperm, e.g. studies have shown that sperm count can be reduced to 30% before effects are seen on fertility (Chahoud, personal communication). Men most probably do not have a similar sperm reserve capacity as rats and effects on this parameter can therefore be potentially serious for humans (i.e. be a functionally significant effect). In recognition of the limited sensitivity of the present OECD test guideline, the OECD TG for two-generation study is at present being updated to include assessment of testicular function.

In humans, no studies of effects of toluene on sperm count were found. Limited data in humans have not shown indication of effects on fertility in men or menstrual function in women. Low daily exposure to toluene seems to be associated with reduced fertility in women; however, other forms of exposure such as noise and stress cannot be totally excluded as having produced part of the finding or the overall result. Also, the study of fertility in men and women has limited value due to the potential for recall bias and therefore it is considered as impossible to draw clear conclusions concerning fertility in humans.

4.1.2.9.4 Developmental toxicity

Studies in animals

Prenatal inhalation studies in rats

Groups of 9 to 21 rats were exposed via inhalation to 6,000 mg/m^3 (1,600 ppm) toluene 24 hours per day on days 1-8, 7-14, 9-14, or 9-21 of gestation (Hudák et al., 1977; in Barlow and Sullivan, 1982). Maternal mortality was found in all groups with 33% as the highest value. Relative to a control group of 28 animals exposed to clean air, maternal weight gain was reduced in all toluene-exposed groups, however, the weight gain reduction was only statistically significant in the group exposed on days 7-14 of gestation. In the group exposed on days 7-14 of gestation a significant reduction in live foetuses per dam was observed, as 17% of the implants were dead or resorbed. Except for this, no clear effect on malformation rate, no. of implants, live foetuses,

dead or resorbed foetuses per dam was seen. Foetal weights were significantly reduced in the groups exposed on days 1-8, 7-14, or 9-21. Retarded ossification was observed in all toluene-exposed groups and skeletal anomalies were significantly increased in the groups exposed on days 7-14, and days 9-14.

The toluene concentration used in this study induced maternal mortality and consequently the study is not useful for the risk characterisation.

Groups of 27 pregnant rats were exposed via inhalation to 0, 375, or 1,500 mg/m^3 (0, 100, or 399 ppm) toluene 6 hours/day on day 6-15 of gestation (API, 1978). There was no evidence of maternal toxicity as seen from maternal body weights on days 0, 6, 15, and 20. At sacrifice a standard teratology examination was carried out with one third of the foetuses being studied for soft tissue changes, and the remaining foetuses being studied for skeletal abnormalities. There was no evidence of variation in foetal sex ratio, embryo toxicity, inhibition of foetal growth and development or teratogenic effect caused by toluene at 100 and 400 ppm.

The study does not fulfil guideline requirements as maternal toxicity was not seen at the high dose. However, the study is in other respects well performed and showed that effects did not occur at dose levels of 400 ppm or lower. Thus from this study a NOAEC of 400 ppm (1,500 mg/m^3) can be set.

Groups of pregnant rats were exposed to toluene via inhalation in concentrations of 1,500 mg/m^3 (400 ppm) 24 hours/day on days 1-8 or 9-14 of gestation (Hudák and Ungváry, 1978), or to air on days 9-14 of gestation. Five out of 9 dams died during the day 1-8 exposure and 2 out of 19 dams died during the day 9-14 exposure. No deaths occurred in the control group. No effect on maternal weight gain of surviving toluene-exposed dams was seen. In the group exposed on days 1-8 a significant reduction in mean foetal weight was seen. 46% of the foetuses were classified as weight retarded and ossification of the foetuses was significantly retarded. In the group exposed on days 9-14 the foetuses showed a significant increase in fused sternebrae and extra ribs. In two other groups of 10 rats exposed to either air or 1,000 mg/m^3 (266 ppm) toluene 8 hours/day on days 1-21 of gestation, no signs of maternal toxicity were found. Weight retarded foetuses were significantly more common in the exposed group, and signs of skeletal retardation were also significantly more common in the exposed group. The litter was the statistical unit in all experiments.

In this study, the 399 ppm concentration caused maternal mortality and the results are therefore not useful for the risk assessment. At 266 ppm, maternal toxicity was absent, but foetal effects were reported. The study, however, has some limitations concerning experimental details and reporting and therefore, the apparent LOAEC at 266 ppm has limited use for the risk characterisation.

In a group of 20 pregnant rats exposed via inhalation to 1,000 mg/m^3 (266 ppm) toluene 24 hours/day on days 7-14 of gestation no signs of maternal toxicity were seen (Tátrai et al., 1980). This group showed, relative to a reference group of 22 rats exposed to clean air, a significantly higher percentage of foetuses with skeletal retardation. The number of foetuses with extra ribs was increased but not significantly.

This study has important limitations concerning experimental details and reporting, especially concerning the procedures for the 24 hours/day exposure periods. Therefore, the apparent LOAEC at 266 ppm is not useful for the risk characterisation.

In a combined two-generation fertility and teratogenicity inhalation study groups of at least 10 male and 20 female Charles River CD rats were exposed to either 0, 375 mg/m^3,

1,875 mg/m^3, or 7,500 mg/m^3 (0, 100, 500, or 2,000 ppm) toluene 6 hours/day, 7 days/week during an 80-day pre-mating period and a 15-day mating period (API, 1985). Females were further exposed on days 1-20 of gestation and during day 5-21 of lactation.

In the P generation a slight inhibition of body weight gain was observed in males at 500 and 2,000 ppm, and minor reductions in maternal body weight were reported during gestation and lactation in the group of females exposed to 2,000 ppm.

The body weights of pups of both sexes from dams exposed to 2,000 ppm toluene were significantly lower than those of the controls throughout lactation. Decreased body weight was observed throughout the F_1-generation in males and females exposed to 2,000 ppm toluene, suggesting that the early growth inhibition may have long-term consequences. No significant differences in gestation length, mean number of stillborn pups, and pup survival through lactation were observed between the control group and the exposed groups. The teratogenicity part of the study showed reduced foetal body weight and delayed ossification in the 2,000 ppm group at Caesarean section. No dams exposed to 100 or 500 ppm toluene were subjected to Caesarean section.

This study shows developmental toxicity (reduced foetal and pup weight, and delayed ossification) at a toluene exposure level of 2,000 ppm. Only minor maternal toxicity was present at this exposure level. In this study, 500 ppm (1,875 mg/m^3) was a NOAEC for developmental toxicity.

Pregnant female High Avoidance (HA) Wistar rats (a rat strain selectively bred for a high rate of electric shock avoidance by lever pressing) and nonselect Wistar rats were exposed to 0 or 375 mg/m^3 (100 ppm) toluene 7 hours/day from day 13 to birth, and together with their offspring until weaning (Shigeta et al., 1986). Offspring was observed for the appearance of physical developmental landmarks. The weaned pups were exposed to the same concentration of toluene until 48 days of age. The day after the last exposure, the offspring were tested for 10 consecutive days in the Sidman avoidance test, a test of operant learning.

Toluene exposure was not related to adverse effects on foetal development. In the avoidance test the normal Wistar rats did not show any difference in avoidance rate. The HA Wistar toluene-exposed rats showed impaired learning seen as lower avoidance rates and high standard deviations of the mean compared with the HA control group. This was highly significant ($p<0.01$) from session 4 through to 10.

The number of dams and litters, and the selection of pups for the various examinations are not described in the study. It appears that the individual, rather than the litter, has been used as the statistical unit. Therefore, the results cannot be used to evaluate the influence of toluene on a litter basis. Also, the relevance of the HA rat strain for the prediction of human response is not known. Consequently, this study will not be used in the risk characterisation.

Groups of pregnant Wistar rats were exposed via inhalation to 0 (11 rats) or 800 mg/m^3 (13 rats) (0 or 213 ppm) toluene for 6 hours/day from day 14 to 20 of gestation (da-Silva et al., 1990). Body weights and food consumption were assessed throughout the experiment. No overt maternal toxicity was observed.

After birth, growth, neuromotor development and performance of the offspring in behavioural tasks were assessed. Litters were used as the unit for statistical analysis. The number of live pups at birth was significantly decreased in the toluene-exposed group. The number of litters with low birth weight pups was significantly increased in the toluene-exposed group. Male toluene-exposed offspring displayed shorter latencies to choose one side of a T maze in a spontaneous alternation test. This test was suggested to provide a measure of emotionality by the authors.

This study shows an effect on litter size and birth weight, along with some effect on a behavioural test at 800 mg/m^3 (213 ppm). The study, however, has some limitations concerning experimental details and reporting and therefore, the LOAEC at 213 ppm has limited use for the risk characterisation.

Groups of 25 pregnant rats were exposed via inhalation to 0, 937, 2,815, 5,625, or 11,250 mg/m^3 (0, 250, 750, 1,500, or 3,000 ppm) toluene 6 hours/day on day 6 to day 15 of pregnancy. The rats were killed on day 20 of pregnancy. The study was carried out according to EPA guideline 40 CFR 798.4350 and was of GLP quality (Huntingdon Research Centre, 1992). During the exposure the following observations were done: at 750 ppm and above awareness of exposure and closed/half-closed eyelids. At 1,500 and 3,000 ppm, abnormal gait/ataxia and hyperresponsivity. At 3,000 ppm limb tremors/uncontrolled movements, lachrymation, increased respiration and salivation and nystagmus of the eyeball were noted on isolated occasions. One animal at 3,000 ppm was found dead after exposure on day 14. No obvious cause of death was established.

Water consumption at 3,000 ppm was significantly ($p<0.01$) increased from day 8 throughout the study. On the last day of exposure the water consumption was significantly ($p<0.05$) higher in the other three exposure groups. Food consumption was significantly ($p<0.01$) reduced in the 3,000 ppm group.

At 3,000 ppm body weight loss occurred during the first two days of exposure and the rate of weight gain remained lower than that of the controls through to day 14. At the end of the study body weight minus gravid uterine weight was significantly ($p<0.01$) less than that of controls.

At 1,500 ppm, body weight or body weight minus gravid uterine weight, did not differ from control. Body weight change during the first two days of exposure (day 6-8 of pregnancy), was lower in the 1,500 ppm group.

At the terminal autopsy of the dams no macroscopic change attributable to toluene was found. The liver weight to body weight minus gravid uterine weight was significantly ($p<0.05$ at 750 and 1,500 ppm, $p<0.01$ at 3,000 ppm) increased in the three highest doses. No histopathological data were provided. The actual mean increase in relative liver weight at the highest dose relative to control was 0.36, equalling a 7% increase. This is considered a physiological response to xenobiotic exposure by the rapporteur.

A total of 24, 22, 20, 19, and 22 females had live young at gestational day 20 in the groups ranging from 0 to 3,000 ppm. There were no dose-related changes in litter size, embryonic losses, or sex ratios. At 3,000 ppm litter and mean foetal weights were significantly ($p<0.05$ and $p<0.01$, respectively) reduced compared with controls. At 1,500 ppm mean foetal weight was still reduced significantly ($p<0.01$). The total number of malformed foetuses and litters was higher in the 250, 1,500, and 3,000 ppm groups (5, 6, and 5, respectively) but not in the 750 ppm group. There was no dose-relation as no increase in occurrence occurred, and as the 750 ppm group did not show malformations. Furthermore the incidence of malformations was within the historical background data. The incidence of foetuses showing visceral or skeletal anomalies was similar among groups, whereas the incidence of foetuses with reduced or unossified sternebrae was significantly increased ($p<0.05$) in the 1,500 and 3,000 ppm groups. The number of foetuses showing reduced sternebrae was also significantly ($p<0.05$) increased in the 250 ppm group.

At an exposure level of 3,000 ppm, maternal toxicity evidenced as reduced maternal body weight occurred. Although body weight change during the first two days of exposure (days 6-8 of pregnancy) was slightly lower in the 1,500 ppm group, this is not considered to be a sign of maternal toxicity by the rapporteur, since this group also exhibited an increased body weight

gain compared with control during pregnancy days 4-6. This shows that the groups were not identical with respect to rate of growth at the start of exposure; and the reduced weight gain after day 6 may be a natural slowing in growth following increased growth rate before this day. The rapporteur considers the total body weight and body weight minus gravid uterus as more reliable indicators of maternal health status than the small variations in growth rate before and a few days after the beginning of the exposure. Since these were similar to control values in the 1,500 ppm group, there is no evidence of effects on maternal weight at 1,500 ppm. The clinical observations made during exposure (abnormal gait and hyperresponsivity to "knock on the chamber door") are not considered evidence of marked maternal toxicity. Only a fraction of dams were observed, the observer was not blind with respect to exposure, and no statistics are presented. Consequently, the NOAEC for maternal toxicity is 1,500 ppm. At this level, foetal toxicity occurred, since foetal body weight was reduced and the incidence of foetuses with reduced or unossified sternebrae was significantly increased. The NOAEC for foetal toxicity was 750 ppm (2,815 mg/m^3).

Groups of 20 pregnant Sprague-Dawley rats were exposed to 0, 2,250, or 7,500 mg/m^3 (0, 600, or 2,000 ppm) toluene 6 hours/day on day 7 to 17 of pregnancy (Ono et al., 1995). Maternal toxicity in the form of significantly decreased body weight was evident from day 14 to 20 of pregnancy in the 2,000 ppm group. On day 20 of pregnancy, 13 rats from each group were killed and subjected to routine teratology examination. No significant effects of exposure were found on number of corpora luteae, implantations, fetal deaths, live foetuses, litter size or sex ratio. The number of dams with a high fetal death rate was slightly increased in the toluene-exposed groups compared with control (control 0/11; 600 ppm 5/11; 2,000 ppm 4/11), and the weight of their foetuses was also smaller. The remaining 7 rats of each group were allowed to litter. The offspring were studied with respect to behavioural (spontaneous activity, learning in Biel water maze, motor function on rotarod) and developmental parameters until postnatal week 7. At birth, the pup weight was significantly lower in both males and females of the 2,000 ppm group, and on day 21 after birth this decreased body weight was still significant for this group. No dose-related effects were observed on spontaneous activity. In female offspring, the elapsed time and the numbers of errors in trial were higher in the learning test in both toluene-exposed groups; this was not statistically significant.

The study is hampered by the small group size, especially for the postnatal study Section (11 dams for teratology, and 5-6 for behavioural testing). The significant observations of lower pup body weight until day 21 after birth after exposure to 2,000 ppm are considered relevant. Due to the limited number of animals included in the behavioral part of the study (N=5-6) as well as the slightly increased number of dams with a higher foetal death rate at both 600 ppm and 2,000 ppm, the study cannot be used to set a reliable developmental NOAEC at 600 ppm.

Groups of female Wistar rats (P generation) were exposed to 0 (n=38), 1,125, 2,250, 3,750, or 4,500 mg/m^3 (0, 300, 600, 1,000 or 1,200 ppm) (n=23 to 29 in exposed groups) toluene 6 hours/day on day 9 to 21 of pregnancy (Thiel and Chahoud, 1997). The pups (F_1) were examined for a number of developmental and behavioural end-points postnatally. The adult F_1-generation was mated and the fertility was determined. No data on the F_2 pups are given.

Decreased maternal body weight gain was reported at 1,000 and 1,200 ppm (P generation). The litter size at 1,200 ppm was smaller size, however, the difference was not statistically significant. Pup weight in the 1,000 and 1,200 ppm F_1 litters were lower than controls during the first seven days after birth. The weight difference lasted until day 21. The postnatal mortality prior to weaning was higher in the 1,200 ppm group. Physical development during the lactation period (pinna unfolding, incisor eruption and eye opening) and reflex ontogeny were similar in the groups, except for a slight delay in incisor eruption at 1,200 ppm. Vaginal opening was delayed

at least 5 days in both the 1,000 and 1,200 ppm groups. No significant effects on spontaneous 24-hour activity, or discrimination learning were found.

This study is well performed and conforms to present standards for developmental toxicity studies. In this study no gross abnormalities were found in the prenatally exposed offspring, but increased mortality, lower body weight and slightly retarded development was found in pups prenatally exposed to 1,200 ppm. At 1,000 ppm, pup weight was lower. At 1,000 and 1,200 ppm, maternal body weights were reported to be slightly reduced at the end of the exposure period, which was interpreted as toxicity signs by the authors. However, the study authors have informed the rapporteur that maternal body weight data were incorrectly presented in the published paper and have provided the correct data. These show that maternal body weights were different in the groups before exposure (**Table 4.36**) and therefore the body weights after exposure cannot be used to evaluate body weight effects in the dams. However, the difference in body weight from the day before exposure, i.e. pregnancy day 9, until postnatal day 1 can be used for the evaluation. As can be seen in **Table 4.36**, there seems to be tendency to slightly decreased body weight in the exposed groups, however, the differences are small and there is no clear dose-response relationship.

The rapporteur is therefore of the opinion that the study shows that toluene induces developmental toxicity in rats manifested as increased pup mortality and growth and developmental retardation at does levels causing no maternal toxicity. The developmental NOAEC is 600 ppm (2,250 mg/m^3), and the LOAEC is 1,000 ppm (3,750 mg/m^3).

Table 4.36 Maternal body weights, mean (sd)

	Day 9 of pregnancy	Postnatal day 1	Body weight change from pregnancy day 9 to postnatal day 1
Control	244 (17)	238 (18)	-5
300 ppm toluene	259* (17)	249* (16)	-10
600 ppm toluene	240 (12)	231 (17)	-9
1,000 ppm toluene	233* (15)	223* (16)	-10
1,200 ppm toluene	233* (13)	220* (12)	-13

Groups of pregnant Wistar rats (N = 13-14) were exposed via inhalation to 0 or 6,750 mg/m^3 (0 or 1,800 ppm) toluene six hours/day on days 7-20 of gestation (Hougaard et al., 1997a and b, Hougaard et al., 1999). The dams were allowed to litter. Developmental and neurobehavioural effects were studied using a battery of tests including assessment of postnatal growth, reflex ontogeny, neuromotor abilities (Rotarod), activity level (Open field), reactivity, habituation and prepulse-inhibition (Acoustic startle), sensory function (Auditory brainstem response) and learning and memory ability (Morris water maze). Since auditory dysfunction in dams might interfere with maternal-pup communication and cause alterations in pup behaviour, evaluation of the dam/offspring relationship and pup-retrieval test was included in the study.

Maternal body weight gain was slightly but non-significantly suppressed in exposed dams during the period of exposure. There were no significant effects on maternal care during the lactation period.

The body weights of exposed offspring were significantly lower until day 10 after parturition.

During the initial acquisition learning in the Morris water maze, the exposed female offspring seemed to use more time to locate the hidden platform in some of the trials, however, the latency was only significantly increased in 1 of the 20 trials. In retention test, the male offspring used a longer swim path to reach the platform, but with an increased swim speed. When the platform was moved to new positions in the pool (reversal and new learning), the exposed females used significantly more time to locate the platform. Swim lengths were similarly increased around 50%, while there were no significant differences in swim speed.

In this study developmental toxicity in the form of reduced body weight until day ten after birth was demonstrated in the absence of maternal toxicity. Furthermore, impairments of learning abilities, most marked in female offspring, were demonstrated at age 2-3 months. The study is well performed and reported, and the behavioural test battery complies with the recommendations in the proposed OECD Test Guideline 426 for Developmental Neurotoxicity Study. The LOAEC for long-lasting developmental neurotoxicity induced by prenatal exposure to toluene is 1800 ppm and a NOAEC cannot be set (see Appendix D, note 2).

Groups of pregnant Wistar rats were exposed via inhalation to 0 (n=7) or 4,500 mg toluene/m^3 (n=13) (0 or 1,200 ppm) six hours/day on days 7 of gestation to day 18 postnatally (Hass et al., 1999). The offspring stayed with their dams and were thus also exposed via inhalation postnatally. The exposure did not cause maternal toxicity or decreased viability of the offspring. In exposed offspring, lower body weight until postnatal day 10 as well as delayed ontogeny of some reflexes was registered. Behavioural testing after weaning was performed in 12-14 offspring of each sex per group. In order to avoid inflation of sample size by the use of more than one pup per litter the statistical analysis included a nested design. Motor activity was significantly increased with around 100% in both male and female offspring. Learning ability in spatial navigation was studied in a Morris water maze. At the age of 3 months, exposed female offspring used significantly more time to locate the hidden platform after the platform was moved to a new position in the pool and the swim length was similarly increased around 50%. The effect was not related to impaired swimming ability, because the swim speed was similar to control values. These Morris water maze data repeat the finding of impaired learning after platform relocation in female offspring exposed prenatally to 1,800 ppm toluene found in the study by Hougaard et al., 1997.

This study demonstrates that pre -and postnatal exposure to 1,200 ppm toluene caused lower offspring body weight and long-lasting developmental neurotoxicity. The study is well-performed and reported, and exposure period as well as the behavioural test battery complies with the recommendations in the proposed OECD Test Guideline 426 for Developmental Neurotoxicity Study. The LOAEC for long-lasting developmental neurotoxicity in the absence of maternal toxicity is 1,200 ppm and a NOAEC can not be set.

Effects of toluene on brain weights and synaptosomal functions were studies in weanling female rats (N = 9) exposed to toluene during brain development (Edelfors et al., 1999). The females were littermates to the offspring in the Hougaard et al. and the Hass et al. studies and were similarly exposed 6 hours per day to 1,800 ppm on days 7-20 of prenatal development or 1,200 ppm from days 7 of gestation to day 18 postnatally. Toluene exposed pups had lower brain weights, although only significantly so at 1800 ppm. The body weights of the pups were included in the analysis as a covariate. In vitro exposure of synaptosomes to toluene led to formation of more reactive oxygen metabolites and increased Ca^{2+}-leakage in synaptosomes from offspring prenatally exposed to 1,800 ppm. The relative protein content in the synaptosomes was not changed by prenatal exposure to 1,800 ppm. However, in synaptosomes from offspring exposed to 1,200 ppm both pre- and postnatally, the protein content was significantly higher compared to synaptosomes from the control offspring.

The results of this study indicate that toluene exposure during brain development can affect brain weights and functions in the nerve cells. As such, these findings support the evidence of developmental neurotoxicity registered in the behavioural studies.

Prenatal inhalation studies in mice

Pregnant mice were exposed via inhalation to 0, 500 mg/m^3, or 1,500 mg/m^3 (0, 133, or 399 ppm) toluene for 24 hours a day on days 6-13 of gestation (Hudák and Ungváry, 1978). All mice in the 1,500 mg/m^3 group died within the first 24 hours of exposure. In the 500 mg/m^3 group no maternal deaths occurred among the 11 mice. No information on maternal weight gain is provided. No effect of exposure on number of implants, live foetuses, dead and resorbed foetuses per dam was seen. Nor were malformation and anomaly rates affected. The 500 mg/m^3 group showed a significant reduction of approximately 10% in mean foetal weight compared with the control group and 276% of the foetuses were classified as weight retarded.

Since no information on maternal weight gain was given in this study, it is not possible to determine whether the effects at 500 mg/m^3 (133 ppm) are signs of true foetotoxicity or consequences of maternal toxicity. The study also has limitations concerning experimental details and reporting and the results are therefore not useful for the risk characterisation.

No embryotoxic or teratogenic effects of toluene were demonstrated by Shigeta et al. (1982). They used exposure for 6 hours/day on days 2-17 of gestation with 15 mice in the control group, 18 mice exposed to 375 mg/m^3 (100 ppm), and 14 mice exposed to 3,750 mg/m^3 (1,000 ppm) toluene (Shigeta et al., 1982). Data on maternal weight gain are not given. Two thirds of the pregnant mice were killed on day 18 of gestation, while the remaining mice were allowed to litter. The offspring was followed to assess postnatal effects of in utero toluene exposure. No such effects were demonstrated. Though not statistically significant the incidence of resorbed foetuses was increased in both toluene-exposed groups. A high incidence of an extra 14th rib in the group exposed to 1,000 ppm toluene was by the authors taken to suggest a possible teratogenicity of toluene.

Since no information on maternal toxicity was given in this study, it is not possible to determine whether the effects are signs of true foetotoxicity or are consequences of maternal toxicity.

Groups of 15-16 pregnant CD-1 mice were exposed via inhalation to 0, 750 mg/m^3 or 1,500 mg/m^3 (0, 200 or 400 ppm) toluene 7 hours/day on days 7-16 of gestation (Courtney et al., 1986). No effect on maternal weight gain was observed nor did concurrently exposed non-pregnant mice exhibit signs of toxicity. The mice were killed on the 17th day of gestation and the gravid uterus was removed and examined. The relative liver weight of the dams was reduced at both toluene concentrations. No differences were found in the number of implantations, live foetuses, fetal mortality, or fetal body weight. The litter was the statistical unit. The incidence of enlarged renal pelvis in foetuses exposed to 200 ppm toluene was significantly increased, this was not the case in the 400 ppm group. Therefore, this may be an incidental finding. A shift in rib profile was observed in the exposed groups at 400 ppm. The shift was statistically significant compared with control, and involved an increase in the number of foetuses with 13 ribs. In this study foetal toxicity (a change in rib profile) was found at 400 ppm in the absence of maternal toxicity.

Groups of 13 pregnant mice were exposed to air, 200, 400, or 2,000 ppm toluene for 60 minutes three times a day on gestational days 12-17 (Jones and Balster, 1997). No group differences were observed in maternal weight gain or food consumption. At birth, pups of the 2,000 ppm group

had lower body weight than controls, weight gain during postnatal days 1-20 was lower, and the development of reflexes was delayed.

This study is well performed and reported. The observed LOAEC is 2,000 ppm, where developmental toxicity was found in the absence of maternal toxicity. The daily exposure periods were however limited to 3 hours and consequently the observed NOAEC for developmental toxicity at 400 ppm therefore has limited use for the risk characterisation.

Prenatal inhalation studies in hamsters

Groups of hamsters were exposed via inhalation to 0 (n=5) or 800 mg/m^3 (n=6) (0 or 213 ppm) toluene/m^3 6 hours daily from gestational day 6 to 11. Growth, neuromotor development and performance of the offspring in behavioural tasks were assessed (Da-Silva et al., 1990).

Rotarod performance was significantly worse on day 25 (the last of three test days). Because no other effects were observed and because the number of litters used in this test was relatively small the authors concluded that this finding should be regarded with caution until additional data were available.

It is the opinion of the rapporteur that no conclusion can be drawn from this study because of the small size of the test groups and the limited exposure period.

Prenatal inhalation studies in rabbits

Exposure of eight pregnant rabbits to 1,000 mg/m^3 (266 ppm) toluene 24 hours/day on day 7 to 20 of gestation resulted in two litters being completely resorbed, four full abortions, and two dead does (Ungváry and Tatrai, 1985). Exposure of 10 pregnant rabbits to 500 mg/m^3 (133 ppm) for the same period did not result in maternal toxicity or foetotoxicity except for a slight, not statistically significant, increase in the percentage of foetuses with skeletal retardation compared to a control group of foetuses from 60 dams.

The doses used in this study were either too toxic (maternal mortality) or not toxic at all. Also, the study has important limitations concerning experimental details and reporting. Therefore, no conclusions regarding the possible foetotoxicity of toluene in rabbits can be drawn from this study.

Groups of 15 pregnant Chbb HM rabbits were exposed via inhalation to 0, 112, 375, or 1,125 mg/m^3 (0, 30, 100, or 300 ppm) toluene 6 hours/day from day 6 after insemination to day 18 (Klimisch et al., 1992). No maternal toxicity and no foeto- or embryotoxicity was observed in this study, except for delayed development of the skeleton in the 100 and 300 ppm groups, this was statistically significant only when the statistical unit was the foetus.

A second study was performed, in which a higher top dose was used, because of lack of toxicity in the first study. In the second study, groups of 20 pregnant Chbb HM rabbits were exposed to 0, 375, or 1,875 mg/m^3 (0, 100, or 500 ppm) toluene 6 hours/day via inhalation from day 6 pi to day 18 pi (BASF, 1989b). The study was carried out according to OECD guideline 414 and GLP. No maternal toxicity was observed in any of the dosed groups. In soft tissue studies of the foetuses separated origin of the carotids was observed in the 100 ppm ($p < 0.05$) and the 500 ppm ($p < 0.01$) groups. This effect, however, can be due to a low occurrence of the phenomenon in the control group. No differences in development of the skeleton were seen.

The study design in these two studies closely resembles that of OECD guideline 414 and the studies are well performed and described. The studies, however, do not fulfil guideline requirements as no maternal toxicity was observed for the high-dose animals. The authors

concluded that 500 ppm was a NOAEC. However, in the opinion of the rapporteur, the delays in skeletal development observed in the first study makes it difficult to establish a clear NOAEC.

Postnatal inhalation exposure in rats

Groups of 7 male rat pups were exposed to 0, 100, or 500 ppm toluene for 12 hours/day on postnatal days 1 through 28 (Slomianka et al., 1990). On postnatal day 28 the rats were sacrificed and their brains processed for histological and volumetric study of the hippocampus. The layers of Ammon's horn and the subiculum were not affected by 500 ppm toluene exposure. Within the area dentata, the volume of the granule layer was 6% smaller in animals exposed to 100 ppm toluene and 13% smaller in animals exposed to 500 ppm toluene. The volumes of the hilus and the commissural-associational zone of the dentate molecular layer were smaller (12% and 19%) in animals exposed to 500 ppm toluene compared to controls. Argyrophilic cells were found in the granule layer of all animals exposed to 500 ppm toluene, while the granule cell layer appeared qualitatively normal in animals exposed to 100 ppm toluene.

This study used two control groups, one for each of the exposed groups, and a significantly lower baseline was observed in the 100 ppm study. Therefore, the significant differences observed at 100 ppm are not considered useful. However, the magnitude of the toluene-induced reductions in volume in the hippocampal regions observed at 500 ppm exceeds the magnitude of the shift in baseline values in the two control groups and therefore this finding is considered relevant. Thus, the study indicates that inhalation of 500 ppm toluene for 28 days after birth causes volumetric changes in certain areas of the hippocampus. A NOAEC cannot be set based on this study.

In a follow-up study to the study described above, groups of 6 male rat pups were exposed to 0 or 500 ppm toluene 12 hours/day from postnatal day 1 to 28 and allowed an exposure-free period until sacrifice on postnatal day 120 (Slomianka et al., 1992). At day 120, no differences were apparent in the volumes of the dentata components in the hippocampus of control and experimental animals.

This finding indicate that the morphological effects identified in the Slomianka et al. study (1990) may be compensated for by for example the continuing growth of the dentata components in the hippocampus in rats.

Groups of 128 male Wistar rats inhaled 0 or 150,000 mg/m^3 (0 or 40,000 ppm) toluene for 15 minutes twice each day on postnatal day 2-32 (Lorenzana-Jimenez and Salas, 1983). Body weights were not affected by treatment. Development of eye and ear opening, and development of adult behaviour in a swimming paradigm was significantly delayed in the exposed rats. Also the exposed rats were impaired in an escape test. Locomotor activity of the exposed rats was significantly increased from day 21 to 35.

In this study, delays in behavioural and physical development were registered after exposure for very short time periods to extremely high concentrations of toluene. The results are not useful for the risk characterisation.

Groups of 64 male and female Wistar rats singly inhaled 0 or 150,000 mg/m^3 (0 or 40,000 ppm) toluene two times/day for 10 minutes from day 2 through day 32 of life. Electrophysiological recordings of sensorimotor primary and secondary responses and of visual primary and secondary responses were carried out repeatedly on six animals from each dose group up to postnatal day 150 (Lorenzana-Jimenez and Salas, 1985).

From 10 days onward, the mean peak latency of both sensorimotor and visual primary responses progressively declined until 18 days of age when the adult appearance was achieved. Toluene affected mean peak latency scores of sensorimotor responses, where the primary response was significantly delayed in the toluene group up to 18 days of age, and in the secondary response, which was significantly delayed in the toluene group up to end of the recordings at day 150 i.e. approximately 120 days after the last characterisation.

The effect seen in the secondary sensorimotor response up to 120 days after dosing indicates that exposure to an extremely high toluene concentration from day 2-32 after birth results in effects on the central nervous system which are not reversible after 120 days without exposure. These results are not useful for the risk assessment.

Postnatal inhalation studies in mice

In a postnatal study by Courtney et al. (1986), pregnant mice were exposed 6 hours/day on days 7-16 of gestation to 0 or 400 ppm toluene. The group size was 8-9. The mice were allowed to deliver. The mortality of the neonates on the day of birth was almost twice that seen in the control group, but was non-significant. Although the increased mortality might be biologically significant the findings are not sufficiently clear to be included in the risk assessment. Body weights of offspring on day 1 and 21 did not differ.

Effects of non-inhalation toluene exposure on development

Groups of 12 pregnant Nya: NYLAR mice received 0, 16, 80 or 400 ppm toluene in the drinking water (0, 2.4, 12, or 60 mg/kg body weight/day, rapporteur´s calculation) throughout pregnancy and lactation (Kostas and Hotchin, 1981). The offspring was maintained on the same solutions from weaning at 21 days of age until behavioural testing. No effects were seen on maternal fluid consumption, offspring body weight gain, mortality rate, development of eye or ear openings, or surface righting response. Open field activity habituation was decreased in the 400 ppm group at 35 days of age. At 45-55 days of age rotarod performance was impaired in all groups of toluene-exposed rats.

The effects observed in open field could be due to acute effects of toluene, and therefore 10 male and 10 female previously unexposed mice (35 days old) were given single doses of toluene by intraperitoneal injection 30 minutes before testing in the open field. The doses given corresponded to the amount taken up by the chronically dosed animals in the 80 and 400 ppm groups during week 5 of life. No effect on activity was found. Therefore, the effect on habituation in open field was most probably related to the exposure to toluene during pre- and postnatal development.

This study shows that perinatal dosing with toluene affects behavioural parameters in the absence of maternal or general toxicity. Due to the administration route (via drinking water), however, the dose levels have limited use for the risk characterisation.

Groups of 11 pregnant Sprague-Dawley rats received 0 or 520 mg toluene/kg in corn oil on day 6-19 of gestation. After sacrifice on day 19 two hours after dosing the foetuses were subjected to standard teratology procedures (Gospe et al., 1994). The maternal weight gain from day 6 to 19 was reduced by 24% ($p<0.002$) in the toluene dosed rats, and at sacrifice they had a blood toluene level of 7-61 µg/ml. The toluene exposure resulted in significant reductions in foetal and placental weights and in foetal liver and kidney weight. The foetal brain to foetal body weight ratio was significantly increased.

As the single dose level used in this study induced clear maternal toxicity, no conclusions regarding foetal toxicity can be drawn.

Animal studies in offspring exposed via mother's milk

A group of 10 lactating rats received 1.2 g toluene/kg in corn oil by subcutaneous injection from postnatal day 2 to 21, while a control group of 9 lactating rats received corn oil for the same period (Da-Silva et al., 1991). Litter size was adjusted to 7 pups (4 males and 3 females if possible) on the day of delivery. Body weight, physical development and reflex ontogeny of the pups were evaluated throughout the lactation period. On day 18 the pups were tested for spontaneous activity and after weaning on day 50 the pups were tested in an open field. Additionally, six toluene exposed litters and six control litters were dosed as above and tested in open field on day 35 and for a two-way shock-avoidance task on day 100. No effects of toluene from dosing via maternal milk on developmental and behavioural parameters were found in this study. A third group of rats (N = 4) was used for measurements of toluene in blood and milk. On the 10^{th} day of lactation, the rats received a single injection of 1.2 mg toluene/kg. The toluene concentrations in milk were 5 times higher that in blood and the blood levels were reported to correspond approximately to toluene levels in human volunteers exposed to 400 ppm toluene for 8 hours.

This study shows no effects of exposure to toluene via maternal milk, but some indication of accumulation of toluene in maternal milk. However, limitations in experimental details and reporting make it difficult to assess the results of the study. Also, the learning test was performed only once and therefore a learning curve was not provided and there was no measure of memory function. Consequently, the testing of learning does not fulfil the criteria recommended for selection of test for cognitive function in the proposed OECD TG 426 Developmental Neurotoxicity Study. Therefore, this study has limited value for the evaluation of developmental effects after toluene exposure via maternal milk.

Summary and discussion on developmental toxicity studies in animals

A great number of studies on developmental effects of toluene have been found. Due to limitations in experimental details and reporting several of the studies are evaluated as not useful for the risk characterisation and therefore the results of these studies are not considered in the following. The studies included in the risk assessment are presented in **Table 4.37** and **Table 4.38**.

Rats

In rats, toluene administered via inhalation does not seem to induce malformations, but has been shown to induce lower birth weight, delayed postnatal development and behavioural effects.

Lower foetal weight, lower birth weight and delayed postnatal development have been reported in a number of studies (Hudák and Ungváry, 1978; API, 1985; da-Silva et al., 1990; Huntingdon, 1992; Ono et al., 1995; Thiel and Chahoud, 1997; Hass et al., 1999; Hougaard et al., 1999). The LOAECs are in the range of 1,000-2,000 ppm (3,750-7,500 mg/m^3), except in two studies where the LOAECs are below 300 ppm (1,125 mg/m^3) (Hudák and Ungváry, 1978; da-Silva et al., 1990). These two studies, however, have limitations concerning experimental design and reporting and the results are not in agreement with the other well-reported and -performed studies. Therefore, these LOAECs are not used for the risk assessment.

The NOAECs are in the range of 400-750 ppm (1,500-2,812 mg/m^3). The NOAEC of 750 ppm in the Huntingdon (1992) study is from a teratology study and therefore the NOAEC covers only malformations and foetal effects observable the day before birth. However, toluene does not seem to induce malformation in rats, but toluene has induced lower birth weight and delayed postnatal development. These types of effects cannot be assessed in a teratology study and the LOAECs are 1,000-1,200 ppm (3,750-4,500 mg/m^3) (Thiel and Chahoud, 1997; Hass et al., 199). Also, the exposure period in a teratology study covers only the period of major organogenesis (i.e. days 6-15 in the rat). This is consistent with the OECD Test Guideline for the Teratology Study at the time when the study was performed, however, it must be considered that the exposure period in the OECD TG has recently been expanded to include also the last part of prenatal development (e.g. days 15-20). The reason for this revision of the guideline is that developmental effects can be induced during this period too. Based on these arguments, it is considered appropriate to use a NOAEC from a study where the relevant effects of toluene are assessed and the exposure period covers at least the prenatal period. Therefore, the NOAEC for effects on birth weight and postnatal development is 600 ppm (2,250 mg/m^3) (Thiel and Chahoud, 1997).

Behavioural effects after exposure to toluene during brain development have been found in two studies (Hougaard et al., 1999, Hass et al., 1999). The behavioural effects include increased spontaneous activity and impairments of cognitive functions.

Increased spontaneous locomotor activity has been found after pre- and postnatal toluene exposure to 1,200 ppm (4,500 mg/m^3) (Hass et al., 1999). Both the male and female offspring exhibited significantly increased short-term activity level in open field and the activity levels were increased around 100% in both sexes. Since only one dose level was used, a NOAEC cannot be determined. This effect was not present when the exposure period only included the prenatal period (Thiel and Chahoud, 1997; Ono et al., 1995, Hougaard et al., 1999). In the Thiel and Chahoud study, prenatal exposure to a similar concentration (i.e. 1,200 ppm (4,500 mg/m^3)) caused no significant effects on long-term locomotor activity (24 hours), although on the first day of testing some of the exposed animals showed a tendency to a higher activity. Investigations of short-term activity after prenatal exposure to 1,800 or 2,000 ppm (6,750 mg/m^3 or 7,500 mg/m^3) toluene have not shown significant effects on activity (Hougaard et al., 1999; Ono et al., 1995). The increased activity level observed in the Hass et al. (1999) study is, therefore, most probably due to the use of both pre- and postnatal toluene exposure. The fact that the effects of developmental exposure depend on the period of exposure has been shown repeatedly in many studies and is a well-known principle in developmental toxicology. The early postnatal period in rats is developmentally similar to the last trimester of human pregnancy and consequently the effects in rats after pre- and postnatal exposure to 1,200 ppm toluene (4,500 mg/m^3) are relevant for the evaluation of risk during human pregnancy. In addition, the result demonstrates the importance of exposure both during pregnancy and lactation as recommended in the recently proposed OECD TG 426 for Developmental Neurotoxicity Study.

Impairment of cognitive functions has been found in one study where rats prenatally exposed to 1,800 ppm toluene (6,750 mg/m^3) were examined as young adults (Hougaard et al., 1999). The most marked effects were observed in the female offspring after the platform was moved to new positions in the pool (reversal and new learning). The study by Hass et al. (1999) using pre- and postnatal exposure to 1,200 ppm of toluene (4,500 mg/m^3) revealed cognitive deficits in exposed females when the platform was relocated to a new position in the pool (new learning). Consequently, effects on cognitive function were consistently observed in the same sub-test across the two studies (new learning) and in the same sex.

Relocation of the platform in the Morris water maze compels the animals to learn new positions of the platform at a time when they have already developed a strategy to locate the platform in the old position. In the Hass study, the exposed females were not impaired when the platform was moved to the quadrant opposite the original position (reversal learning), but they were impaired when the platform was moved to the center of the pool (new learning). The reason may be that it was easier to generalise from the original position of the platform to the location in the opposite quadrant, because the distance from the rim of the pool is the same. The two studies show that the effects on cognitive function were more widespread after 1,800 ppm toluene (Hougaard et al., 1999) than after 1,200 ppm (Hass et al., 1999), i.e. there is a dose-response relation. The results also indicate that the effects of toluene on cognitive function are at least partially induced during prenatal development.

In general, the increased latencies in exposed females were not related to poorer swimming capabilities, because the swimming lengths were increased in proportion to the increased latencies and swim speeds were similar to control values. Also, no differences were observed in Rotarod, a test of neuromotor abilities. The biological significance of the cognitive effect cannot be considered as minimal, since the swimming lengths were increased around 50% in both studies (see Appendix D, note 3).

Effects on Morris water maze performance after relocation of the platform has also been demonstrated in female offspring after prenatal exposure to an organic solvent similar to toluene, i.e. xylene (Hass et al., 1993). Morris water maze has also been used to examine the effects of prenatal or early postnatal exposure to e.g. alcohol, glucocorticoids, and monosodium glutamate in rodents.

Two other studies have investigated cognitive function following prenatal exposure to toluene, but with no reports of exposure related changes (Ono et al., 1995; Thiel and Chahoud, 1997). In one study of effects in the water maze multiple T-maze test after prenatal exposure to 600 or 2,000 ppm (2,250 or 7,500 mg/m^3), the elapsed time and the number of errors in trial were higher in female offspring, but the differences were not statistically significant (Ono et al., 1995). This may, however, be due to the limited number of animals tested for cognitive function, i.e. 5-6 animals per group. In the other study using 22-24 animals per group, visual discrimination learning was tested after prenatal exposure to 300, 600, 1,000 or 1,200 ppm toluene (1,125, 2,250, 3,750, or 4,500 mg/m^3) and no concentration-dependent adverse effects were detected (Thiel and Chahoud, 1997). This result, however, does not contradict the consistent finding of cognitive impairment in the Morris water maze (Hougard et al., 1999, Hass et al., 1999), because the Morris water maze task compels the animals to use cognitive functions that may not be essential in a visual discrimination task, e.g. spatial mapping for orientation.

Impaired performance in Morris water maze has been linked to hippocampal dysfunction in adult rats. The task has been shown to be sensitive to a variety of experimental insults to the hippocampal formation or closely related structures. In a study using postnatal exposure inhalation of 500 ppm toluene (1,875 mg/m^3) for 28 days after birth volumetric changes in certain areas of the hippocampus was found at the age of 28 days (Slomianka et al., 1990). Although exposure was performed only postnatally, it still offers some indications as to which structures of the brain can be vulnerable to the effects of toluene during development. In a follow-up study, no differences were apparent in the volumes of the dentata components in the hippocampus of control and experimental animals at the age of 4 months (Slomianka et al., 1992). This finding indicate that the morphological effects may be compensated for by for example the continuing growth of the dentata components in the hippocampus in rats.

A study using female littermates to the offspring in the Hougaard et al. (1999) and the Hass et al. (1999) studies indicates that toluene exposure during brain development can cause decreased brain weights and affect functions in the nerve cells (Edelfors et al., 1999). As such, these findings support the evidence of developmental neurotoxicity registered in the behavioural studies.

The LOAEC for the behavioural effects is 1,200 ppm (4,500 mg/m^3) and a NOAEC cannot be established since lower exposure levels were not investigated.

Maternal toxicity has to be evaluated as a contributing factor in developmental toxicity studies. At 2,000 ppm (7,500 mg/m^3) developmental toxicity has been observed simultaneously with slight maternal toxicity, i.e. decreased body weight gain in the dams. At dose levels between 1,000-1800 ppm (3,750-6,750 mg/m^3), no clear indications of decreased body weight in dams have been registered. There can be concern for ototoxicity in adults at 1,800 ppm, i.e. the dose level associated with developmental neurotoxicity in Hougaard et al., 1999. However, the possibility that non-specific influences due to ototoxicity in the dams could influence the maternal behavior was investigated in this study. There were no significant differences between control and toluene dams concerning location relative to the nest, amount of contact with the litter, number of pups in the nest, or in the pup retrieval test.

Concerning potential ototoxicity in adults at 1,000-1,200 ppm, i.e. the dose level associated with decreased birth weight, delayed postnatal development and developmental neurotoxicity (Thiel and Chahoud, 1997; Hass et al., 1999), this has not been demonstrated.

In addition, the existence of other toxicological effects than developmental toxicity does not automatically exclude that toluene should be considered as a developmental toxicant, since the criteria for classification for developmental toxicity states:

- Category 2 “dose levels not associated with marked maternal toxicity”;
- Category 3 “the possibility that non-specific influences such as generalised toxicity cannot be excluded”.

Thus, concern for ototoxicity in dams has not been demonstrated at 1,000-1,200 ppm and at 1,800 ppm, it cannot be considered as ‘marked maternal toxicity’ in the sense that it causes ‘non-specific influences’ on the development.

Consequently, the conclusion is that toluene causes developmental toxicity in rats in the absence of maternal toxicity.

Only one study concerning effects via maternal milk has been found (Kostas and Hotchin, 1981). In rats, no effects of exposure to toluene via maternal milk, but some indication of accumulation of toluene in maternal milk was found. However, limitations in experimental details and reporting make it difficult to assess the results of the study. It is stated by the authors that ‘sex effects indicate that testing was sensitive enough to detect group differences’. The data given in the paper, however, do not support this conclusion. Also, the learning test was performed only once and therefore a learning curve was not provided and there was no measure of memory function. Consequently, the testing of learning does not fulfil the criteria recommended for selection of test for cognitive function in the proposed OECD TG 426 Developmental Neurotoxicity Study. Therefore, this study has limited value for the evaluation of developmental effects after toluene exposure via maternal milk.

Mice

There are only a few studies useful for risk assessment in mice. Courtney et al. (1986) found some signs of foetotoxicity of toluene in mice at 400 ppm (1,500 mg/m^3). Jones and Balster (1997) found lower birth weight, decreased postnatal weight gain, and delayed reflex development in the absence of maternal toxicity at 2,000 ppm toluene (7,500 mg/m^3). The NOAEC was 400 ppm (1,500), but the daily exposure periods were limited to 3 hours and consequently the observed NOAEC has limited value for the risk assessment.

Effects on behaviour in the absence of maternal or general toxicity have been reported after perinatal dosing with approximately 60 mg/kg/day toluene (Kostas and Hotchin, 1981). Due to the administration route (via drinking water), the dose level is difficult to use for the risk assessment.

Rabbits

A study comprising two teratology tests in rabbits support a NOAL for developmental effects at 500 ppm (1,875 mg/m^3) (Klimisch et al., 1992). However, in the first part of the test slight delays in skeletal development were registered, which may be a first sign of developmental toxicity at higher dose levels. Although this effect was not observed in the second part of the study, the increase in number of animals/group from 14 in the first part to 20 in the second part is not considered as sufficient to contradict the finding in the first part. Consequently, the data are not regarded as sufficient to state that 500 ppm is a clear NOAEC. No signs of maternal toxicity were seen at 500 ppm and higher dose levels were not been investigated. This is not in agreement with the OECD guideline and limits the possibility to evaluate developmental toxicity of toluene in rabbits, i.e. it is not possible to evaluate whether the foetus or the maternal animal is the most sensitive when the highest dose level does not induce maternal toxicity.

Species differences

Developmental toxicity of toluene has mainly been studied in rats. Comparison to the limited data in mice indicates that toluene induces similar effects in rats and mice, e.g. lower birth weight, delayed postnatal development and behavioural effects. The NOAEC and LOAEC in mice are at similar magnitudes as those in the rat, however, the limitations in the data in mice make it difficult to assess if species differences in sensitivity may exist. The data in rabbits are insufficient to evaluate the sensitivity of this species compared to rats and mice.

Table 4.37 Studies examining developmental effects of toluene exposure via inhalation in rats

Type of study	Dose levels	LOAEC and developmental effects	Maternal toxicity at LOAEC	NOAEC	Reference
Teratogenicity	0, 100, 400 ppm 6h/d, d 6-15	>400 ppm	No	400 ppm	API (1978)
Teratogenicity and postnatal	0, 100, 500, 2,000 ppm 6h/d, 7d/w	2,000 ppm reduced foetal body weight, delayed ossification, reduced pup weight	Yes slight	500 ppm	API (1985)
Postnatal	0, 100 and 500 ppm 6h/d, day 1-28 postnatally	500 ppm day 28 reduction in volumes of dentate layers, and argyrophilic cells in the granule layer in hippocampus	Not applicable		Slomianka et al. (1990)
Postnatal	0 and 500 ppm 12 h/d, day 1-28 postnatally	day 120 no apparent differences	Not applicable		Slomianka et al. (1992)
Teratogenicity	0, 250, 750, 1,500, 3,000 ppm 6h/d, d 6-15	1,500 ppm reduced foetal weight and reduced or unossified sternebrae	No *	750 ppm	Huntingdon (1992)
Teratogenicity and postnatal	0, 600, 2,000 ppm 6h/d, d7-17	2,000 ppm reduced foetal and pup weight	Yes slight	600 ppm ?	Ono et al. (1995)
Postnatal	0, 300, 600, 1,000, 1,200 ppm 7h/d, day 9-21 of gestation	1,000, 1,200 ppm increased pup mortality (1,200 ppm), educed pup weight, retarded postnatal development	No *	600 ppm	Thiel and Chahoud (1997)
Postnatal	0, 1,800 ppm 6h/d, d7-20	1800 ppm reduced pup weight, impaired learning	Slight maternal hearing loss	<1800 ppm	Hougaard et al. (1997a;b; 1999)
Postnatal	0, 1,200 ppm 6h/d, gestational d7-postnatal d18	1,200 ppm reduced pup weight, delayed reflex development, increased motor activity, impaired learning	No	<1,200 ppm	Hass et al. (1998)

* For discussion of maternal toxicity, see Section 4.1.2.9.5
Note: The table represents the rapporteur's conclusions

Table 4.38 Studies examining developmental effects of toluene exposure via inhalation in the mouse, hamster and rabbit

Species and type of study	Dose levels	LOAEC and effect	Maternal toxicity present at LOAEC	NOAEC	Reference
Mice, teratogenicity	0, 200, 400 ppm 7h/d, d 7-16	400 ppm change in rib profile	No	200 ppm	Courtney et al. (1986)
Mice, postnatal	0, 400 ppm 6h/d, d 7-16	400 ppm increased mortality at birth?	No		Courtney et al. (1986)
Mice, postnatal	0, 200, 400, 2,000 ppm 60 min 3 times daily, d 12-17	2,000 ppm reduced birth weight, reduced postnatal weight gain, delayed reflex development	No	400 ppm ?	Jones and Balster (1997)

Table 4.38 continued overleaf

Table 4.38 continued Studies examining developmental effects of toluene exposure via inhalation in the mouse, hamster and rabbit

Species and type of study	Dose levels	LOAEC and effect	Maternal toxicity present at LOAEC	NOAEC	Reference
Hamsters, postnatal	0, 213 ppm, 6h/d, d 6-11	213 ppm reduced rotarod performance	No information		Da-Silva et al. (1990)
Rabbits, teratogenicity	0, 30, 100, 300 ppm, 6h/d, d 6-18 pi	100 and 300 ppm delayed development of skeleton	No	?	Klimisch et al. (1997)
Rabbits, teratogenicity	0, 100, 500 ppm, 6h/d, d 6-18 pi	>500 ppm	No	500 ppm	Klimisch et al. (1997)

Note: The table represents the rapporteur's conclusions

In vitro studies

Toluene was tested in the Mouse Ovarian Tumour (MOT) cell attachment assay at eight doses ranging from 8.4 to 2,150 µg/ml. Toluene was not considered likely to be a teratogen in this test (API, 1990a).

Toluene was tested in the human embryonic palatal mesenchyme (HEPM) cell growth inhibition assay with toluene in 8 doses ranging from 16.9 to 2.150 µg/ml both with and without activation with S-9. Toluene was non-inhibitory at the highest soluble concentration (2,150 µg/ml). Toluene was not considered a teratogen based on the results of the test (API, 1990b,c).

Toluene was tested in a *in vitro* assay for chemical teratogenic potential the inhibition of proteoglycan synthesis in mouse embryo limb bud cells. The substance was found to be inactive in this assay up to a maximum testable concentration of 5 µl/ml (API, 1988)

The relevance of these *in vitro* tests in the prediction of developmental toxicity in humans is not known.

Studies in humans

Several case reports of mothers giving birth to children with so-called toluene embryopathy as a result of toluene sniffing during pregnancy have appeared (Hersh et al., 1985; Streicher et al., 1981; Toutant and Lippmann, 1979; Pearson et al., 1994,; Hoyme et al., 1993, Arnold et al., 1994). In the first detailed report (Toutant and Lippmann, 1979) three cases are described. In these cases microcephaly, narrow bifrontal diameter, short palpebral fissures, deep-set eyes, small midface, low-set, prominent ears, micrognathia, spatulate fingertips, small fingernails, hypotonia, and hyperreflexia were found in all children. The other reports describe essentially the same phenomena, and Arnold et al. (1994) and Pearson et al. (1994) have in their studies examined a total of 24 children born after in utero exposure to toluene caused by the abuse of toluene by the mothers. In total about 45 cases are described in the literature according to Pearson et al. (1994). These cases all very much resemble the foetal alcohol syndrome, and there might be a common mechanism.

Toluene was among the volatile chemicals identified qualitatively in at least 7 out of 12 total samples of human milk from 4 urban areas of the US (Jensen and Slorach, 1991).

Spontaneous abortions among women working in laboratories, and congenital malformations and birth weights of the children were examined in a retrospective case-referent study (Taskinen et

al., 1994). The exposure to toluene was assessed on the basis of the reported frequency of the use of the chemical and classified as frequent if the chemical was handled at least 3 days a week and rare if the toluene was handled 1 or 2 days a week. Significant associations with spontaneous abortions were found for frequent exposure to toluene (odds ratio 4.7, confidence interval 1.4 to 15.9) after adjustment for various covariates (206 cases and 329 referents). No association with congenital malformation was found (36 cases and 105 referents), however, the number of persons in the malformation study was too small for drawing final conclusions.

This study suggests an association between exposure to toluene during early pregnancy and increased risk of spontaneous abortion. The result should, however, be interpreted cautiously because the women were often exposed to several solvents and other chemicals simultaneously. Furthermore, no information on exposure levels is presented and, therefore, the results are of limited use for the risk assessment of toluene.

Rates of late spontaneous abortions were determined using a reproductive questionnaire in 55 women with 105 pregnancies exposed to toluene (mean 88 ppm, range 50-150 ppm), 31 women (68 pregnancies) working in the same factory in departments where little or no exposure to toluene occurred (0-25 ppm), and an external community control group of 190 working class women with 444 pregnancies (Ng et al., 1992b). Significantly higher rates for late spontaneous abortions defined as pregnancy loss between weeks 12 to 28 were noted in the toluene exposed women compared with those in the internal and external control groups (12.9% vs. 2.9-4.5%). The rate differences between groups were not likely to be confounded by classical risk factors such as maternal age, gravidity, smoking, or alcohol, which were taken into account both in the study design and the analysis. Information on pregnancy outcomes might be biased by questionnaire interview. The pregnancies and abortions in the factory were not validated by access to medical records or with biological methods. However, relatively unequivocal endpoints were used in the questionnaire, thus excluding doubtful pregnancies and abortions. The women in the factory was only told that the study was aiming at studying the health of working women in general and the relation to toluene was not mentioned. It is therefore assumed by the authors that the women in the factory with little or no exposure to toluene would be equally biased as the toluene exposed women.

This study suggests an increased risk of late spontaneous abortions associated with exposure to toluene at levels around 88 ppm (range 50-150 ppm) (see Appendix D, note 4).

A discussion of the use of these results as a basis for risk charaterisation has taken place at the Technical Meetings and the rapporteur contacted Dr. Ng and obtained further information on crucial aspects of the study.

Concerning *"low rate of spontaneous abortions" in the internal and external control group and case-definition of spontaneous abortion,* Dr. Ng has provided the following: "I agree that spontaneous abortion is generally defined as spontaneous fetal loss up to 28 weeks. However, since the study was a cross-sectional observational study that relied on the questionnaire information obtained by the subject's recall of her recent pregnancy(ies), it was difficult to determine with absolute certainty whether a spontaneous abortion had indeed occurred, especially in the first two months after conception. We know that fetal loss is a lot more common than was generally supposed especially in the first month immediately after conception. However, when it occurs, it is often disregarded as a 'missed period', after menstruation resumes a month or two later. To include such "fetal loss" would certainly have the effect of inflating the spontaneous abortion rate closer to what would generally be regarded as the true "background" rate of spontaneous abortion. For the purpose of the study, however, we have chosen to use a very stringent operational case definition of spontaneous abortion. We recognised that by doing

so, the spontaneous abortion rate would be lower than would generally be reported, and expected it to be so. But we wanted to be certain that those spontaneous abortions reported by the subjects would be associated with the highest probability of actual fetal loss. In other words, in the interest of validity, a tradeoff was made in favour of greater specificity at the expense of lower sensitivity. Yes, the spontaneous abortions that we studied were indeed late abortion."

Concerning *verification using medical records*, Dr. Ng has informed: "Note that we have administered the same questionnaire, using the same interviewers, to obtain information on pregnancy and abortion, in the same way, from the women in the community, as we did with the toluene-exposed workers. This procedure was used to ensure there was no differential bias in ascertainment of information in the two groups. The information obtained from the community 'control' group of women were still questionnaire-based information, as were those for the toluene-exposed women, not post hoc information verified from their medical records. Although we mentioned in our discussion that 90% of the pregnancies and abortions in the community group were verified in the medical reports, the statement was meant to give an idea of the degree of validity of the questionnaire information on abortion that we were getting in the study. It was only possible to make post-hoc verification of abortion occurrence from the community group, and not from the toluene-exposed group, simply because medical records were available for the community group and not for the toluene-exposed group. It would be reasonable to suppose that the same degree of validity of outcome ascertainment would apply to both groups, if the information were ascertained in as near identical fashion in both groups as possible. Which we did."

This further information from Dr. Ng does not change the initial evaluation of the study, i.e. the study suggests an increased risk of late spontaneous abortions associated with exposure to toluene at levels around 88 ppm (range 50-150 ppm). The study cannot be used to establish definitively a causal relationship between late spontaneous abortions and toluene exposure or the magnitude of the LOAEL To establish a definite relationship, a prospective study of pregnant women exposed to toluene at similar exposure levels (mean 88 ppm, range 50-150 ppm) with individually monitored data on toluene exposure and fetal loss would be needed. However, based on the current evidence suggesting an increased risk for late spontaneous abortions, exposure of pregnant women to such exposure levels would raise serious ethical concerns. Consequently, the results of the Ng study are used as a basis for the risk characterisation of developmental toxicity in humans.

4.1.2.9.5 Summary and conclusions for toxicity for reproduction

The data for toxicity for reproduction of toluene conform to the requirements of Annex VIIA of Directive 67/548/EEC.

Toluene does not have clear effects on fertility in rats, however, decreased sperm count was found in a study at 2,000 ppm (90 days, 6 hours/day). The NOAEC for this effect was 600 ppm (Ono et al., 1996). In humans, no study of adequate quality has been found.

Case studies on high-level toluene exposure of pregnant women (sniffing) provide evidence of developmental toxicity (physical and neurological abnormalities) in humans.

Two studies suggest an increased risk of spontaneous abortions associated with exposure to toluene in the workplace. One of the studies provides no data on exposure levels, while the levels were around 88 ppm (range 50-150 ppm) in the other study (Ng et al., 1992b). The Ng et al. 1992 study cannot be used to establish definitively a causal relationship between late

spontaneous abortions and toluene exposure or the magnitude of the LOAEL To establish a definite relationship, a prospective study including pregnant women exposed to toluene at similar exposure levels (mean 88 ppm, range 50-150 ppm) with individually monitored data on toluene exposure and fetal loss would be needed. However, based on the current evidence suggesting an increased risk for late spontaneous abortions, exposure of pregnant women to such exposure levels would raise serious ethical concerns. Consequently, the results of the Ng study are used as a basis for the risk characterisation of developmental toxicity in humans.

There is no indication that toluene cause malformations in rats, mice or rabbits.

Rat inhalation studies provide strong evidence of developmental toxicity (lower birth weight and long-lasting developmental neurotoxicity) in the absence of maternal toxicity. The effective dose levels are around or more than 1,000 ppm. The NOAEC for lower birth weight and delayed postnatal development is 600 ppm (Thiel and Chahoud, 1997). A NOAEC for developmental neurotoxicity cannot be determined from the available studies. The LOAEC for this effect is 1,200 ppm (Hass et al., 1999).

Developmental toxicity of toluene has mainly been studied in rats. Comparison to the limited data in mice indicates that toluene induces similar effects in rats and mice, e.g. lower birth weight, delayed postnatal development and behavioural effects. The NOAEC and LOAEC in mice are at similar magnitudes as those in the rat, however, the limitations in the data in mice make it difficult to assess if species differences in sensitivity may exist. The data in rabbits are insufficient to evaluate the sensitivity of this species compared to rats and mice.

The results concerning pregnant women sniffing toluene are difficult to use for the risk characterisation due to the high exposure levels and other limitations. However, the findings of low birth weight and neurological dysfunction both in humans and in animals developmentally exposed to toluene, point to toluene as the cause of these effects in humans.

In conclusion, limited data in humans indicate an increased risk for late spontaneous abortions at dose levels around 88 ppm. Human data as well as studies in rats and limited data in mice provide evidence of similar developmental effects, i.e. lower birth weight, delayed postnatal development and developmental neurotoxicity. Only very high exposure levels were investigated in humans. In animals, the NOAEC for lower birth weight and delayed postnatal development is 600 ppm. A NOAEC for developmental neurotoxicity cannot be determined from the available studies. The LOAEC for this effect is 1,200 ppm.

The human LOAEC of 88 ppm (330 mg/m^3) and the rat NOAEC of 600 ppm (2,250 mg/m^3) will be taken forward to the risk characterisation.

Toluene is classified as a Reproductive Category 3, R63 (Possible risk of harm to the unborn child). For classification, see Section 1.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Toluene is absorbed rapidly via inhalation and the amount absorbed depends on pulmonary ventilation. Absorption from the gastrointestinal tract seems to be high. Dermal uptake occurs. Toluene distributes widely throughout the body with the highest concentrations in fat. Toluene readily passes the placenta and is excreted in human breast milk. Toluene biotransformation occurs by oxidation in the liver. The major metabolite is benzoic acid, which is linked to glycine, resulting in the formation of hippuric acid. Toluene is mainly eliminated as hippuric acid in the urine, while a proportion is exhaled unchanged via the lungs.

Toluene has low acute toxicity. In humans experimentally exposed to toluene, concentrations of 75 ppm (285 mg/m^3) and above caused headache, dizziness, and feeling of intoxication, irritation and sleepiness. A NOAEC of 40 ppm (150 mg/m^3) for these effects has been identified and will be taken forward to the risk characterisation.

Furthermore, toluene causes impaired neuropsychological function. This acute effect of toluene has been demonstrated in performance tests. For impaired function in performance tests a LOAEC of 75 ppm (281 mg/m^3) will be taken forward to the risk characterisation.

In rats, a inhalation LC50 of 28,100 mg/m^3/4 hours has been reported. However, for inhalation the risk characterisation will be based on the human NOAEC and LOAEC mentioned above.

A dermal LD50 of 12,400 mg/kg has been determined in the rabbit. This value will be taken forward to the risk characterisation for acute toxicity by dermal exposure, as no human studies are available.

Toluene has been shown to be irritating to the skin in rabbits, mice, and guinea pigs. According to textbooks, it is well known that toluene has a degreasing effect on the skin of humans. One study in rabbits has been performed according to a method of EU guideline standard, however, the non-irritating concentration is not known, as the data are on the undiluted substance.

Liquid toluene is irritating to eyes in animals, while toluene vapours in concentrations at and above 75 ppm causes complaints of eye irritation in humans. A NOAEC of 40 ppm (150 mg/m^3) for eye irritation has been identified and will be taken forward to the risk characterisation.

The results of a guinea pig maximisation test indicates that toluene is not a skin sensitiser. It is unlikely that toluene is a respiratory allergen.

In the rat a NOAEL for general systemic toxicity of 625 mg/kg/day for repeated oral exposure was identified in a 90-day study. At higher levels (1,250 mg/kg and above) neurone necrosis and organ weight increases were found. In a similar 90-day mouse study non-specific effects (liver enlargement and one death) was found at 1,250 mg/kg.

Also in the rat, a NOAEC for general systemic toxicity of 625 ppm (2,344 mg/m^3) for repeated exposure via inhalation was identified in a 15-week study. At the higher exposure level (1,250 ppm (4,688 mg/m^3)) a decrease in leukocyte count in females, and relative organ weight increases were found. In a two-year rat study a NOAEC of 300 ppm (1,125 mg/m^3) was found, this was the highest dose level tested. In another two-year rat study, the lowest dose tested, 600 ppm ((2,280 mg/m^3) was a LOAEC for increased occurrence of nasal toxicity and forestomach ulcers in males. For general systemic toxicity after repeated dosing, the 90-day rat

oral NOAEL of 625 mg/kg/day, and the two-year rat inhalation NOAEC of 300 ppm (1,125 mg/m^3) will be taken forward to the risk characterisation.

For the dermal route, no data on repeated dose toxicity have been found.

Repeated exposure to toluene via inhalation has been shown to affect the central nervous system and the inner ear. These endpoints were not part of the studies investigating general toxicity, but are toxicologically important, and are therefore treated as separate endpoints in the risk characterisation.

Long-term high-level exposure to toluene (abuse) via inhalation has caused serious damage to the brain including severe neurological abnormalities and brain atrophy. This effect is not considered in the risk characterisation, as it is not an effect associated with normal use of toluene.

Many scientists believe that long-term exposure to volatile solvents at exposure levels possible in occupational settings may lead to organic brain syndrome. Two studies show an increased prevalence in toluene-exposed workers compared with the control group. In both studies the length of employment was high, while only recent exposure data were well documented. Exposure during the years preceding the investigation was not well described. LOAECS and NOAECS cannot be determined for organic brain syndrome, since well-documented exposure information covering a considerable proportion of the entire period of employment would be necessary, but is not available. Consequently this endpoint cannot be evaluated quantitatively in the risk characterisation.

No evidence suggesting that the levels of toluene found in the working environment can cause damage to the peripheral nervous system has been found.

In animals several effects on the central nervous system have been found. These effects will not be evaluated as separate endpoints in the risk characterisation, but form part of the database on the neurotoxic effects of toluene.

Neuronal cell necrosis in the dentate gyrus and Ammons horn of the hippocampus was seen in both male and female rats that received 1,250 or 2,500 mg/kg in a 90-day study. Also necrosis and/or mineralisation were present in the granular layer of the cerebellar cortex.

A reduced number of neurones in the hippocampus and a reduced hippocampal weight in rats exposed to 1,500 ppm (5,625 mg/m^3) of toluene via inhalation for 6 months have been found.

In very young rats exposed to toluene via inhalation on postnatal day 1-28 reduced volume of certain hippocampal structures was found at 100 and 500 ppm (380 and 1,900 mg/m^3).

Changes in brain neurochemistry in rats have been described. Effects were found at an exposure level of 80 ppm (300 mg/m^3) after only 3 days of exposure. Long-term exposure has been shown to cause effects on brain neurochemistry at 500 ppm (1,900 mg/m^3) still present six months after the last exposure indicating possibly irreversible changes.

Occupational exposure to toluene at high concentrations may increase the risk of developing mild high-frequency hearing loss. However, the studies showing this effect are not appropriate for determining a LOAEC or NOAEC.

The ototoxicity of toluene in the rat is well documented by behavioural, electrophysiological, and morphological techniques. It is therefore possible to carry out a separate risk characterisation for this endpoint by use of the animal data. Impaired hearing function in the rat has been demonstrated at exposure concentration levels of 1,000 ppm (3,750 mg/m^3) for as little as

2 weeks. A 16-week NOAEC of 700 ppm (2,625 mg/m^3) has been reported and will be taken forward to the risk characterisation.

Toluene is considered to be non-genotoxic, and was not carcinogenic to rats or mice in inhalation studies.

In the mouse study, adenomas of the pars intermedia in the pituitary gland, a very rare tumour type, were found in all toluene-exposed groups of females, and in the highest dose group of males. A single adenoma was found in each of these groups. In a skin painting study, toluene was found to cause skin irritation and tumour development. The difference in tumour incidence was just below statistical significance (p=0.055).

In male rats exposed to 2,000 ppm (7,500 mg/m^3), reduced sperm count was found with a NOAEC of 600 ppm (2,250 mg/m^3).

Toluene abuse has been related to a syndrome in human foetuses characterised by physical and neurological abnormalities, resembling the foetal alcohol syndrome. In rats, lower foetal and birth weight has been found in offspring of dams exposed to inhalation concentrations around 1,000 ppm (3,750 mg/m^3). Long-lasting developmental neurotoxicity (impairment of learning ability) has been demonstrated in offspring exposed prenatally or pre- and postnatally to 1,200 ppm (4,560 mg/m^3). The NOAECs for lower birth weight were around 600 ppm (2,250 mg/m^3).

Limited data in humans indicate an increased risk for spontaneous abortions at dose levels around 88 ppm (330 mg/m^3).

A rat NOAEC of 600 ppm (2,250 mg/m^3) and a human LOAEC of 88 ppm (330 mg/m^3) for reproductive toxicity will be taken forward to the risk characterisation.

Overall, the hazardous properties of toluene have been evaluated in animals to the extent that the minimum data requirements according to Article 9(2) of Regulation 793/93 have been met. The key health effects with respect to acute toxicity, skin and eye irritation, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity, and reproductive toxicity have been identified.

In the risk characterisation the human exposure levels are compared directly with NOAELs/LOAELs and NOAECs/LOAECs; and LD50 (LC50) values from animal or human studies when available.

Factors influencing the magnitude of the required minimal "Margin Of Safety" (MOS)

Acute toxicity (inhalation)

Headache, dizziness, feeling of intoxication, irritation and sleepiness

Human data from the inhalation route are available. In addition to characterising risk of acute toxicity based on animal data, risk of acute toxicity will also be characterised for inhalation exposure based on these human data.

A NOAEC of 150 mg/m^3 will be used.

The effects have been reported in several studies at approximately the same exposure levels. It is not necessary to take the variability in the experimental data into account in the evaluation of the MOS for this endpoint.

Duration of exposure was appropriate.

These effects could impair the quality of life without necessarily threatening the health of the affected individual. Consequently lower MOSs will be acceptable. In addition the NOAEC for this endpoint is derived from human data, and even lower MOSs will be acceptable

Based on the considerations above the following minimal MOSs will be required:

- workers: $MOS_{min} = 2$
- consumers: $MOS_{min} = 6$

Impaired neuropsychological function

Human data from the inhalation route are available. In addition to characterising risk of acute toxicity based on animal data, risk of acute toxicity will also be characterised for inhalation exposure based on these human data.

A LOAEC of 281 mg/m^3 will be used.

The effects have been reported in several studies at approximately the same exposure levels. It is not necessary to take the variability in the experimental data into account in the evaluation of the MOS for this endpoint.

These effects could interfere with work performance without in itself necessarily, threatening the health of the affected individual. However, reduced neuropsychological function may lead to dangerous situations in the occupational setting where optimum reactions are necessary for safe operation of machinery.

Duration of exposure was appropriate.

Using an effect level in the risk characterisation requires an increased MOS. On the other hand the NOAEC for this endpoint is derived from human data, and a smaller MOS will thus be acceptable.

Based on the considerations above the following minimal MOSs will be required:

- workers: $MOS_{min} = 5$
- consumers: $MOS_{min} = 15$

Acute toxicity (dermal)

For the dermal route the dermal LD50 of 12,400 mg/kg will be used.

Only a single study on acute dermal toxicity is available, and consequently variability cannot be evaluated.

Duration of exposure was appropriate.

The effect (death) is clearly severe, which means that the MOS should be large. However, as explained in Section 4.1.1, evaporation from the skin has not been accounted for when modelling dermal exposure values. For all exposure scenarios except spray painting these are consequently overestimated to an unknown degree. When characterising risk after dermal exposure lower MOSs can consequently be accepted.

Based on the considerations above the following minimal MOSs will be required:

- workers: $MOS_{min} <100$
- consumers: $MOS_{min} <300$

Skin irritation

Animal data from the dermal route are available. Toluene has been shown to be irritating to the skin in rabbits, mice, and guinea pigs. However, the non-irritating concentration is not known, as the data are on the undiluted substance. It is therefore not possible to perform a quantitative risk characterisation for this endpoint.

Skin irritation is not a life threatening effect. There is, however, some indication that dermal cancer may occur after long-term exposure, which may be related to the irritative properties of toluene. Dermal carcinogenicity is clearly a serious toxic effect, which should be considered in the risk characterisation.

Duration of exposure was appropriate.

Eye irritation

Human data from eye exposure to vapour are available. A NOAEC of 150 mg/m^3 will be used. Eye irritation is not a health threatening effect and this calls for lower MOSs.

Duration of exposure was appropriate.

The NOAEC for this endpoint is derived from human data, which means that lower MOSs will be acceptable.

Based on the considerations above the following minimal MOSs will be required:

- workers: $MOS_{min} = 1$
- consumers: $MOS_{min} = 3$

Repeated dose general toxicity

Risk of general toxicity after repeated exposures will be characterised for both dermal and inhalation exposure as well as for the estimated total systemic dose caused by these two exposure routes combined.

Inhalation

For the characterisation of risk in relation to exposure via inhalation an inhalation NOAEC of 1,125 mg/m^3 will be used.

The estimates for a LOAEC following exposure by inhalation are derived from a 15-week, a 2-year, a combined 15-month and 2-year rat study, and a 2-year mouse study. A NOAEC for general systemic toxicity of 625 ppm (2,344 mg/m^3) for repeated exposure via inhalation was identified in the 15-week study. At higher exposure level (1,250 ppm (4,750 mg/m^3)) a decrease in leukocyte count in females, and relative organ weight increases were found. In the 2-year study a NOAEC of 300 ppm (1,125 mg/m^3) was found, this was the highest dose level tested. In the combined 15-month and 2-year study, the lowest dose tested, 600 ppm (2,250 mg/m^3) was a LOAEC for increased occurrence of nasal toxicity and forestomach ulcers in males. In the two-year mouse study, non-malignant pituitary adenomas were found in all exposed groups. The lowest exposure level in this study was 120 ppm (456 mg/m^3).

The variation in the toxicological findings may be related to the varying experimental conditions. Therefore, the variability in the experimental data for inhalation exposure does not justify a change in the evaluation of the MOS.

The NOAEC is based on a two-year study where no effects were found. At the LOAEC, which is based on another two-year study, increased occurrence of nasal toxicity and forestomach ulcers in males was found. These effects are toxicologically important and this calls for higher MOSs.

The inhalation NOAEL was derived from a 2-year study.

Duration of exposure was appropriate.

Based on the considerations above the following minimal MOSs will be required:

- workers: $MOS_{min} = 15$
- consumers: not relevant with the assumed use patterns

Dermal

As no toxicity data for the dermal route are available the oral NOAEL of 625 mg/kg/day will be used for the dermal risk characterisation.

Two repeated dose (90-day) oral studies, one in rats and one in mice, have been considered. Consistent effects were not found, however, the LOAELs and NOAELs were identical in the two studies. In the rat study the LOAEL was 1,250 mg/kg for brain effects with a NOAEL of 625 mg/kg. In the mouse study non-specific effects (liver enlargement and one death) was found at 1,250 mg/kg. Part of the difference can be explained by species differences. Both studies were of good quality and therefore both are relevant for the risk assessment. As the LOAELs and NOAELs were the same, it is not necessary to take the variability in the experimental data into account in the evaluation of the MOS for this endpoint.

In the rat, a NOAEL for general systemic toxicity of 625 mg/kg/day for repeated oral exposure was identified in a 90-day study. At higher levels (1,250 mg/kg and above) neurone necrosis and organ weight increases were found. In the similar mouse study non-specific effects (liver enlargement and one death) was found at 1,250 mg/kg. Neurone necrosis is toxicologically important and this calls for a higher MOS.

The oral NOAEL was derived from a 90-day study. As this is short in relation to lifetime exposure, this also calls for a higher MOS.

As explained in Section 4.1.1, evaporation from the skin has not been accounted for when modelling dermal exposure values. For all exposure scenarios except spray painting these are consequently overestimated to an unknown degree. This means that lower MOSs will be acceptable when characterising risk after dermal exposure.

Based on the considerations above the following minimal MOSs will be required:

- workers: $MOS_{min} < 30$
- consumers: not relevant with the assumed use patterns

Total systemic dose

For the total systemic dose the same oral NOAEL of 625 mg/kg/day will be used (cf. discussion above).

Lower MOS's could be accepted when characterising the risk based on total systemic effects, depending on the dermal contribution to the total systemic dose.

Based on the considerations above the following minimal MOSs will be required:

- workers: MOS_{min} <30 (depending on the dermal contribution to the total systemic dose)
- consumers: not relevant with the assumed use patterns

Repeated dose specific organ toxicity

Exposure data on organic brain syndrome are inadequate, and hence no risk characterisation will be carried out for this endpoint. However extensive data on auditory system toxicity after exposure by inhalation are available and a characterisation of the risk after inhalation exposure for this endpoint will be carried out. For ototoxicity an animal NOAEC of 700 ppm (2,625 mg/m^3) will be used. Many studies have repeatedly shown that toluene in concentrations at and above 1,000 ppm causes ototoxicity in the rat.

It is likely that the rat must be exposed to a certain minimum concentration of toluene for a certain minimum of time before ototoxicity will develop. The size of this minimum concentration is not known; nor has it been sufficiently documented that a certain low concentration will not cause ototoxicity after long-term exposure. The study with the longest exposure period is the study by Pryor (1984) in which 700 ppm (2,625 mg/m^3) toluene for up to 16 weeks was a NOAEC with a 14-hour daily exposure duration. In the same study, the LOAEC was 1,000 ppm (3,750 mg/m^3) (14 hours/day). At 1,000 ppm, an exposure duration of only 2 weeks was associated with hearing loss. The exposure duration in the study used to derive the NOAEL was 16 weeks. As this is short in relation to lifetime exposure, the MOS should be larger.

In addition, auditory function was evaluated by estimation of auditory sensitivity by ABR, which may not be the most sensitive method, as it is known that damage to the auditory system can be present without being detected by estimation of auditory sensitivity.

Furthermore, transient auditory effects have been shown to be induced at a lower level than 700 ppm.

This uncertainty about the Pryor (1984) 700 ppm NOAEL means that larger MOSs are required for ototoxicity.

Loss of hearing is an impairment of function. The effects of toluene in humans have been described as a mild hearing loss. Although this may not seem serious, it should be taken into consideration that hearing deteriorates with age, and that if a mild hearing loss is added to the age-related impairment, a person may experience clinical hearing difficulty at a younger age than would otherwise be the case. The MOS should be larger.

Based on the considerations above the following minimal MOSs will be required:

- workers: MOS_{min} = 30
- consumers: not relevant with the assumed use patterns

Carcinogenicity

There is no indication of carcinogenicity via inhalation. There is some indication of carcinogenicity via dermal contact. This concern relates to effects found in one study only, which however is of good quality. A number of other studies on dermal carcinogenicity were negative, but suffered from various methodological weaknesses. The variation in the toxicological findings may be related to the varying experimental conditions.

Dermal cancer is a serious effect.

Toxicity to reproduction (fertility and developmental)

Data from the inhalation route are available. Risk of toxicity for reproduction (fertility and development) will be characterised for inhalation exposure only, as extrapolation from the inhalation route to the dermal route is highly uncertain.

A rat NOAEC of 600 ppm (2,250 mg/m^3) will be used.

Several studies indicate similar effects in rat foetuses at similar dose levels. Developmental neurotoxicity occurred at a higher exposure level (1,200 ppm). This effect has not been examined at a lower exposure level. The uncertainty of whether the 600 ppm NOAEC for reproductive toxicity (for fertility and reduced birth weight) also covers developmental neurotoxicity, means that a larger MOS is required for this endpoint.

The effects on reproduction and development are serious. The reduced sperm count found in the rat was not associated with reduced male fertility. However, the rat is known to possess a large reserve capacity which men do not have, and a reduced sperm count may be associated with infertility in men and therefore more serious than in the rat. The reduced foetal weights and birth weights in rats are toxicologically important adverse effects in the offspring of exposed mothers. Even more serious is the long-lasting developmental neurotoxicity, manifest as impaired learning ability. This also calls for larger MOS's for this endpoint.

Duration of exposure was appropriate.

Based on the considerations above the following minimal MOS's will be required:

- workers: $MOS_{min} = 30$
- consumers: see Section 4.1.3.3.8, risk characterisation, consumers, reproductive toxicity

Toxicity to reproduction (spontaneous abortions)

A human LOAEC of 88 ppm (330 mg/m^3) will be used.

Early abortions in relation to toluene exposure in humans have been reported in a single study, and consequently variability cannot be evaluated.

Data from the inhalation route are available. Duration of exposure was appropriate.

As the NOAEC for this endpoint is derived from human data, a smaller MOS will be acceptable, however, using an effect level in the risk characterisation requires an increased MOS.

Based on the considerations above the following minimal MOS's will be required:

- workers: $MOS_{min} = 5$
- consumers: see Section 4.1.3.3.8, risk characterisation, consumers, reproductive toxicity

4.1.3.2 Workers

4.1.3.2.1 General considerations

The exposure conditions that are considered in this risk characterisation have all been described and discussed in Section 4.1.1.2. The exposure routes considered are inhalation and dermal exposure, and the MOS for exposure by each route is considered separately.

In addition, for scenarios with conclusion (ii) for both these exposure routes, the significance of the MOS for total systemic exposure is also considered. Exposure concentrations in mg/m^3 have been converted to an estimated internal dose in mg/kg/day (see Appendix E). The significance of the MOS for total systemic exposure is not however considered where conclusion (iii) has been drawn for either or both of the exposure routes separately, as the possible concerns have already been identified.

If the MOS is below the minimal acceptable MOS this leads to concern, while MOSs higher than the minimal acceptable MOS indicates no concern. The magnitude of the minimal acceptable MOS is discussed in the section above.

4.1.3.2.2 Acute toxicity

Inhalation

The risk for acute toxicity by inhalation will be characterised based on the human NOAEC of 150 mg/m^3 for headache, dizziness, feeling of intoxication, irritation and sleepiness and the human LOAEC of 281 mg/m^3 for impaired functional performance.

Table 4.39 MOSs and conclusions for acute toxicity by inhalation by different workers exposure scenarios

X. Scenario x) sub-scenario	Headache, dizziness…			Functional performance		
	Exp.[a)]	MOS	Conc.	Exp. [a)]	MOS	Conc.
Q. Production and use as an intermediate						
a) production and use as an intermediate	100	1.5	**iii**	100	2.8	**iii**
b) use as an intermediate	100	1.5	**iii**	100	2.8	**iii**
c) maintenance (regularly)	100	1.5	**iii**	100	2.8	**iii**
R. Production of gasoline						
a) drumming, maintenance and tank cleaning	140			140		
b) operators at production sites	30			30		
c) transfer of gasoline	100			100		
d) attendants at service stations	6			6		
S. Production of products (transfer, filling and drumming)	200	<1	**iii**	200	1.4	**iii**
T. Use of toluene containing products						
a) manual cleaning	240	<1	**iii**	240	1.2	**iii**
mechanical cleaning	90	1.7	**iii**	90	3.1	**iii**
b) use of adhesives	500	<1	**iii**	500	<1	**iii**
c) printing	700	<1	**iii**	700	<1	**iii**
d) painting: manual	100	1.5	**iii**	100	2.8	**iii**
spraying	100	1.5	**iii**	100	2.8	**iii**
mechanical coating	340	<1	**iii**	340	<1	**iii**

a) mg/m^3

For scenarios Q, S and T, MOSs are lower than acceptable. There is concern for acute effects by exposure via inhalation: **conclusion (iii)**.

No formal risk characterisation has been performed for the production of gasoline (scenario R), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

Dermal

For the evaluation of risk for acute effects by dermal exposure the rabbit LD50 of 12,400 mg/kg will be used.

Table 4.40 MOSs and conclusions for acute toxicity by dermal exposure by different workers exposure scenarios

X. Scenario x) sub-scenario	Dermal		
	Exposure (mg/kg bw/day)	MOS	Conclusion
Q. Production and use as an intermediate			
a) production and use as an intermediate	9	1,378	ii
b) use as an intermediate	9	1,378	ii
c) maintenance (regularly)	9	1,378	ii
R. Production of gasoline			
a) drumming, maintenance and tank cleaning	2		
b) operators at production sites	1.2		
c) transfer of gasoline	1.2		
d) attendants at service stations	0.6		
S. Production of products (transfer, filling and rumming)	6	2,067	ii
T. Use of toluene containing products			
a) manual cleaning	90	138	ii
mechanical cleaning	0,6	20,667	ii
b) use of adhesives	279	44	**iii**
c) printing	6	2,067	ii
d) painting: manual	29	428	ii
spraying	279	44	**iii**
mechanical coating	6	2,067	ii

For all scenarios related to the production and use of toluene as an intermediate (scenarios Q) MOSs are considered to be sufficiently high. For these scenarios there is no concern for acute effects by dermal exposure: **conclusion (ii)**.

No formal risk characterisation has been performed for the production of gasoline (scenario R), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

For all scenarios related to the production of toluene containing products (scenario S) MOSs are considered to be sufficiently high. For these scenarios there is no concern for acute effects by dermal exposure: **conclusion (ii)**.

For the use of toluene containing products in use of adhesives (scenario T b) and spray painting (scenario T d) the MOS's are 44 which is both cases are considered below the acceptable level. There is concern for acute effects by dermal exposure: **conclusion (iii)**.

For all other scenarios related to the use of toluene containing products MOSs are considered to be sufficiently high. For these scenarios there is no concern for acute effects by dermal exposure: **conclusion (ii)**.

Toluene is classified as a skin irritant with Xi; R38 (Irritating to skin). Whether this provides adequate protection against dermal exposure and consequently acute toxicity during spray painting should be considered when the risk reduction strategy is addressed.

4.1.3.2.3 Irritation

Skin

Toluene has been shown to be irritating to the skin in rabbits, mice, and guinea pigs. However, the non-irritating concentration is not known, as the data are on the undiluted substance. It is therefore not possible to perform a quantitative risk characterisation for this endpoint.

Skin tumours have been observed in one long-term skin painting study with toluene, but not in other studies. There is uncertainty over the relationship of these tumours to toluene exposure, but the skin painting study resulted in significant long-term severe skin irritation.

Toluene as a skin irritant with Xi; R38 (Irritating to skin). Given that workers thus are expected to take measures to limit exposure it is considered unlikely that such severe irritation would occur. There is no concern for skin irritation: **conclusion (ii)**.

Eye

For the characterisation of the risk of eye irritation the human NOAEC of 150 mg/m^3 will be used.

Table 4.41 MOSs and conclusions for eye irritation by different workers exposure scenarios

X. Scenario x) sub-scenario	Exposure (mg/m^3)	MOS	Conclusion
Q. Production and use as an intermediate			
a) production and use as an intermediate	100	1.5	ii
b) use as an intermediate	100	1.5	ii
c) maintenance (regularly)	100	1.5	ii
R. Production of gasoline			
a) drumming, maintenance and tank cleaning	140		
b) operators at production sites	30		
c)transfer of gasoline	100		
d) attendants at service stations	6		
S. Production of products (transfer, filling and drumming)	200	<1	**iii**
T. Use of toluene containing products			
a) manual cleaning	240	<1	**iii**
mechanical cleaning	90	1.7	ii
b) use of adhesives	500	<1	**iii**
c) printing	700	<1	**iii**
d) painting: manual	100	1.5	ii
praying	100	1.5	ii
mechanical coating	340	<1	**iii**

For all scenarios related to the production and use of toluene as an intermediate (scenarios Q) MOSs are considered to be sufficiently high. For these scenarios there is no concern for eye irritation: **conclusion (ii)**.

No formal risk characterisation has been performed for the production of gasoline (scenario R), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

For the production toluene containing products (scenarios S) the MOS is below the acceptable level. For this scenario there is concern for eye irritation: **conclusion (iii)**.

For manual cleaning (scenario T a) the MOS is below the acceptable level. For this scenario there is concern for eye irritation: **conclusion (iii)**.

For mechanical cleaning (scenario T a), the MOS is considered to be sufficiently high. For this scenario there is no concern for eye irritation: **conclusion (ii)**.

For the use of adhesives (scenario T b) and for printing (scenario T c), MOSs are below the acceptable level. For these scenarios there is concern for eye irritation: **conclusion (iii)**.

For manual painting and spray painting (scenario T d) MOS are considered to be sufficiently high. For these scenarios there is no concern for eye irritation: **conclusion (ii)**.

For mechanical coating (scenario T d) the MOS is below the acceptable level. For this scenario there is concern for eye irritation: **conclusion (iii)**.

4.1.3.2.4 Corrosivity

Toluene is not corrosive. There is no concern for corrosivity: **conclusion (ii)**.

4.1.3.2.5 Sensitisation

Toluene is not a sensitiser. There is no concern for sensitisation: **conclusion (ii)**.

4.1.3.2.6 Repeated dose toxicity

General toxicity

For the evaluation of risk for general toxicity by repeated exposure via inhalation, the NOAEC of 1,125 mg/m^3 will be used. There are no data on repeated dose toxicity by dermal exposure. Therefore the evaluation of risk for general toxicity by repeated dermal exposure will be based on a comparison of the estimated full-shift dermal exposure and the oral NOAEL of 625 mg/kg. In cases where a conclusion (ii) applies for both inhalation and dermal exposure, an evaluation of the risk, based on the total systemic dose due to exposure via both of these pathways, is relevant. For this again the oral NOAEL of 625 mg/kg will be used.

Table 4.42 MOSs and conclusions for repeated dose general toxicity by inhalation, dermal exposure and total systemic dose by different workers exposure scenarios

X. Scenario x) sub-scenario	Inhalation			Dermal			Total systemic dose c)		
	Exp. a)	MOS	Conc.	Exp. b)	MOS	Conc.	Exp. b)	MOS	Conc.
Q. Production and use as an intermediate									
a) production and use as an intermediate	45	25	ii	6	104	ii	12+6=18	35	ii
b) use as an intermediate	15	75	ii	6	104 69	ii	4+6=10	63	ii
c) maintenance (regularly)	45	25	ii	9		ii	12+9=21	29	ii
R. Production of gasoline									
a) drumming, maintenance and tank cleaning	70			1.9			19+2=21		
b) operators at production sites	20			1.2			5+1=6		
c) transfer of gasoline	50			1.2			14+1=15		
d) attendants at service stations	3			0.6			0.8+0.6=1.4		
S. Production of products (transfer, filling and drumming)	98	11	**iii**	6	104	ii	27+6=33	19	**iii**
T. Use of toluene containing products									
a) manual cleaning	120	9	**iii**	90	7	**iii**	33+90=123	5	**iii**
mechanical cleaning	44	26	ii	0,6	1,042	ii	12+1=13	49	ii
b)use of adhesives	400	2.8	**iii**	279	2	**iii**	110+279=389	1.6	**iii**
c) printing	350	3.2	**iii**	6	104	ii	69+6=75	8	**iii**
d) painting: manual	50	23	ii	29	22	ii	14+29=43	15	**iii**
spraying	50	23	ii	279	2	**iii**	14+279=293	2	**iii**
mechanical coating	170	6.6	**iii**	6	104	ii	47+6=53	12	**iii**

a) mg/m^3
b) mg/kg bw/day
c) the sum of the reasonable worst-case inhalation exposure and the estimated reasonable worst-case dermal exposure, assuming a 100% uptake (see Appendix E). If inhalation either exposure in itself or dermal exposure in itself gives rise to concern the combined total systemic dose will logically also give rise to concern. Therefore, the MOS for total systemic dose need only be considered if conclusion (ii) applies to both inhalation and dermal exposure.

For the production and use as an intermediate (scenario Q a - c), the MOSs for both inhalation and dermal are considered being sufficiently high. For production and use as an intermediate (scenario Q a) and maintenance (scenario Q c), the MOSs for total systemic dose are slightly below the acceptable level. However, for these two scenarios almost half of the total systemic dose can be attributed to dermal exposure, which may be overestimated. For the use as an intermediate (scenario Q b) the MOS for total systemic dose is considered to be sufficiently high. Consequently there is no concern for any of these scenarios (scenario Q a - c): **conclusion (ii)**.

No formal risk characterisation has been performed for the production of gasoline (scenario R), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

For the production of products containing toluene (scenario S), the MOS for inhalation is 11, which is considered to be below the acceptable level. The MOS for dermal exposure is considered to be sufficiently high. For this scenario there is concern for general toxicity after repeated exposure via inhalation and consequently also for the total systemic dose: **conclusion (iii)**.

For manual cleaning (scenario T a), the MOSs for inhalation and dermal exposure are 9 and 7, respectively. In both cases this is considered to be below the acceptable level. For this scenario

there is concern for general toxicity after repeated exposure via inhalation and dermal exposure and consequently also for the total systemic dose: **conclusion (iii)**.

For mechanical cleaning (scenario T a), the MOSs for inhalation and dermal exposure are 26 and 1,042, respectively. In both cases this is considered to be sufficiently high. The MOS for total systemic dose is 49, which is also considered to be sufficiently high. Hence, for this scenario there is no concern: **conclusion (ii)**.

For the use of adhesives (scenario T b), the MOSs for inhalation and dermal exposure are 2.8 and 2, respectively. In both cases this is considered to be below the acceptable level. For this scenario there is concern for general toxicity after repeated exposure via inhalation and dermal exposure and consequently also for the total systemic dose: **conclusion (iii)**.

For printing (scenario T c), the MOS for inhalation is 3.8, which is considered to be below the acceptable level. For dermal exposure the MOS is 104, which is considered to be sufficiently high. For this scenario there is concern for general toxicity after repeated exposure via inhalation and consequently also for the total systemic dose: **conclusion (iii)**.

For manual painting (scenario T d), the MOS for inhalation is 23, which is considered to be sufficiently high. For dermal exposure the MOS is 22. Though the MOS of 22 is borderline it is considered to be sufficiently high. The MOS for total systemic dose is 15. Though approximately two thirds of the estimated total systemic dose can be attributed to the dermal exposure, which is overestimated to an unknown degree, a MOS of 15 is considered to be below the acceptable level. Thus, for this scenario there is concern for general toxicity as a consequence of the total systemic dose arising from dermal and inhalation exposure combined: **conclusion (iii)**.

For spray painting (scenario T d), the MOS for inhalation is 23, which is considered to be sufficiently high. For dermal exposure the MOS is 2, which is clearly below the acceptable level. For this scenario there is concern for general toxicity after repeated exposure via dermal exposure and consequently also for the total systemic dose: **conclusion (iii)**.

For mechanical coating (scenario T d), the MOS for inhalation is 6.6, which is considered to be below the acceptable level. For dermal exposure the MOS is 104, which is considered to be sufficiently high. For this scenario there is concern for general toxicity after repeated exposure via inhalation and consequently also for the total systemic dose: **conclusion (iii)**.

Toluene is classified as a skin irritant with Xi; R38 (Irritating to skin). Whether this provides adequate protection against dermal exposure and consequently repeated dose general toxicity during manual cleaning, the use of adhesives and painting (manual and spray) should be considered when the risk reduction strategy is addressed.

Specific organ toxicity

As a NOAEC or a LOAEC cannot be determined for the organic brain syndrome this endpoint cannot be evaluated quantitatively.

For the evaluation of risk for specific organ toxicity (auditory system toxicity) by repeated exposure via inhalation, the NOAEC of 2,625 mg/m^3 will be used. The risk for effects after repeated dermal exposure is considered to be sufficiently evaluated in relation to general toxicity.

Table 4.43 MOSs and conclusions for repeated dose specific organ toxicity by inhalation for different workers exposure scenarios

X. Scenario x) sub-scenario	Inhalation		
	Exposure (mg/m³)	**MOS**	**Conclusion**
Q. Production and use as an intermediate			
a) production and use as an intermediate	45	58	ii
b) use as an intermediate	15	175	ii
c) maintenance (regularly)	45	58	ii
R. Production of gasoline			
a) drumming, maintenance and tank cleaning	70		
b) operators at production sites	20		
c) transfer of gasoline	50		
d) attendants at service stations	3		
S. Production of products (transfer, filling and drumming)	98	27	**iii**
T. Use of toluene containing products			
a) manual cleaning	120	22	**iii**
mechanical cleaning	44	60	ii
b) use of adhesives	400	7	**iii**
c) printing	350	8	**iii**
d) painting: manual	50	53	ii
spraying	50	53	ii
mechanical coating	170	15	**iii**

a) mg/m³

For the production and use as an intermediate (scenario Q a-c), the MOSs are all considered to be sufficiently high. For these scenarios there no concern for specific organ toxicity (auditory toxicity) after repeated exposure: **conclusion (ii)**.

No formal risk characterisation has been performed for the production of gasoline (scenario R), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

For the production of products containing toluene (scenario S), the MOS is 27 which is considered to be below the acceptable level. For this scenario there is concern for specific organ toxicity (auditory toxicity) after repeated exposure via inhalation: **conclusion (iii)**.

For manual cleaning (scenario T a), use of adhesives (scenario T b), printing (scenario T c) and for mechanical coating (scenario T d), MOSs are considered to be below the acceptable level. For these scenarios there is concern for specific organ toxicity (auditory toxicity) after repeated exposure via inhalation: **conclusion (iii)**.

4.1.3.2.7 Mutagenicity

Toluene is not considered to be mutagenic. Consequently there is no concern for this endpoint: **conclusion (ii)**.

4.1.3.2.8 Carcinogenicity

There is no indication of carcinogenicity via inhalation. There is no concern for carcinogenicity by inhalation: **conclusion (ii)**.

Skin tumours have been observed in one long-term skin painting study with toluene, but not in other studies. There is uncertainty over the relationship of these tumours to toluene exposure, but the skin painting study resulted in significant long-term severe skin irritation.

Toluene is classified as a skin irritant with Xi; R38 (Irritating to skin). Given that workers thus are expected to take measures to limit dermal exposure there is no concern for carcinogenicity by dermal exposure: **conclusion (ii)**.

4.1.3.2.9 Toxicity for reproduction

For the evaluation of risk for toxicity for reproduction by exposure via inhalation, the NOAEC of 2,250 mg/m^3 for effects on fertility and developmental and the human LOAEC of 330 mg/m^3 for spontaneous abortions will be used.

There are no data on toxicity for reproduction by dermal or oral exposure. Consequently no risk characterisation will be carried out for the dermal exposure nor for the total systemic dose arising from combined contribution by exposure via inhalation and dermal exposure.

Table 4.44 MOSs and conclusions for reproductive toxicity by inhalation by different workers exposure scenarios

X. Scenario x) sub-scenario	Fertility and developmental			Spontaneous abortions [b]		
	Exp.[a]	MOS	Conc.	Exp.[a]	MOS	Conc.
Q. Production and use as an intermediate						
a) production and use as an intermediate	45	50	ii	45	7	ii
b) use as an intermediate	15	150	ii	15	22	ii
c) maintenance (regularly)	45	50	ii	45	7	ii
R. Production of gasoline						
a) drumming, maintenance and tank cleaning	80			80		
b) operators at production sites	50			50		
c) transfer of gasoline	60			60		
d) attendants at service stations	5			5		
S. Production of products (transfer, filling and drumming)	98	23	**iii**	98	3	**iii**
T. Use of toluene containing products						
a) manual cleaning	120	19	**iii**	120	3	**iii**
mechanical cleaning	44	51	ii	44	8	ii
b) use of adhesives	400	6	**iii**	400	<1	**iii**
c) printing	350	6	**iii**	350	1	**iii**
d) painting: manual	50	45	ii	50	7	ii
spraying	50	45	ii	50	7	ii
mechanical coating	170	13	**iii**	170	2	**iii**

a) mg/m^3
b) see Appendix D, note 5

For the production and use as an intermediate (scenario Q a-c), the MOSs are considered to be sufficiently high. Consequently, for these scenarios there is no concern for fertility, development, or spontaneous abortions after repeated exposure: **conclusion (ii)**.

No formal risk characterisation has been performed for the production of gasoline (scenario R), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

For the production of products containing toluene (scenario S), the MOSs for both fertility and development as well as for spontaneous abortions are below the acceptable level. For these scenarios there is concern for both fertility and development as well as for spontaneous abortions after repeated exposure: **conclusion (iii)**.

For manual cleaning (scenario T a), the use of adhesives (scenario T b), printing (scenario T c), and for mechanical coating (scenario T d), the MOSs for both fertility and development as well as for spontaneous abortions are below the acceptable level. For these scenarios there is concern for both fertility and development as well as for spontaneous abortions after repeated exposure: **conclusion (iii)**.

For mechanical cleaning (scenario T a), manual painting (scenario T d), and for spray painting (scenario T d), the MOSs are considered to be sufficiently high. Consequently, for these scenarios there is no concern for fertility, development, or spontaneous abortions after repeated exposure: **conclusion (ii)**.

4.1.3.2.10 Results of the risk characterisation for workers

Table 4.45 Conclusions of the risk characterisation for workers for different exposure scenarios and toxicological endpoints

X. Scenario x) sub-scenario	Toxicological endpoint										
	Acute toxicity (inhalation)	Acute toxicity (dermal)	Skin irritation	Eye irritation	Corrosivity	Repeated dose toxicity (inhalation)	Repeated dose toxicity (dermal)	Repeated dose toxicity (total systemic dose)	Mutagenicity	Carcinogenicity	Toxicity for reproduction
Q. Production and use as an intermediate											
a) production and use as an intermediate	**iii**	ii	ii	ii	ii	ii	Ii	ii	ii	ii	ii
b) use as an intermediate	**iii**	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
c) maintenance (regularly)	**iii**	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
R. Production of gasoline											
a) drumming, maintenance and tank cleaning											
b) operators at production sites											
c) transfer of gasoline											
d) attendants at service stations											
S. Production of products (transfer, filling & drumming)	**iii**	ii	ii	**iii**	ii	**iii**	ii	**iii**	ii	ii	**iii**
T. Use of toluene containing products											
a) manual cleaning	**iii**	ii	ii	**iii**	ii	**iii**	**iii** *	**iii**	ii	ii	**iii**
mechanical cleaning	**iii**	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
b) use of adhesives	**iii**	**iii**	ii	**iii**	ii	**iii**	**iii** *	**iii**	ii	ii	**iii**
c) printing	**iii**	ii	ii	**iii**	ii	**iii**	ii	**iii**	ii	ii	**iii**
d) painting: manual	**iii**	ii	ii	ii	ii	ii	ii	**iii** *	ii	ii	ii
spraying	**iii**	**iii**	ii	ii	ii	ii	**iii** *	**iii** *	ii	ii	ii
mechanical coating	**iii**	ii	ii	**iii**	ii	**iii**	ii	**iii**	ii	ii	**iii**

a) mg/m^3

* Conclusion (iii) arising from or (mainly from) dermal exposure. Toluene is classified as a skin irritant with Xi; R38 (Irritating to skin). Whether this provides adequate protection against dermal exposure and thus against effects arising from dermal exposure should be considered when the risk reduction strategy is addressed.

For the production of gasoline (scenario R) no formal risk characterisation has been performed, since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

As a NOAEC or a LOAEC cannot be determined for the organic brain syndrome this endpoint has not been evaluated quantitatively.

4.1.3.3 Consumers

The exposure conditions that are considered in this risk characterisation have all been described and discussed in Section 4.1.1.3. The exposure routes considered are inhalation and dermal exposure (where relevant), and the MOS for exposure by each route is considered separately.

In addition, for scenarios with conclusion (ii) for both exposure routes, the significance of the MOS for total systemic exposure is also considered. Exposure concentrations in mg/m^3 have

been converted to an estimated internal dose in mg/kg/day (see Appendix E). The significance of the MOS for total systemic exposure is not however considered where conclusion (iii) has been drawn for either or both of the exposure routes separately, as the possible concerns have already been identified.

If the MOS is below the minimal acceptable MOS, this leads to concern, while MOSs higher than the minimal acceptable MOS indicate no concern. The magnitude of the minimal acceptable MOS is discussed in the Section 4.1.3.1 General aspects (Factors influencing the "Margin Of Safety" (MOS)).

4.1.3.3.1 Acute toxicity

Inhalation

The risk for acute effects by inhalation will be characterised based on the human NOAEC of 150 mg/m^3 for headache, dizziness, feeling of intoxication, irritation and sleepiness and the human LOAEC of 281 mg/m^3 for impaired functional performance.

Table 4.46 MOSs and conclusions for acute effects by dermal exposure for different consumer exposure scenarios

X. Scenario x) sub-scenario	Headache, dizziness…			Functional performance		
	Exp.[a)]	MOS	Conclusion	Exp. [a)]	MOS	Conclusion
U1: Gluing	7.1	21	ii	7.1	40	ii
U2: Spray painting	1,000	0.15	**iii**	1,000	0.28	**iii**
U3A: Car maintenance (car polishing)	10	15	ii	10	28	ii
U3B: Car maintenance (cleaning hands)	Neg.	-	ii	Neg.	-	ii
U4: Carpet laying	195	0.76	**iii**	195	1.4	**iii**
U5: Filling gasoline at self- service stations	63			63		

a) mg/m^3

For spray painting (scenario U2) and for carpet laying (scenario U4) MOSs are below the acceptable level. For these scenarios, there is concern for acute toxicity by inhalation: **conclusion (iii)**.

For gluing (scenarios U1) and for car maintenance (scenarios U3A and U3B), there is no concern for acute toxicity by inhalation: **conclusion (ii)**.

No formal risk characterisation has been performed for filling gasoline at self service stations (scenario U5), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

Dermal

For the evaluation of risk for acute effects by dermal exposure the rabbit LD50 of 12,400 mg/kg will be used.

Table 4.47 MOSs and conclusions for acute effects by dermal exposure for different consumer exposure scenarios

X. Scenario x) sub-scenario	Dermal		
	Exposure [a)]	MOS	Conclusion
U1: Gluing	0.01	10^6	ii
U2: Spray painting	1.4	10^4	ii
U3A Car maintenance (car polishing)	0.01	10^6	ii
U3B: Car maintenance (cleaning hands)	9	10^3	ii
U4: Carpet laying	30	413	ii
U5: Filling gasoline at self-service stations	Neg.		

a) mg/kg bw/event

For all consumer exposure scenarios evaluated (scenarios U1 – U4) MOSs are considered sufficiently high. There is no concern for acute effects by dermal exposure for these scenarios: **conclusion (ii)**.

No formal risk characterisation has been performed for filling gasoline at self service stations (scenario U5), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

4.1.3.3.2 Irritation

Skin

Toluene has been shown to be irritating to the skin in rabbits, mice, and guinea pigs. However, the non-irritating concentration is not known, as the data are on the undiluted substance. It is therefore not possible to perform a quantitative risk characterisation for this endpoint.

Skin tumours have been observed in one long-term skin painting study with toluene, but not in other studies. There is uncertainty over the relationship of these tumours to toluene exposure, but the skin painting study resulted in significant long-term severe skin irritation.

As consumers using products containing toluene would be exposed only intermittently to the substance it is unlikely that long-term skin irritation would occur. There is no concern for skin irritation: **conclusion (ii)**.

No formal risk characterisation has been performed for filling gasoline at self service stations (scenario U5), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

Eye

For the risk characterisation of the eye irritation, the human NOAEC of 150 mg/m^3 will be used.

Table 4.48 MOSs and conclusions of the eye irritation for different consumer exposure scenarios

X. Scenario x) sub-scenario	Exposure [a)]	MOS	Conclusion
U1: Gluing	7.1	21	ii
U2: Spray painting	1,000	0.15	**iii**
U3A: Car maintenance (car polishing)	10	15	ii
U3B: Car maintenance (cleaning hands)	Neg.	-	ii
U4: Carpet laying	195	0.77	**iii**
U5: Filling gasoline at self-service stations	63		

a) mg/m^3

For Gluing (scenario U1) and for Car maintenance (scenarios U3A and U3B), MOSs are all considered to be sufficiently high. For these scenarios, there is no concern for eye irritation: **conclusion (ii)**.

For Spray painting (scenario U2) and for Carpet laying (scenario U4), MOSs are considered to be below the acceptable level. For these scenarios, there is concern for eye irritation: **conclusion (iii)**.

No formal risk characterisation has been performed for filling gasoline at self service stations (scenario U5), since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

4.1.3.3.3 Corrosivity

Toluene is not corrosive. There is no concern for corrosivity: **conclusion (ii)**.

4.1.3.3.4 Sensitisation

Toluene is not a sensitiser. There is no concern for sensitisation: **conclusion (ii)**.

4.1.3.3.5 Repeated dose toxicity

For scenarios U1 to U4 there is no concern for repeated dose toxicity by neither inhalation nor dermal exposure, as no repeated exposure is expected for these scenarios: **conclusion (ii**).

For scenario U5 (Filling gasoline at self-service stations) the frequency of exposure is expected to repeated, however no formal risk characterisation will be performed for this scenario, since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

4.1.3.3.6 Mutagenicity

Toluene is not considered to be mutagenic. Consequently there is no concern for this endpoint: **conclusion (ii)**.

4.1.3.3.7 Carcinogenicity

There is no indication of carcinogenicity via inhalation. There is no concern for carcinogenicity by inhalation: **conclusion (ii)**.

Skin tumours have been observed in one long-term skin painting study with toluene, but not in other studies. There is uncertainty over the relationship of these tumours to toluene exposure, but the skin painting study resulted in significant long-term severe skin irritation.

As consumers using products containing toluene would be exposed only intermittently to the substance there is no concern for carcinogenicity by dermal exposure: **conclusion (ii)**.

For scenario U5 (Filling gasoline at self-service stations) the frequency of exposure is expected to repeated, however no formal risk characterisation will be performed for this scenario, since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

4.1.3.3.8 Toxicity for reproduction

For scenario U1 to U4 the frequency of the exposure is assumed to be low (cf. Section 4.1.1.3). The exposure arising from these scenarios is therefore regarded as being short-term exposures. The available database on the toxicity for reproduction of toluene, however, arises from studies where exposure in all cases has been repeated. As there is no information on the relationship between the observed effects on reproduction and the duration of the exposure leading to these effects, it is not possible to exclude that even single exposures might produce effect on reproduction. However, a quantitative comparison of the estimated exposure levels for these particular scenarios and the NOAEC of 2,250 mg/m^3 for fertility and development (see **Table 4.49**) is considered to be a cautious approach.

Table 4.49 MOSs and conclusions of reproductive toxicity by inhalation for different consumer exposure scenarios

X. Scenario x) sub-scenario	Development	
	Exposure [a]	MOS
U1: Gluing	7.1	317
U2: Spray painting	1,000	2
U3A Car maintenance (car polishing)	10	225
U3B: Car maintenance (cleaning hands)	Neg.	-
U4: Carpet laying	195	12
U5: Filling gasoline at self-service stations	63	

a) mg/m^3

For scenarios U1, U3A and U3B (Gluing, Car maintenance (car polishing) and Car maintenance (cleaning hands)) the MOSs are considered to be sufficiently high. This should be seen in the light of the assumed low frequency of these exposure scenarios. There is therefore no concern for toxicity for reproduction for these scenarios: **conclusion (ii)**.

For scenarios U2 and U4 (Spray painting and Carpet laying) the MOSs are 2 and 12, respectively. These MOSs are considered low even though the approach is regarded to be

cautious. Hence, at present it cannot be excluded that these particular scenarios lead to concern for reproduction. However, the available information is insufficient, and further information on the relationship between the observed effects on reproduction and the duration of the exposure leading to these effects is needed: **conclusion (i)**.

The issue of reproductive effects and short-term exposure is not normally dealt with in the ESR. The present testing and risk assessment methodology do not cover this problem. The approach applied in this report is in accordance with the recommendation of the 26th Technical Meeting on Existing Chemicals.

There are no data on toxicity for reproduction by dermal or oral exposure. Consequently no risk characterisation will be carried out for the dermal exposure or for the total systemic dose arising from combined contribution by exposure via inhalation and dermal exposure.

For scenario U5 (Filling gasoline at self-service stations) the frequency of exposure is expected to repeated, however no formal risk characterisation will be performed for this scenario, since toluene exposures arising from the production and handling of gasoline are not formally a part of this risk assessment (cf. Section 0).

4.1.3.3.9 Results of the risk characterisation for consumers

Table 4.50 Conclusions of the risk characterisation for consumers

X. Scenario x) sub-scenario	Toxicological endpoint									
	Acute toxicity (inhalation)	Acute toxicity (dermal)	Skin irritation	Eye irritation	Corrosivity	Repeated dose toxicity (inhalation)	Repeated dose toxicity (dermal)	Mutagenicity	Carcinogenicity	Toxicity for reproduction
U1: Gluing	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
U2: Spray painting	**iii**	ii	ii	**iii**	ii	ii	ii	ii	ii	i
U3A Car maintenance (car polishing)	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
U3B: Car maintenance (cleaning hands)	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
U4: Carpet laying	**iii**	ii	ii	**iii**	ii	ii	ii	ii	ii	**i**
U5: Filling gasoline at self- service stations	-		-	-	-	-	-	-	-	-

4.1.3.4 Humans exposed via the environment

The maximum total local intake, taking account of exposure via air, drinking water and food is 2 mg/kg/day (Chemical industry, processing). Based on the subchronic NOAEL 625 mg/kg bw/d, the calculated margin of safety (MOS) for total exposure of humans via the environment is above 300 for all local and regional scenarios. This is considered to be sufficiently high to provide reassurance that adverse health will not occur, and there is thus no concern for effects of toluene in humans exposed indirectly to toluene itself via the environment: conclusion (ii).

As discussed in Section 3.1.4.3.2 it is known that toluene contributes to tropospheric VOC and contributes to the tropospheric formation of ozone and volatile air pollutants e.g. DNOC. 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 may or may not depending on locations within the EU lead to changes in ozone creation, i.e. depend on the occurrence of NOx, 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 toluene may differ substantially between different regions in the EU.

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

Based on a rough estimation utilising available information, the current risk assessment indicates that emission of toluene from the use and production of the commercial product toluene may be in the order of 3% 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 toluene. Even a simple evaluation of the photochemical ozone creation potential of the emission of isolated toluene is difficult to perform, when the emission pattern of individual NMVOCs is not available.

The current risk assessment does not cover non-isolated toluene. Thus evaluation of the possible effects of emission of toluene from motor vehicles is outside the scope of this risk assessment. However, on the basis of monitoring of NMVOCs in street air there is indication that non-isolated can contribute substantially (~ 30%) to the overall ozone formation due to NMVOCs.

Ozone exposure has been documented to give rise to severe effects in humans.

In 1995, 90% of the EU population (both urban and rural) experienced exceedence of the current EU threshold for health protection (110-240 $\mu g/m^3$, 8 hours on 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 ($\geq$240 $\mu g/m^3$) were recorded in Italy and Greece (WHO, 1999).

In 1999 the threshold for information of the public in the EU (180 $\mu g/m^3$, 1 hour on 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 and Camu, 1999). On average 27% of all monitoring stations in the EU did exceed the threshold. The number of days that the threshold was exceeded ranged from 2 days in Luxembourg to 68 days in Italy (out of 153 days in the reporting season).

The severity of exceedence of the EU threshold for health protection (110 $\mu g/m^3$, 8 hours on average) has been estimated by WHO (1999). The 1995 summer ozone incidence is estimated to have caused 1,500-3,700 deaths (0.1-0.2% of all deaths) and further 300-1,000 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 $\mu g/m^3$ level.” (WHO, 1999).

If these figures are used to estimate the impact of emissions from the production and use of the commercial product toluene through formation of ozone then this emission may have caused around 100 deaths in the summer of 1995 if a linear relationship exists between the emission of toluene, the emission of NMVOCs and the creation of ozone.

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

Based on this, risk reduction measures seem necessary to consider a **conclusion (iii)**. This conclusion applies in the context of the Regulation of Existing Substances to the contribution of the commercial product toluene to the formation of ozone and other harmful substances i.e. smog formation. Regarding which risk reduction measures would be 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 toluene to the complex issue of ozone and smog formation and the resulting impact on air quality.

4.1.3.5 Combined exposure

Combining local environmental exposure and occupational exposure will not influence the characterisation of the risks associated with environmental exposure alone.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Risk assessment concerning the properties listed in Annex IIA of Regulation 1488/94.

4.2.1 Risk characterisation (physico-chemical properties)

Regarding physico-chemical properties, flammability is the only property of concern for toluene since it is a volatile liquid which is highly flammable.

In production and in occupational use, the flammability risk is not of concern provided adequate safety measures are taken. Information is provided on the label and in the safety data sheet.

Concerning use by consumers, information about the flammability risk and precautionary measures must be given by a label on the containers. In the EU, symbol, risk phrases and safety phrases are used for the labelling of highly flammable substances and preparations (mixtures), cf. Section 1 - Classification.

Conclusion

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

5 RESULTS

5.1 ENVIRONMENT

Toluene is a high production volume substance. In 1995, the production volume of toluene in the EU was 2,600 Ktonnes. Import and export volumes were imprecise but the EU consumption is estimated to be approximately 2,750 Ktonnes (1995 values). Toluene occurs naturally and is present in crude oil. Most of the refinery streams containing toluene are used as a base or blending feedstock to produce motor gasoline. The commercial toluene is isolated from the refinery streams and is used as an intermediate in closed systems to manufacture other chemicals, as a solvent carrier in paints, thinners, adhesives, inks and pharmaceutical products and as an additive in cosmetic preparations. Toluene is used in a large number of industrial branches and consumer products.

Toluene may be released to the environment when substances containing toluene or preparations thereof are produced, distributed and handled. Besides the releases from use, distribution and handling of commercial toluene are the releases from natural sources (volcanos, forest fires, etc.) and from the combustion of fuels. As these latter sources may well be significantly higher than releases from manufactured toluene, they may be the main source for background concentrations and should be considered.

Toluene is estimated to be stable to hydrolysis and photodegradation in surface water. The photochemical oxidative degradation is measured to have a half-life of 1-2 days. Toluene is readily biodegradable, but simulation types of data suggest a decreased biodegradation at environmentally realistic low concentration in surface water: The half-life in sewage treatment plants (STP) is estimated to be 0.0289 days (rate constant of 1 $hour^{-1}$and in surface water around 30 days. Only scarce data are available for degradation in soil, and the half-life is estimated to be 90 days under aerobic conditions according to "the realistic worst-case" concept. Toluene has a low-adsorption capacity with an estimated Koc of 177 indicating a moderate to high mobility potential. The log Kow 2.65 indicates a low bioaccumulation potential, which was confirmed in tests where BCF in two fish species were 13 and 90, respectively.

Toluene has been tested in a wide variety of aquatic species. Due to the nature of the substance (high volatility) only a few of the studies were considered valid. The acute toxicity to fish ranges from an LC50 of 5.4 for Pink salmon to 26 mg/l for Fathead minnow. The lowest valid acute toxicity for *Daphnia magna* was 3.78 mg/l. Other crustaceans ranged from 3.5 mg/l for *Crangon franciscorum* to 33 mg/l for *Artemia salina*. For algae, the acute toxic EC50 was not available in valid tests but in two species (*Selenastrum capricornutum* and *Skeletonema costatum*), the NOECs were 10 mg/l. The long-term toxicity NOEC for fish ranged from 1.4 mg/l for *Oncorhynchus kisutch* to 4 mg/l for *Pimephales promelas*. The chronic NOEC for *Daphnia magna* ranged from 0.53 mg/l to 1.0 mg/l and for *Ceriodaphnia dubia* 0.74 mg/l. For the terrestrial compartment, the earthworm acute EC50 was >150 but <280 mg/kg soil, NOEC values for mortality and cocoon production was ≤150 and <280 mg/kg, respectively, whereas a NOEC based on visual inspection was between 15 and 50 mg/kg soil. For plants, a yield decrease was observed in *Lactuca sativa* at 1,000 mg/kg. For soil microorganisms, NOEC for nitrification was <26 mg/kg soil dw. For microorganisms in the STP, EC50 for respiration was between 110 and 292 mg/l whereas EC50 for nitrification was 84 mg/l. In regard to toxicity to green plants exposed via the air a NOEC of 60 mg/m^3 after 14 days of exposure have been observed.

An assessment factor of 10 was used to calculate a predicted no effect concentration (PNEC) for toluene in the aqueous environment since long-term data were present for fish, crustacea and algae: $PNEC_{aqua}$ 0.074 mg/l. For STP the most sensitive microbial process (nitrification) along with an assessment factor of 10 were used to derive the $PNEC_{STP}$= 8.4 mg/l. For the terrestrial environment, an assessment factor of 50 was used because availability of two long-term tests on soil organisms: $PNEC_{soil}$ 0.3 mg/kg. Toluene may after reactions catalysed by light contribute to formation of ozone and other air pollutants in near surface atmosphere. Green plants, animals and humans seem to be equally sensitive to the toxic effects of ozone.

Aquatic environment and sewage 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

The conclusion applies in relation to releases from two production sites, one combined production and processing site and one off site production site. A risk is also identified for a number of downstream processing sites according to generic assessments for the following use categories:

- industry use as an intermediate and as a basic chemical,
- mineral oil and fuel formulation,
- formulation of polymers,
- formulation of paints,
- textile processing.

Atmosphere

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

The conclusion applies in the context of the Council Regulation (EEC) 793/93 of Existing Substances to the contribution of the commercial product toluene 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 be the most appropriate, it is recommended that under the relevant air quality Directives a specific in-depth evaluation is performed. Such an evaluation should focus on the contribution of isolated as well as non-isolated toluene to the complex issue of ozone and smog formation and the resulting impact on air quality.

Terrestrial compartment

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

The conclusion applies to release via sludge application to soil from one processing site and to a range of downstream processing sites according to generic assessments for the following use categories:

- industry use as an intermediate and as a basic chemical,
- mineral oil and fuel formulation,
- formulation of polymers,
- formulation of paints,
- textile processing.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 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 acute toxicity as a consequence of dermal exposure arising from spraying painting or the use of adhesives,
- concerns for acute toxicity (headache, dizziness, feeling of intoxication, sleepiness and impaired functional performance) as a consequence of inhalation exposure arising from production and use as an intermediate, production of products containing the substance and use of products containing the substance,
- concerns for eye irritation as a consequence of exposure arising from production of products containing the substance and use of products containing the substance in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating),
- concerns for general systemic toxicity as a consequence of inhalation exposure arising from production of products containing the substance and use of products containing the substance in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating),
- concerns for general systemic toxicity as a consequence of dermal exposure arising from use of products containing the substance in the sectors of manual cleaning, use of adhesives and spray painting,
- concerns for general systemic toxicity as a consequence of the combined dermal and inhalation exposure arising the use of products containing the substance in the sectors of manual painting,
- concerns for specific organ toxicity (auditory system toxicity) as a consequence of inhalation exposure arising from production of products containing the substance and use of products containing the substance in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating),
- concerns for fertility and developmental effects and spontaneous abortions as a consequence of inhalation exposure arising from production of products and use of toluene containing products in the sectors of manual cleaning, use of adhesives, printing and painting (mechanical coating).

Risk reduction measures should therefore be considered that will ensure a reduction in the levels of toluene found in the workplace during the production and use of toluene and during the production and use of toluene containing products**.**

5.2.1.2 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 for acute toxicity (headache, dizziness, feeling of intoxication, sleepiness and impaired functional performance) and eye irritation as a consequence of inhalation exposure or eye exposure to vapours arising from spray painting and carpet laying.

The conclusion is based on the estimated exposure during use of toluene containing glues and paints. Risk reduction measures should therefore be considered that will ensure a reduction in the levels of toluene found when using consumer products containing toluene.

and

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

This conclusion is reached because of:

- concerns for effects on reproduction as a consequence of inhalation exposure.

The information and/or test requirement is:

- information on the relationship between the observed effects on reproduction and the duration of the exposure leading to these effects.

The need to actually obtain the information allowing the performance of the risk characterisation for this endpoint, will be considered when the recommended risk reduction strategy is published in the Official Journal.

Hence, any formal request for further information should be seen in the light of other possible risk reduction measures for the consumer scenarios based on the concerns for acute toxicity by inhalation and eye irritation identified for the Scenarios U2 (spray painting) and U4 (carpet laying).

5.2.1.3 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.

The conclusion applies in the context of the Council Regulation (EEC) 793/93 of Existing Substances to the contribution of the commercial product toluene to the formation of ozone and other harmful substances i.e. smog formation. Regarding which risk reduction measures would 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 toluene to the complex issue of ozone and smog formation and the resulting impact on air quality.

5.2.2 Human health (risks from physico-chemical properties)

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

6 REFERENCES

Aarhus (1998). Miljøfremmede stoffer i Århus Amt - fase 2 og 3, 1997-1998. Århus amt, Natur- og Miljøkontoret. Danmark.

Abou-El-Makarem MM, Millburn P, Smith RL, Williams RT (1967). Biliary excretion of foreign compounds. Benzene and its derivatives in the rat. Biochem. J. **105**, 1269-1274.

Adema DMM (1991). The Acute Aquatic Toxicity of Alkylbenzenes. Organisation for Applied Scientific Research (TNO), TNO Report R91/198, Delft, The Netherlands.

ACGIH (1997). American Conference Governmental Industrial Hygienist (ACGIH). Cincinnati, OH.

ACGIH (1999). Guide to Occupational Exposure Values - 1999. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

Al-Rekabi H, Sojak L, Kminiak M (1996). Purgeable aromatic hydrocarbons in water and sediments from the river Morava catchment (Slovakia). Bull. Environ. Contam. Toxicol. **56**, 90-97.

Andersen I, Lundqvist GR, Mølhave L, Pedersen OF, Proctor DF, Væth M, Wyon DP (1983). Human response to controlled levels of toluene in six-hour exposures. Scand. J. Work. Environ. Health. **9**, 405-418.

Andersson K, Nilsen OG, Toftgard R, Eneroth P, Gustafsson J-A, Battistini N, Agnati LF (1983). Increased amine turnover in several hypothalamic noradrenaline nerve terminal systems and changes in prolactin secretion in the male rat by exposure to various concentrations of toluene. Neurotoxicology **4**, 43-56.

Andersson-Sköld Y, Grennfelt P, Pleijel K (1992). Photochemical ozone creation potentials: A study of different concepts. J. Air Waste Manage. Assoc. **42**(9), 1152-1158.

Anon. Fax from Exxon Chemical 1996-11-15.

Antti-Poika M, Juntunen J, Matikainen E, Suoranta H, Hänninen H, Seppäläinen AM, Liira J (1985). Occupational exposure to toluene: neurotoxic effects with special emphasis on drinking habits. Int. Arch. Occup. Environ. Health **56**, 31-40.

AOPWIN (1995). Atmospheric oxidation Program for Microsoft Windows 3.1 (AOPWIN) prepared by Meylan W and Howard P, Syracuse Research Corporation, Merrill Lane, Syracuse, NY.

APA TF (1996). A Report on the Assessment of Releases and Exposures of Toluene for Environmental Risk Assessment. CEFIC Aromatic Producers Association/Toluene Risk Assessment Task Force, draft 21 Nov. 1996 prepared by KH den Haan.

APA (1996). Toluene Risk Assessment. Review of Workplace Personal Exposure Data. Prepared by Chris Money, Exxon Chemical.

APA (1998). Letter from Aromatic Producers Association of 1998-12-22.

APA (1998b). Letter of 1998-08-24 from Chris Money.

APA (1998c). E-mail from Magne Borge, Exxon Chemical. 1998-09-14.

APA, CEPE, EITUG (1999). A Paper concerning Production and Uses Figures for Toluene. Aromatic Producers Association (APA), European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE) and European Industrial Toluene Users group (EITUG).

APA (2000). Revised information regarding production and processing as Excel spreadsheet.

API (1978). Teratology Study in rats. Toluene. American Petroleum Institute (API), API Med. Res. Publ. 26-60019. Washington.

API (1985). Two-Generation Inhalation Reproduction/Fertility Study on Petroleum derived Hydrocarbon with Toluene. American Petroleum Institute (API), API Med Res Publ. 32-32854, Washington.

API (1988). Evaluation of Toluene in the *in vitro* Assay for Chemical Teratogenic Potential: I. Inhibition of Proteoglycan Synthesis. American Petroleum Institute (API), API HESD Publ. No. none.

API (1990a). Mouse Ovarian Tumor (MOT) Cell Attachment Assay with Toluene. American Petroleum Institute (API), API HESD Publ. No. 37.31150.

API (1990b). Human Embryonic Palatal Mesenchyme (HEPM) Cell Growth Inhibition Assay S-9 Mediated Assay with Toluene. American Petroleum Institute (API), API HESD Publ No. [none].

API (1990c). Human Embryonic Palatal Mesenchyme (HEPM) Cell Growth Inhibition Assay with Toluene. American Petroleum Institute (API), API HESD Publ. No. [none].

API (1991). Gasoline Vapour Exposure Assessment at Service Stations. American Petroleum Institute (API), API Med. Res. Publ. 40-31151, Washington DC.

Aranyi C, O'Shea WJ, Sherwood RL, Graham JA, Miller FJ (1985). Effects of toluene inhalation on pulmonary host defenses of mice. Toxicol. Lett. **25**, 103-110.

Arbeitsstoffe. MAK- und BAT-Werte-Liste (1999). Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: Wiley-VCH, **71** (Mitteilung 35).

Arbejdstilsynet (1996). Exposure Limit Value for Substances and Materials. Arbejdstilsynet, Instruction No. 3.1.0.2, Copenhagen, Denmark.

Arendt G, Haag F, Pruggmayer D (1977). Mainwasseruntersuchungen. Bericht zum Auftrag 198-13. Batelle Institute, Frankfurt am Main.

Arlien-Søborg P (1992). Solvent Neurotoxicity. CRC Press, Boca Raton, Florida.

Arnold GL, Kirby RS, Langendoerfer S, Wilkins-Haug L (1994). Toluene embryopathy: Clinical delineation and developmental follow-up. Pediatrics, 93, 216-20.

ARW (1984). Organische Spurenstoffe im Rhein und bei der Trinkwasseraufbereitung. Teil 5. **In**: 41. Bericht der Arbeitsgemeinschaft Rhein-Wasserwerke E.V., 177-190.

ARW (1985). 42. Bericht der Arbeitsgemeinschaft Rhein-Wasserwerke E.V., 35-37, 115-119.

ARW (1986). 43. Bericht der Arbeitsgemeinschaft Rhein-Wasserwerke E.V., 34-37, 77-90.

Askergren A (1982). Organic solvents and kidney function. Adv. Mod. Environ. Toxicol. **2**, 157-172.

Atkinson R (1990). Gas-phase tropospheric chemistry of organic compounds: A review. Atmospheric Environment **24(**1), 1-41.

Ballesta PP, Saeger E De (1995). Benzene, Toluene and Xylene Measurements in the Vicinity of Petrol Stations. European Commission, Joint Research Center, Environment Institute, EUR 16309 EN, Ispra, Italy.

Ballesta PP, Payrissat M, Saeger E De, Cancelinha J, Galata R (1997). BTX Monitoring Campaign in the City of Catania. European Commission, Joint Research Center, Environment Institute, EUR 17272 EN, Ispra, Italy.

Ballesta PP, Connolly R, Boix A, Cancelinha J, Cao N, Baldan A, Payrissat M (1998). Benzene, Toluene and Xylene Monitoring Campaign in Bologna. European Commission, Joint Research Center, Environment Institute, EUR 18093 EN, Ispra, Italy.

Banerjee S (1984). Solubility of organic mixtures in water. Environ. Sci. Technol. **18**, 587-591.

BASF (1980). Bestimmung der akuten Inhalationstoxizität LC_{50} von Toluol min. 99.5% (Merck AG) als Dampf bei 4stundiger Exposition an Sprague-Dawley-Ratten.

BASF (1987). Dampf-Flüssig-Phasengleichgewicht, Toluol. Analytical Report BRU 87.099. May 15.

BASF (1989a). Pränatale Toxizität von Toluol in Kaninchen nach inhalativer aufnahme. Projekt-Nr. 90R0105/8611.

BASF (1989b). Pränatale Toxizität von Toluol in Kaninchen nach inhalativer aufnahme. Projekt-Nr. 90R0105/86064.

BauA (2000). Proposal: Assessing Dermal Exposure under Consideration of the Evaporation of Highly Volatile Substances.

Bauchinger M, Schmid E, Dresp J, Kolin-gerresheim J, Hauf R, Suhr E (1982). Chromosome changes in lymphocytes after occupational exposure to toluene. Mutat. Res. **102**, 439-445.

Beije B (1993). Dieselavgaser. Arbete och Hälsa 34. National Institute of Occupational Health, Sweden.

Belgium comments on exposure and risk assessment on draft of 18 September 1998. COM.ECB4/032/98 add.6.

Benignus VA (1981). Health effects of toluene: A review. Neurotoxicol. **2**, 567-588.

Benignus VA, Muller KE, Barton CN, Bittikofer JA (1981). Toluene levels in blood and brain of rats during and after respiratory exposure. Toxicol. Appl. Pharamacol. **61**, 326-334.

Benignus VA, Muller KE, Barton CN, Bittikofer JA (1984). Toluene blood level following subcutaneous injection of toluene in the rat. Environ. Res. **33**, 441-453.

Bennett RH, Forman HR (1980). Hypokalemic periodic paralysis in chronic toluene exposure. Arch. Neurol. **37**, 673.

Benville PE, Korn S (1977). The acute toxicity of six monocyclic aromatic crude oil components to striped bass (*Morone saxatilis*) and bay shrimp (*Crangon franciscorum*). Calif. Fish Game **63**(4), 204-209.

Bergman K (1979). Whole-body autoradiography and allied tracer techniques in distribution and elimination studies of some organic solvents. Scand. J. Work. Environ. Health. **5**, suppl 1, 1-263.

Bergman K (1983). Application and results of whole-body autoradiography in distribution studies of organic solvents. CRC Crit. Rev. Toxicol. **12**, 59-118.

Bertorelli V, Derwent R (1995). Air quality A to Z: a directory of air quality data for the United Kingdom in the 1990s. Bracknell: Atmospheric Process Research Branch, Meteorological Office.

BG Comments on Risk Assessment "Toluene" (1998). Letter from Berufsgenossenschaft Druck und Papierverarbeitung 1998-11-18. The Netherlands.

BGAA (1998). Berufsgenossenschaftlicher Arbeitskreis Altstoffe. Toluene, Occupational Exposure. Description of Exposure No. 40 (V.7.0415). Letter of 1998-03-27.

Bio/dynamics Inc. (1980). A 26 Week Inhalation Toxicity Study of Toluene in the Rat. Project No. 78-7234.

Black JA, Birge WJ, McDonnell WE, Westerman AG, Ramey BA, Bruser DM (1982). The Aquatic Toxicity of Organic Compounds to Embryo-larval Stages of Fish and Amphibians. Water Resources Research Institute, University of Kentucky. Research Report No. 133. PB82-224601, NTIS, US Department of Commerce.

Blum DJW, Speece RE (1991). A database of chemical toxicity to environmental bacteria and its use in interspecies comparisons and correlations. Res. J. Water Pollut. Contr. Fed. **63**(3), 198-207.

Bobra AM, Shiu Wy, Mackay D (1983). A predictive correlation for the acute toxicity of hydrocarbons and chlorinated hydrocarbons to the water flea (*Daphnia magna*). Chemosphere **12**(9), 1121-1129.

Bonnet P, Morele Y, Raoult G, Zissu D, Gradiski D (1982). Détermination de la concentration léthale$_{50}$ des principaux hydrocarbures aromatiques chez le rat. Arch. Mal. Prof. **34**, 261-65.

Bos RP, Brouns RME, Doorn R van, Theuws JLG, Henderson PT (1981). Non-mutagenicity of toluene, o-, m- and p-xylene, o-methylbenzylalcohol and o-methylbenzylsulfate in the Ames assay. Mutat. Res. **88**, 273-279.

Boor JW, Hurtig HI (1977). Persistent cerebellar ataxia after exposure to toluene. Ann. Neurol. **2**, 440-442.

Boey KW, Foo SC, Jeyaratnam J (1997). Effects of occupational exposure to toluene: a neuropsychological study on workers in Singapore. Ann. Acad. Med. Singapore **26**, 184-187 (abstract).

Bogadi-Sare A, Brumen V, Turk R, Karacic V, Zavalic M (1997). Genotoxic effects in workers exposed to benzene: with special reference to exposure biomarkers and confounding factors. Ind. Health **35**, 367-73

Bonnet P, Raoult G, Gradiski D (1979). Concentration léthales 50 des principaux hydrocarbures aromatiques. Arch. Mal. Prof. **40**, 805-810.

Bonnet P, Morele Y, Raoult G, Zissu D, Gradiski D (1982). Détermination de la concentration léthale$_{50}$ des principaux hydrocarbures aromatiques chez le rat. Arch. Mal. Prof. **34**, 261-65.

Bos RP, Brouns RME, Doorn R van, Theuws JLG, Henderson PT (1981). Non-mutagenicity of toluene, o-, m- and p-xylene, o-methylbenzylalcohol and o-methylbenzylsulfate in the Ames assay. Mutat. Res. **88**, 273-279.

Boor JW, Hurtig HI (1977). Persistent cerebellar ataxia after exposure to toluene. Ann. Neurol. **2**, 440-442.

Braier L (1953). Traitement des leucoses chroniques par le benzene et ses homologues. Le role des donneurs de méthyles. Le Sang **24**, 603-612.

Brandt-Lassen R, Lund SP, Jepsen GB (2000). Rats exposed to toluene and noise may develop loss of auditory sensitivity due to synergistic interaction. Noise and Health **3**(9), 33-44.

Bremmer HJ, en Veen van MP (1999). Factsheet Verf. ten behoeve van de schatting van de risico's voor de consument. National Institute of Public Health and Environmental Protection (RIVM), RIVM Report 612810010, Bilthoven, The Netherlands.

Bremmer HJ, en Veen van MP (1999). Factsheet Algemeen, randvoorwaarden en betrouwbaarheid, ventilatie, kamergrootte, lichaamsoppervlak. National Institute of Public Health and Environmental Protection (RIVM), RIVM Report 612810 009, Bilthoven, The Netherlands.

Brenniman G, Hartung R, Weber WJ (1976). A continuous flow bioassay method to evaluate the effects of outboard motor exhausts and selected aromatic toxicants on fish. Water Res. **19**, 165-169.

Bridie AL, Wolff CJM, Winter M (1979). BOD and COD of some petrochemicals. Water Res. **13**, 627-630.

Bringmann G, Kühn R (1980). Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. **14**, 231-241.

Broddle WD, Dennis MW, Kitchen DN, Vernot EH (1996). Chronic dermal studies of petroleum streams in mice. Fundamental and Applied Toxicology **30**, 47-54.

Browning E (1965). Toxicity and Metabolism of Industrial Solvents. Elsevier Publ. Co., Amsterdam, 6-76.

Brozovsky M, Winkler EG (1965). Glue sniffing in children and adolescents. New York State J. Med. **65**, 1984-1989.

Brugnone F, Perbellini L, Apostoli P, Locatelli M, Mariotto P (1983). Decline of blood and alveolar toluene concentration following two accidental human poisonings. Int. Arch. Occup. Environ. Health **53**, 157-165.

Brusick DJ, Mazursky S (1981). Mutagenicity Evaluation of Toluene. Mouse Dominant Lethal Assay. Litton Bionetics Inc., Kensington, Maryland.

Buccafusco RJ, Ells Sj, LeBlanc GA (1981). Acute toxicity of priority pollutants to Bluegill (*Lepomis macrochirus*). Bull. Environ. Contam. Toxicol. **26**, 446-452.

Buringh E, Lanting R (1991). Exposure variability in the workplace: Its implication for the assessment of compliance. Am. Ind. Hyg. Assoc. J. **52**(1), 6-13.

Bælum J, Andersen I, Lundqvist GR, Mølhave L, Pedersen OF, Væth M, Wyon DP (1985). Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand. J. Work. Environ. Health **11**, 271-280.

Bælum J, Lundqvist GR, Mølhave L, Andersen NT (1990). Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health **62**, 65-71.

Caldwell RS, Calderone EM, Mallon WH (1976). Effects of a seawater-soluble fraction of Cook inlet crude oil and its major aromatic components on larval stages of the Dungeness Crab, *Cancer magister dana*. **In**: Fate and Effects of Petroleum Hydrocarbons in Marine Organisms and Ecosystems. Pergamon Press, New York, 210-220.

Cameron GR, Paterson JLH, De Saram GSW, Thomas JC (1938). The toxicity of some methyl derivatives of benzene with special reference to pseudocumene and heavy coal tar naphtha. J. Path. Bact. **46**, 95-107.

Campo P, Lataye R, Cossec B, Placidi V (1997). Toluene-induced hearing loss: A mid-frequncy location of the cochlear lesions. Neurotoxicol. Teratol. **19**, 129-140.

Carlsson A (1982). Exposure to toluene. Uptake, distribution and elimination in man. Scand. J. Work. Environ. Health **8**, 43-55.

Carlsson A, Lindqvist T (1977). Exposure of animals and man to toluene. Scand. J. Work. Environ. Health **3**, 135-143.

Carlsson A, Ljungquist E (1982). Exposure to toluene. Concentration in subcutaneous adipose tissue. Scand. J. Work Environ. Health **8**, 56-62.

Carpenter CP, Geary DL Jr, Myers RC, Nachreiner DJ, Sullivan LJ, King JM (1976). Petroleum hydrocarbon toxicity studies. XIII. Animal and human response to vapors of toluene concentrate. Toxicol. Appl. Pharmacol. **36**, 473-490.

Casto BC (1981). Detection of chemical carcinogens and mutagens in hamster cells by enhancement of adenovirus transformation. **In**: Mishra N, Dunkel V, Mehlman I (eds.) Advances in Modern Environmental Toxicology. Vol. 1, Princeton, NJ, Senate Press, 241-271.

CEPE (1999). Letter of 1999-02-26.

Chang MJW, Hsu KH, Chen YC, Hsieh LL, Luo JJ (1996). Biological monitoring of urinary hippuric acid in a Taiwanese semiconductor company. Abstracts of the International Symposium on Biological Monitoring in Occupational and Environmental Health. Sept 11-13, Espoo, Helsinki. Finnish Institute of Occupational Health.

Cherry N, Johnston JD, Venables H, Waldron HA, Buck L, MacKay CJ (1983). The effects of toluene and alcohol on psychomotor performance. Ergonomics **26**, 1081-1087.

Cherry N, Venables H, Waldron HA (1984). British studies on the neuropsychological effects of solvent exposure. Scand. J. Work. Environ. Health **10**, suppl 1, 10-13.

Christ RA (1996). Die Wirkung von organischen Substanzen (Lösemitteln) in der Gasphase auf höhere Pflanzen. Gefahrstoffe - Reinhaltung der Luft **56**, 345-350.

Christensen CS, Skov H, Palmgren F (1999). C_5 – C_8 non-methane hydrocarbon measurements in Copenhagen: concentrations, sources and emission estimates. Sci. Total. Env. **236**, 163-171.

Clayton Environmental Consultants, Inc. (1989). Health Effects of gasoline refueling vapors and measured exposures at service stations. **In:** Page and Melmann, Toxicol. Ind. Health **5**, 869-890.

COLCHIC (1998). Retrieval of data from the National French Occupational Exposure Database.

Company A (1999). (company name confidential). Information from Industry.

CONCAWE (1995). Exposure to Hydrocarbon Vapours during Production and Handling of Motor Gasoline. German Society for Petroleum and Coal Science and Technology, DGMK Project 477.

CONCAWE (1997). Exposure Profile: Gasoline. Concawe Report No. 97/52. Brussels.

CONCAWE (2000). Comments on Exposure Assessment in the Toluene Risk Assessment Report (draft of 11 February 2000). 30 March 2000.

Connor TH, Theiss JC, Hanna HA, Monteith DK, Matney TS (1985). Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol. Lett. **25**, 33-40.

Currier HB (1951). Herbicidal properties of benzene and certain methyl derivates. Hilgardia **20**, 383-406.

Courtney KD, Andrews JE, Springer J, Ménache M, Williams T, Dalley L, Graham JA (1986). A perinatal study of toluene in CD-1 mice. Fundam. Appl. Toxicol. **6**, 145-154.

CSTE (1993). The setting of water quality objectives for chemicals dangerous to the aquatic environment - List 1 chemicals - in accordance with European Council Directive 76/464/EEC. EEC Scientific Advisory Committee to Examine the Toxicity and Ecotoxicity of Chemical Compounds (Ecotoxicology Section), CSTE 93/03 XI - Final, December 1993.

CSTEE (1999). 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. http://europa.eu.int/comm/dg24/health/sc/sct/out38_en.html.

Danish EPA (1995). Forekomst og effekter af miljøfremmede organiske stoffer i spildevandsslam (Presence and effects of unnatural organic substances in wastewater sludge) (In Danish). Arbejdsrapport Nr.15, Miljøstyrelsen. Working report from the Danish Environmental Protection Agency, Copenhagen.

Danish Product Register (1999). Personal Communication with Poul E Andersen.

Da-Silva VA, Malheiros LR, Bueno FMR (1990). Effects of toluene exposure during gestation on neurobehavioral development of rats and hamsters. Brazilian J. Med. Biol. Res. **23**, 533-537.

Da-Silva VA, Malheiros LR, Figueiredo LFH, Sá-Rego MM, Paumgarten FJR (1991). Neurobehavioral development of rats exposed to toluene through maternal milk. Brazilian J. Med. Biol. Res. **24**, 1239-1243.

Davis JW, Madsen S (1996). Factors affecting the biodegradation of toluene in soil. Chemosphere **33**(1), 107-130.

De Ceaurriz JC, Micillino JC, Bonnet P, Guenier JP (1981). Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. **9**, 137-143.

De Witt (1999). Toluene and Xylenes Annual. De Witt and Company Inc. Houston, Texas, 143-181.

Demes P, Willer H, Zupanic M, van Thriel C, Golka K, Seeber A (1998). Untersuchung des Hörvermögens an 332 Beschäftigen von Druckereien. Poster presented at 38. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltsmedizin, Wiesbaden.

Derwent (1998). Atmospheric Environment **32**, 2429-2441.

De Leeuw F, Sluyter R, van Zantvoort E (1996). Air Pollution by Ozone in the European Union. Air Quality, European Environment Agency, Topic Report 29, Copenhagen.

DETR (1998). Water Framework Directive: COMMPS Procedure. Paul Hoey, Dept. of the Environmment, Transport and the Regions, Water Quality Div., London, 25 August 1998.

Devathasan G, Wan SH, Low D, Wong PK, Teoh PC (1984). Complications of chronic glue (toluene) abuse in adolescents. Aust. NZ. J. Med. **14**, 39-43.

Devlin EW, Brammer JD, Puyear RL (1982). Acute toxicity of toluene to three age groups of Fathead minnows (*Pimephales promelas*). Bull. Environm. Contam. Toxicol. **29**, 12-17.

DGMK (1994). Composition of gasolines from German refineries. Deutsche Gesellschaft für Mineralölwissenschaft und Kohlechemie, DGMK Project 502. German Society for Petroleum and Coal Science and Technology, Hamburg.

Dietzel B (1994). Zusammensetzung von Ottokraftstoffen aus deutschen Raffinerien. Deutsche Gesellschaft für Mineralölwissenschaft und Kohlechemie, DGMK Projekt 502. German Society for Petroleum and Coal Science and Technology, Hamburg.

DIPPR (1993). Data Compilation of Pure Compound Properties, Version 6.0. US Department of Commerce. National Institute of Standard and Technology, Gaithersburg.

Donner M, Husgafvel-Pursiainen K, Mäki-Paakkanen J, Sorsa M, Vainio H (1981). Genetic effects of *in vivo* exposure to toluene. Mutat. Res. **85**, 293-294.

Doucette WJ, Andren AW (1988). Estimation of octanol/water partition coefficients: Evaluation of six methods for highly hydrophobic aromatic hydrocarbons. Chemosphere **17**, 345-359.

Dueck TA (1996). Amsterdam Arena. Onderzoek naar vluchtige organische verbindingen (VOCs). AB.DLO Nota 38, Wageningen, The Netherlands.

Dunovant VS, Clark CS, Que Hee SS,Hertzberg VS, Trapp JH (1986). Volatile organics in the wastewater and airspaces of three wastewater treatment plants. J. Water Pollut. Control Fed. **58**(9), 886-895.

Dyreborg S, Arvin E, Broholm K (1996). The influence of creosote compounds on the aerobic degradation of toluene. Biodegradation **6**, 97-107.

Døssing M, Bælum J, Hansen SH, Lundqvist GR (1984). Effect of ethanol, cimetidine and propranolol on toluene metabolism in man. Int. Arch. Occup. Environ. Health **54**, 309-315.

Eadsforth CV, Moser P (1983). Assessment of reverse-phase chromatographic methods for determining partition coefficients. Chemosphere **12**, 1459-1475.

EC DGXI (1996). Air quality report of the Auto Oil Programme. Report of Subgroup 2. European Commission, Brussels.

EC DG XI (1998). Economic evaluation of air quality targets for tropospheric ozone. Part A: Methodology and databases. European Commission, Final Report November 1998.

ECDIN (1993). Environmental Chemicals Data and Information Network database (CD-ROM). European Commission, Joint Research Center, Environmental Institute, Ispra, Italy.

Echeverria D, Fine L, Langolf G, Schork A, Sampaio C (1989). Acute neurobehavioural effects of toluene. Br. J. Ind. Med. **46**, 483-495.

Edelfors S, Hougaard KS, Hass U (1999). Exposure to toluene during brain development: Effects on brain weight and synaptosomes. Abstract for European Teratology Society meeting Sep 99.

EEA (1999). Joint EMEP/CORINAIR Atmospheric Emission Inventory Guidebook. Second Edition. European Environment Agency, Copenhagen.

EEA (2000). Trends in Emissions of Ozone Precursors (CLRTAP). European Environment Agency Data Services. Http://warehouse.eea.eu.int.

Eerens HC, Sliggers CJ, Hout KD, van den (1993). The CAR model. The Dutch method to determine city street air quality. Atmos. Environ. **278**(4), 389-399.

Egle JL, Gochberg BJ (1976). Respiratory retention of inhaled toluene and benzene in the dog. J. Toxicol. Environ. Health **1**, 531-538.

EITUG (1998). Usage of toluene as a solvent in Europe. European Industrial Toluene User Group. Draft, July 1998.

Eitzer BD (1995). Emissions of volatile organic chemicals from municipal solid waste composting facilities. Environ. Sci. Technol. **29**, 896-902.

El Masry AM, Smith JN, Williams RT (1956). Studies in detoxication. 69. The metabolism of alkyl-benzenes: n-propyl-benzene and n-butyl-benzene with further observations on ethyl-benzene. Biochem. J. **64**, 50-56.

EN 689 (1995). Workplace Atmospheres-Guidance for the Assessment of Exposure by Inhalation to Chemical Agents for Comparison with Limit Values and Measurement Strategy. European Committee for Standardization (CEN), Brussels.

EPA (2000). Response to German proposal: "Assessing dermal exposure under consideration of the evaporation of highly volatile substances."

EPIWIN (1995). Estimation programs interface for Microsoft Windows 3.1. Syracuse Research Corporation, Syracuse, NY.

Esmen NA, Hammad Y (1977). Log-normality of environmental sampling data. J. Environ. Sci. Health, **A12**(1&2), 29-41.

EUROPIA/ACEA (1996). European Programme on Emissions, Fuels, and Engine Technologies. European Oil Industry Association. Brussels.

Exxon (1988). Primary Dermal Irritation Study in the Rabbit. Exxon Biomedical Sciences. Project Number 225904.

Exxon (1995). Ocular Irritation Study in the Rabbit without Eyewash with Toluene (compliant with OECD test guideline 405. Exxon Biomedical Sciences. Project Number 191813.

Feldt EG, Zhurkov VS, Sysin AN (1984). Study of the mutagenic effects of benzene and toluene in the mammalian somatic and germ cells. XIV Annual meeting of the European Environmental Mutagen Society. Abstracts. 163. Moskva.

Fischman CM, Oster JR (1979). Toxic effects of toluene: A new cause of high anion gap metabolic acidosis. J. Am. Med. Ass. **241**, 1713-1715.

Fishbein L (1985). An overview of environmental and toxicological aspects of aromatic hydrocarbons. II. Toluene. Sci. Total. Environ. **42**, 267-288.

Florin I, Rutberg L, Curvall M, Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using Ames' test. Toxicology **18**, 219-232.

Fodor GG (1972). Schädliche Dämpfe. VDI Verlag, Düsseldorf.

Foo SC, Jeyaratnam J, Koh D (1990). Chronic neurobehavioural effects of toluene. British J. of Ind. Med. **47**, 480-484.

Fornazzari L, Wilkinson DA, Kapur BM, Carlen PL (1983). Cerebellar, cortical and functional impairment in toluene abusers. Acta Neurol. Scand. **67**, 319-329.

Forni A, Pacifico E, Limonta A (1971). Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health **22**, 373-378.

Forni A, Pacifico E, Limonta A (1971). Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health **22**, 373-378.

Franchini I, Cavatorta A, Falzoi M, Lucertini S, Mutti A (1983). Early indicators of renal damage in workers exposed to organic solvents. Int. Arch. Occup. Environ. Health **52**, 1-9.

Freie Universität Berlin (1996). Feldstudie Toluol (Tiefdruck). Universitätsklinikum Benjamin Franklin, Institut für Toxikologie.

Freitag D, Ballhorn L, Geyer H, Korte F (1985). Environmental Hazard profile of organic chemicals. Chemosphere **14**(10). 1589-1616.

Funes-Cravioto F, Zapata-Gayon C, Kolmodin-Hedman B, Lambert B, Lindsten J, Norberg E, Nordenskjöld M, Olin R, Swensson Å (1977). Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. Lancet **2**, 322-325.

Fuxe K, Andersson K, Nilsen OG, Toftgård R, Eneroth P, Gustafsson JÅ (1982). Toluene and telencephalic dopamine: selective reduction of amine turnover in discrete DA nerve terminal systems of the anterior caudate nucleus by low concentrations of toluene. Toxicol. Lett. **12**, 115-123.

Gad-El-Karim MM, Harper BL, Legator MS (1984). Modifications in the myeloclastogenic effect of benzene in mice with toluene, phenobarbital, 3-methylcholanthrene, aroclor 1254 and SKF-525A. Mutat. Res. **135**, 225-243.

Geiger DL, Brooke LT, Call DJ (eds.) (1990). Acute Toxicity of Organic Chemicals to Fathead minnow (*Pimephales promelas*). Vol.V. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior.

Gerarde HW (1960). Toxicology and Biochemistry of Aromatic Hydrocarbons. Elsevier Publishing Company, Amsterdam, 141-150.

Gerner-Smidt P, Friedrich U (1978). The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res. 313-316.

GEUS (1998). Grundvandsovervågning 1998. Danmarks og Grønlands Geologiske Undersøgelser.

Geyer H, Sheehan P, Kotzias D, Freitag D Korte F (1982). Prediction of ecotoxicological behaviour of chemicals. Relationships between physico-chemical properties and bioaccumulation of organic chemicals in the mussel *Mytilus edulis*. Chemosphere **11**, 1121-1134.

Geyer H, Politzki G, Freitag D (1984). Prediction of ecotoxicological behaviour of chemicals: Relationship between n-octanol/water partition coefficient and bioaccumulation of organic chemicals by alga *Chlorella*. Chemosphere **13**, 269-284.

Ghantout H, Danielsson BRG (1986). Placental transfer and distribution of toluene, xylene and benzene, and their metabolites during gestation in mice. Biological Research in Pregnancy **7**, 98-106.

Gibson JE, Hardisty JF (1983). Chronic toxicity and oncogenicity bioassay of inhaled toluene in Fisher-344 rats. Fundam. Appl. Toxicol. **3**, 315-319.

Gibson DT, Subramanian V (1984). Microbial degradation of aromatic hydrocarbons. **In**: Gibson DT (ed.) Microbial Degradation of Organic Compounds. Marcel Dekker, 181-252.

Glockle AH, Cuno E, Hensel T, Schultz HJ, Sandstede RP (1996). Feldstudie "Toluol in Tiefdruckerien" Berufsgenossenschaft Druck und Papierverarbeitung. Wiesbaden.

Glowa JR, Dews PB (1983). Behavioral toxicology and organic solvents. II. Comparison of results on toluene by flow-through and closed chamber procedures. J. Amer. Coll. Toxicol. **2**, 319-323.

Gomez-Belinchon JI, Grimalt JO, Albaigès (1991). Volatile organic compounds in two polluted rivers in Barcelona (Catalonia, Spain). Water Res. **25**(5), 577-589.

Gontea I, Bistriceanu E, Manea M, Draghicescu M (1968). Importanta aportului proteic in intoxicatia cronica cu toluen. Stud. Cerc. Biochim. **11**, 159-166.

Gospe SM, Saeed DB, Zhou SS, Zeman FJ (1994). The effects of high-dose toluene on embryonic development in the rat. Pediatric. Research. **36**, 811-815.

Gossett RW, Brown DA, Young DR (1983). Predicting the bioaccumulation of marine compounds in marine organisms using octanol/water partitioning coefficients. Marine Pollut. Bull. **14**(10), 387-392.

Grüttner H, Jacobsen BN (1994). Miljøfremmede stoffer i renseanlæg (Xenobiotic substances in sewage treatment plants. In Danish). The Danish Environmental Protection Agency, Environmental Project No. 278, Copenhagen.

Guicherit R, Schulting FL (1985). The occurence of organic chemicals in the atmosphere of the Netherlands. Sci. Total. Environ.. **43**, 193-219.

Guillot JP, Gonnet JF, Clement C, Caillard L, Truhaut R (1982a). Evaluation of the cutaneous-irritation potential of 56 compounds. Fd. Chem. Toxic. **20**, 563-72.

Guillot JP, Gonnet JF, Clement C, Caillard L, Truhaut R (1982b). Evaluation of the ocular-irritation potential of 56 compounds. Fd. Chem. Toxic. **20**, 573-82.

Haag F, Reinhard M, McCarty PL (1991). Degradation of toluene and p-xylene in anaerobic microcosms: Evidence for sulfate as a terminal electron acceptor. Environ. Toxicol. Chem. **10**, 1379-1389.

Haglund U, Lundberg I, Zech L (1980). Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. Scand. J. Work. Environ. **6**, 291-198.

Hammer KD, Mayer N, Pfeiffer EH (1998). Sister chromatid exchange in rotogravure printing plant workers. Int. Arch. Occup. Environ. Health **71**, 138-142.

Hansch C, Leo A (1979). Substitute Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons, New York.

Hansch C, Leo AJ (1985). Medchem Project Issue No. 26. Claremont CA, Pomona College.

Harland BJ, Whitby FJ, Comber MHI (1985). Measurements of volatile aromatic hydrocarbons in an industrial estuary. Int. J. Environ. Anal. Chem. **20**, 295-311.

Hass U, Lund SP, Hougaard KS, Simonsen L (1998). Toluene causes developmental neurotoxicity in rats (abstract for European Teratology Society, 1998 and draft manuscript for Neurotox and Teratol).

Hass U, Lund SP, Hougaard KS, Simonsen L (1999). Developmental neurotoxicity after toluene inhalation exposure in rats. Neurotoxicol. Teratol. **21**(4), 349-57.

Hauschild M, Wenzel H (1998). Photochemical ozone formation as a criterion in the environmental assessment of products. **In**: Environmental Assessment of Products. Hauschild M, Wenzel H (eds). Chapman and Hall, 93-154.

Hawkins NC, Evans JS (1989). Subjective estimation of toluene exposures: A calibration study of industrial hygienists. Appl. Ind. Hyg. **4**, 61-68.

Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983). Salmonella mutagenicity test results for 250 chemicals. Env. Mutagen. **5** suppl 1, 3-142.

Heijden CA van der, Mulder HCM, de Vrijer F, Woutersen RA, Davis PB, Vink GJ, Heijna-Merkus E, Janssen PJCM, Canton JH, van Gestel CAM (1988). Integrated criteria document toluene effects. National Institute of Public Health and Environmental Protection (RIVM), Appendix to Report 758473010, Bilthoven, The Netherlands.

Heipieper HJ, Loffeld B, Keweloh H, de Bont JAM (1995). The cis/trans isomerisation of unsaturated fatty acids in *Pseudomonas putida* S12: An indicator for environmental stress due to organic compounds. Chemosphere **30**(6), 1041-1051.

Henrik Skov (2000). pers. comm. May 5 2000. National Environmental Research Institute, Department of Atmospheric Environment. Denmark.

Heringa JW (1951). The Phytotoxicity of Hydrocarbons and Related Products. In-house Report No. 17419. Shell, Amsterdam.

Hermens J, Canton H, Janssen P, de Jong R (1984). Quantitative structure-activity relationships and toxicity studies of mixtures of chemicals with anaesthetic potency: acute lethal and sublethal toxicity to Daphnia magna. Aquat. Toxicol. **5**, 143-154.

Herrchen M, Müller M (1997). Selection scheme for substances dangerous to surface waters - second level. Final report. Frauenhofer Institute for Environmental Chemistry and Ecotoxicology, Schmallenberg, Germany.

Hersh JH, Podruch PE, Rogers G, Weisskopf B (1985). Toluene embryopathy. J. Pediatr. **106**, 922-927.

Hougaard KS, Lund SP, Hass U, Simonsen L (1996). Organic solvents may inflict maternal toxicity not normally assessed in neurobehavioural teratology studies, e.g. hearing impairment. Abstract submitted to European Teratology Society.

Hougaard KS, Lund SP, Hass U, Simonsen L (1997a). Toluene and hearing in rats: Effects on dams and their offspring after exposure during pregnancy. Abstract for EUROTOX 1997.

Hougaard KS, Hass U, Lund SP, Simonsen L (1997b). Deficits on a spatial navigation task following prenatal exposure to toluene. Abstact for INA 1997.

Hougaard KS, Lund SP, Hass U, Simonsen L (1999). Effects of prenatal exposure to toluene on postnatal development and behaviour in rats. Neurotoxicol. Teratol. **21**, 241-250.

Howard PH (ed) (1990). Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Vol. II: 435-444. Lewis Publ., Michigan.

Hoyme HE, Seaver LH, Pearson MA, Rimeza ME (1993). Reproductive Toxicology **3**, 158-9.

Huang J, Asaeda N, Takeuchi Y, Shibata E, Hisanaga N, Ono Y, Kato K (1992). Dose dependent effects of chronic exposure to toluene on neuronal and glia cell marker proteins in the central nervous system of rats. Br. J. Ind. Med. **49**, 282-86.

Huff J (1990). Toxicology and Carcinogenesis Studies of Toluene (CAS no. 108-88-3) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). US Department of Health and Human Services, National Toxicology Program, Technical Report Series No. 371.

Hudák A, Rodics K, Stuber I, Ungváry G (1977). Effects of Toluene Inhalation on Pregnant CFY Rats and their Offspring. Munkavedelem, 23, 25-30. Cited from Barlow SM, Sullivan FM (1982). Reproductive Hazards of Industrial Chemicals. Academic Press, London.

Hudák A, Ungváry G (1978). Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. Toxicology **11**, 55-63.

Huff J (1990). Toxicology and Carcinogenesis Studies of Toluene (CAS no. 108-88-3) in F344/N Rats and B6C3F1 Mice (Inhalation studies). US Department of Health and Human Services, National Toxicology Program, Technical Report Series No. 371.

Hughes TJ, Simmons DM, Monteith LG, Claxton LD (1987). Vaporization technique to measure mutagenic activity of volatiles organic chemicals in the Ames/Salmonella assay. Environ. Mutagen. **9**, 421-41.

Hulzebos EM, Adema DMM, Dirven-van Bremen EM, Henzen L, van Dis WA, Herbold HA, Hoekstra JA, Baerselman R, van Gestel CAM (1993). Phytotoxicity studies with *Lactuca sativa* in soil and nutrient solution. Environ. Toxicol. Chem. **12**, 1079-1094.

Hunter WJ, Aresini G, Haigh R et al. (1997). Occupational exposure limits for chemicals in the European Union. Occup. Environ. Med. **54**, 217-22.

Huntingdon Research Centre (1992). Toluene - The Effect on the Pregnancy of the Rat (Inhalation Exposure). HRC Report No. APT 2/91279, Huntingdon.

Hutchinson TC, Hellebust JA, Tam D, Mackay D, Mascarenhas RA, Shiu WY (1980). The correlation of the toxicity to algae of hydrocarbons and halogenated hydrocarbons with their physical-chemical properties. Environ. Sci. Res. **16**, 577-586.

Hydén D, Larsby B, Andersson H, Ödkvist LM, Liedgren SRC, Tham R (1983). Impairment of visuo-vestibular interaction in humans exposed to toluene. ORL (Karger), **45**, 262-269.

Hänninen H, Antti-Poika M, Savolainen P (1987). Psychological performance, toluene exposure and alcohol consumption in rotogravure printers. Int. Arch. Occup. Environ. Health **59**, 475-483.

Häsänen E, Karlsson V, Leppämaki E, Juhala M (1981). Benzene, toluene and xylene concentrations in car exhausts and in city air. Atmos. Environ. **15**, 1755-1757.

Hauschild M, Wenzel H (1998). Environmental Assessment of Products. Vol. 2. Scientific background. Chapman and Hall, London.

IARC (1989). Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. International Agency for Research on Cancer (IARC), Evaluation of Carcinogenic Risk of Chemicals to Humans, Monograph No 47, Lyon, France.

IARC (1999). Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. International Agency for Research on Cancer (IARC), Evaluation of Carcinogenic Risk of Chemicals to Humans, Monograph No 71, Lyon, France.

IEA (1995). Oil and gGas Information, 1994. International Energy Agency. OECD, Paris.

Ikeda M, Othsuji H (1971). Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. Toxicol. Appl. Pharmacol. **20**, 30-43.

Ikeda M, Koizumi A, Kesahara M, Fujita H (1986). Combined effects of n-hexane and toluene on norepinephrine and dopamine levels in rat brain tissues after long-term exposures. Bull. Environ. Contam. Toxicol. **36**, 510- 517.

Inoue O, Seiji K, Watanabe T, Kasahara M, Nakatsuka H, Yin S, Li G, Cai S, Jin C, Ikeda M (1988). Mutual metabolic suppression between benzene and toluene in man. Int. Arch. Occup. Environ. Health **60**, 15-20.

IPCS (1985). Toluene. World Health Organixation (WHO), International Programme on Chemical Safety (IPCS), Environmental Health Criteria 52, Geneva.

IPCS (1996). Diesel Fuel and Exhaust Emissions. World Health Organixation (WHO), International Programme on Chemical Safety (IPCS), Environmental Health Criteria 171, Geneva.

Iregren A (1982). Effects on psychological test performance of workers exposed to a single solvent (toluene) - A comparison with effects of exposure to a mixture of organic solvents. Neurobehav. Toxicol. Teratol. **4**, 695-701.

Iregren A, Åkerstedt T, Olson BA, Gamberale F (1986). Experimental exposure to toluene in combination with ethanol intake. Scand. J. Work. Environ. Health **12**, 128-136.

Isnard P, Lambert S (1989). Aqueous solubility and n-octanol/water partition coefficient correlations. Chemosphere **18**, 1837-1853.

IUCLID (1994). IUCLID data sheet, Toluene. Deutsche SHELL Chemie, 30-Jun-1994.

Jagannath DR, Matheson D, Brusick D (1978). Mutagenicity Evaluation of Toluene. Litton Bionetics Inc., Kensington, Maryland.

Jensen AA, Slorach SA (1991). Chemical Contaminants in Human Milk. CRC Press, Bocan Raton.

Jensen B, Olsen E, Wolkoff P (1996). Toluene in rotogravure printed brochures: High speed emission testing and comparison with exposure data. Appl. Occup. Environ. Hyg. **11**(8), 1055-1063.

Jin Y, O'Connor GA (1990). Behavior of toluene added to sludge amended soils. J. Environ. Qual. **19**, 575-579.

Johnson AC, Juntunen L, Nylén P, Borg E, Höglund G (1988). Effect of interaction between noise and toluene on auditory function in the rat. Acta Otolaryngol. (Stockh), **105**, 56-63.

Johnson, AC, Nylén P, Borg E, Höglung G (1990). Sequence of exposure to noise and toluene can determine loss of auditory sensitivity in the rat. Acta Otolaryngol. (Stockh) **109**, 34-40.

Johnson AC, Canlon B (1994a). Progressive hair cell loss induced by toluene exposure. Hear Res. **75**, 201-208.

Johnson AC, Canlon B (1994b). Toluene exposure affects the functional activity of the outer hair cells. Hear Res. **72**, 189-196.

Jones HE, Balster RL (1997). Neurobehavioral consequences of intermittent prenatal exposure to high concentrations of toluene. Neurotoxicol. Teratol. **19**(4), 305-13.

Juntunen J, Matikainen E, Antti-Poika M, Suoranta H, Valle M (1985). Nervous system effects of long-term occupational exposure to toluene. Acta Neurol. Scand. **72**, 512-7.

Kahl MD, Russom CL, DeFoe DL, Hammermeister DE (1999). Saturation units for use in aquatic bioassays. Chemosphere **39**(3), 539-551.

Karacic V, Skender L, Bosner-Cucancic B, Bogadi-Sare A (1995). Possible genotoxicity in low level benzene exposure. Am. J. Ind. Med. **27**, 379-88.

Kelly TW (1975). Prolonged cerebellar dysfunction associated with paintsniffing. Pediatrics **56**, 605-606.

Kemp K, Palmgren F, Manscher OH (1998). The Danish Air Quality Monitoring Programme. Annual Report for 1997. National Environmental Research Institute, NERI Technical Report No.245, Roskilde, Denmark.

Kimura ET, Ebert DM, Dodge PW (1971). Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. **19**, 699-704.

King MD (1982). Neurological sequelae of toluene abuse. Human Toxicol. **1**, 281-287.

Kirchmann H, Åström H, Jönsäll G (1991). Organic pollutants in sewage sludge. 1. Effect of toluene, naphthalene, 2-methylnaphthalene, 4-n-nonylphenol and di-2-ethylhexyl phthalate on soil biological processes and their decomposition in soil. Swedish J. agric. Res. **21**, 107-113.

Kirk-Othmer (1983). Encyclopedia of Chemical Technology. 3rd Ed. Vol 23, J.Wiley and Sons, New York, 246-273.

Kishi R, Harabuchi I, Ikeda T, Yokota H, Miyake H (1988). Neurobehavioural effects and pharmakokinetics of toluene in rats and their relevance to man. Br. J. Ind. Med. **45**, 396-408.

Klein AW, Harnisch M, Poremski HJ, Smidt-Bleek F (1981). OECD chemicals testing programme. Physico-chemical tests. Chemosphere **10**, 153.

Klein W, Herrchen M, Müller M, Storm U, Storm A (1997). Hazard Ranking of Substances Relevant for the Aqueous Environment. Frauenhofer Institute for Environmental Chemistry and Ecotoxicology, Final Report, Schmallenberg, Germany.

Klimisch HJ, Hellwig J, Hofmann A (1992). Studies on the prenatal toxicity of toluene in rabbits following inhalation exposure and proposal of a pregnancy guidance value. Arch. Toxicol. **66**, 373-381.

Knoop F, Gerhrke M (1925). Über die Oxydation von Essigsäure, Aceton und Toluol. I. Über die Oxydation von Essigsäure und Aceton mit Hydro peroxyd. II. Über die Oxydation des Toluols im Tierkörper. Hoppe-Seyler's Zeitschr. Physiol. Chem. **146**, 63-71.

Koch R (1995). Umweltchemikalien. Physikalisch-chemische Daten, Toxicitäten, Grenz- und Richtwerte, Umweltverhalten. Dritte Auflage. VCH Verl., Weinheim, Germany.

Koga K, Ohmiya Y (1978). Potentiation of toluene toxicity by hepatic enzyme inhibition in mice. J. Toxicol. Sci. **3**, 25-30.

Korbo L, Ladefoged O, Lam HR, Østergård G, West MJ, Arlien-Søborg P (1996). Neuronal loss in hippocampus in rats exposed to toluene. NeuroToxicology **17**, 359-366.

Korn S, Hirsch N, Struhsaker JW (1977). The uptake and depuration of ^{14}C-benzene and ^{14}C-toluene in pacific herring, *Clupea harengus pallasi*. Fish. Bull. **75**, 633-636.

Korn S, Moles DA, Rice SD (1979). Effects of temperature on the median tolerance limit of pink salmon and shrimp exposed to toluene, naphthalene, and Cook Inlet crude oil. Bull. Environ. Contam. Toxicol. **21**, 521-525.

Kostas J, Hotchin J (1981). Behavioral effects of low-level perinatal exposure to toluene in mice. Neurobehav. Toxicol. Teratol. **3**, 467-469.

Kristensen P, Tørsløv J, Samsøe-Petersen L, Rasmussen JO (1996). Anvendelse af affaldsprodukter til jordbrugsformål. Danish Environmental Protection Agency, Miljøprojekt Nr. 328 (In Danish), Copenhagen.

Kroeger RM, Moore RJ, Lehman TH, Giesy JD, Skeeters CE (1980). Recurrent urinary calculi associated with toluene sniffing. J. Urol. **123**, 89-91.

Kromhout H, Oostendorp Y, Heederik D, Boleij JSM (1987). Agreement between qualitative exposure estimates and quantitative exposure measurements. Am. J. Ind. Med. **12**, 551-562.

Kühn R, Pattard M, Pernak KD, Winter (1989). Results of the harmful effects of water pollutants to *Daphnia magna* in the 21 day reproduction test. Water Res. **23**(4), 501-510.

La Chapelle J, Duplantis F, Rousseau S, Boileau J, Roy LE (1982). Dégénérescence cérébelleuse par toxicité au toluène. L'Union Médicale Canada, **111**, 132-133.

Ladefoged O, Strange P, Møller A, Lam HR, Østergaard G, Larsen JJ, Arlien-Søborg P (1991). Irreversible effects in rats of toluene (inhalation) exposure for six months. Pharmacol. Toxicol. **68**, 384-390.

Lagorio S, Tagesson C, Forastiere F, Iavarone I, Axelson O, Carere A (1994). Exposure to benzene and urinary concentrations of 8-hydroxydeoxyguanosine, a biological marker of oxidative damage to DNA. Occup. Environ. Med. **51**, 739-43.

Larsby B, Tham R, Eriksson B, Ödkvist LM (1986). The effect of toluene on the vestibulo- and opto-oculomotor system in rats. A computerized nystamographic study. Acta Otolaryngol. (Stockholm) **101**, 422-428.

Larsen F, Leira HL (1988). Organic brain syndrome and long-term exposure to toluene: A clinical, psychiatric study of vocationally active printing workers. J. Occup. Med. **30**, 875-878.

Lataye R, Campo P (1997). Combined effects of a simultaneous exposure to noise and toluene on hearing function. Neurotoxicol. Teratol. **19**, 373-382.

Lauwerys R (1983). Human Biological Monitoring of Industrial Chemicals Series. Toluene. Industrial Health and Safety. Alessio L, Berlin A, Roi R, Boni M (eds). Ispra, Italy, 175 pp.

Lazar RB, Ho SU, Melen O, Daghestani AN (1983). Multifocal central nervous system damage caused by toluene abuse. Neurology **33**, 1337-40.

Leblanc GA (1980). Acute toxicity of priority pollutants to water flea (*Daphnia magna*). Bull. Environm. Contam. Toxicol. **24**, 684-691.

Lee BK, Lee SH, Lee KM, Cho KS, Ahn KD, Kim SB, Ukai H, Natatsuka H, Watanabe T, Ikeda M (1988). Dose-dependent increase in subjective symptom prevalence among toluene-exposed workers. Ind. Health **26**, 11-23.

Leidel AA, Busch KA, Lynch JR (1997). Occupational Exposure Sampling Strategy Manual. US Department of Health, Education and welfare.

Lewis JD, Moritz D, Mellis LP (1981). Long-term toluene abuse. Am. J. Psychiatry **138**, 368-369.

Lide DR (ed) (1996). CRC Handbook of Chemistry and Physics. 77th edition, 1996-1997. The Chemical Rubber Company. CRC Press. Boca Raton, Florida.

Ligocki MP, Leuenberger C, Pankow JF (1985). Trace organic compounds in rain - II. Gas scavenging of neutral organic compounds. Atmospheric Environment **19**(10), 1609-1617.

Lindqvist T (1977). Fördelingskoefficienterna blod/luft och vatten/luft för några vanliga lösningsmedel. Arbete och Hälsa **8**, 1-5.

Litton Bionetics (1981). Mutagenicity Evaluation of Toluene. Mouse Dominant Lethal Assay. Report submitted to American Petroleum Institute, LBI project No 21141-05.

Lorenzana-Jimenez M, Salas M (1983). Neonatal effects of toluene on the locomotor behavioral development of the rat. Neurobehav. Toxicol. Teratol. **5**, 195-199.

Lorenzana-Jimenez M, Salas M (1985). Effects of neonatal toluene exposure on the development of evoked and spontaneous cortical activity in the rat. Neurobehav. Toxicol. Teratol. **7**, 215-220.

Lundberg I, Håkansson M, Gustavsson P (1983). Relativ leverskadande effekt av 14 organiska lösningmedel vid intraperitoneal injektion på råtta. Arbete och Hälsa **22**, 1-20.

Lyapkalo AA (1973). Bensens och toluens genetiska aktivitet (Original in Russian, translated to Swedish). Gig. Tr. Prof. Zabol. **17**, 24-28.

Lyman WJ, Reehl WF, Rosenblatt DH (1982). Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co., New York.

Löf A, Wigaeus Hjelm E, Colmsjö A, Lundmark BO, Norström Å, Sato A (1993). Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to $^{2}H_{8}$-toluene. Br. Journ. Ind. Med. 50, 55-59.

Mackay D, Paterson S (1981). Calculating fugacity. Environm. Sci. Technol. **15**(9), 1006-1014.

Mackay D, Wolkoff AW (1973). Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environm. Sci. Technol **7**(7), 611-614.

Mackay D, Shiu WY, Ma KC (1992). Illustrated Handbook of Physical-chemical Properties and Environmental Fate for Organic Chemicals. Vol 1. Monoaromatic Hydrocarbons, Chlorobenzenes and PCB. Lewis Publ., 66-73.

Magnussen Z, Fossan GO (1983). Nevrasteni og polynevropati. Farer ved kronisk toluenpåvirkning. Tidsskr. Nor. Lægeforen **103**, 2039-2041.

Malm G, Lying-Tunell U (1980). Cerebellar dysfunction related to toluene sniffing. Acta Neurol. Scand. **62**, 188-190.

Maltoni C, Conti B, Cotti G (1983). Benzene: A multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. **4**, 589-630.

Maltoni C, Conti B, Cotti G, Belpoggi F (1985). Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology : Current results and ongoing research. Am. J. Ind. Med. **7**, 415-446.

Marchand M, Caprais JC, Pignet P (1988). Hydrocarbons and halogenated hydrocarbons in coastal waters of the Western Mediterranean (France). Marine Environ. Res. **25**, 131-159.

Marchand M (1989). Les polluants organiques toxiques dans les rejets urbains en milieu main ou estuarien. T.S.M.-L'Eau **84**, 7-18.

Massengale ON, Glaser HH, LeLievre RE, Dodds MJB, Klock ME (1963). Physical and psychologic factors in glue sniffing. New Engl. J. Med. **269**, 1340-1344.

Matsushita T, Arimatsu Y, Ueda A, Satoh K, Nomura S (1975). Hematological and neuro-muscular response of workers exposed to low concentration of toluene vapor. Ind. Health **13**, 115-121.

Mayan O, Pires A, Neves P, and Capela F (1999). Shoe manufacturing and solvent exposure in Northern Portugal. Appl. Occup. and Env. Hyg. **14**(11), 785-790.

McCarrol NE, Keech BH, Piper CE (1981a). A microsuspension adaptation of the Bacillus subtilis "rec" assay. Environ. Mutagenesis **3**, 607-616.

McCarrol NE, Piper CE, Keech BH (1981b). An E. coli microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. Environ. Mutagenesis **3**, 429-444.

McGregor D (1994). The genetic toxicology of toluene. Mutat. Res. **317**, 213-28.

McWilliams ML, Chen GD, Fechter LD (2000). Low level toluene disrupts auditory function in guinea pigs. Submitted to Toxicology and Applied Pharmacology.

Merck Index (1989). 11th Ed. Merck Co Inc, Rahway New Jersey.

Ministerie van Sociale Zaken en Werkgelegenheid (SZW) (1999). De nationale MAC-lijst 1999. Ministerie van Sociale Zaken en Werkgelegenheid, , Servicecentrum Sdu Uitgevers, The Hague, The Netherlands.

Mohtashamipur E, Norpoth K, Woelke U, Huber P (1985). Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic erythrocytes of mice. Arch. Toxicol. **58**, 106-109.

Mohtashamipur E, Sträter H, Triebel R, Norpoth K (1987). Effects of pretreatment of male NMRI mice with enzyme inducers or inhibitors on clastogenicity of toluene. Arch. Toxicol. **60**, 460-463.

Moles A, Bates S, Rice SD, Korn S (1981). Reduced growth of Coho salmon fry exposed to two petroleum components, Toluene and naphthalene in fresh water. Transactions A. Fish. Soc. **110**, 430-436.

Morata TC, Dunn DE, Kretschmer LW, Lemasters GK, Keith RW (1993). Effects of occupational exposure to organic solvents and noise on hearing. Scand. J. Work Environ. Health. **19**, 245-254.

Morata TC, Fiorini AC, Fischer FM, Colacioppo S, Wallingford KM, Krieg EF, Dunn DE, Gozzoli L, Padrão MA, Cesar LG (1997). Toluene-induced hearing loss among rotogravure printing workers. Scand. J. Work Environ. Health **23**, 289-98.

Morata T (1999). Response to the critiques offered by Dr. B.W. Lawson, on the paper:

Morata TC, Fiorini AC, Fischer FM, Colacioppo S, Wallingford KM, Krieg EF, Dunn DE, Gozzoli L, Padrão MA, Cesar CLG (1997). Toluene-induced hearing loss among rotogravure printing workers. Scandinavian Journal Work Environmental Health **23**, 289-298.

Morata T (2000). Personal comunication at the expert workshop on toluene and auditory toxicity. Danish EPA, 27.01.00.

Moss AH, Gabow PA, Kaehny WD, Goodman SI, Haut LL, Haussler MR (1980). Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. Ann. Intern. Med. **92**, 69-70.

Moussiopoulos N, Sahm P, Tourlou PM, Friedrich R, Wickert B, Reis S, Simpson D (1998). Technical Expertise in the Context of the Commission's Communication on an Ozone Strategy. Final Report to European Commission DGXI. Submitted in fulfillment of Contract B4-3040/98/000052/MAR/D3. October 1998.

Mulhausen JR and Damiano JD (1998). A Strategy for Assessing and Managing Occupational Exposures. 2nd Edition. AIHA Press.

Muller J, Greff G (1984). Recherche de relations entre toxicité de molécules d'intérêt industriel et propriétés physico-chimiques: test d'irritation des voies aériennes supérieures appliqué à quatre familles chimiques. Fd. Chem. Toxicol. **22**, 661-664.

Mullin LS, Krivanek ND (1982). Comparison of unconditioned reflex and conditioned avoidance tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene or ethanol. Neurotox. **3**, 126-137.

Muttray A, Wolters V, Mayer-Popken O, Schicketanz KH, Konietzko J (1995). Effect of subacute occupational exposure to toluene on color vision. Int. J. Occup. Med. Environ. Health **8**, 339-345 (abstract).

Mäki-Paakkanen J, Husgafvel-Pursiainen K, Kalliomäki P-L, Tuominen J, Sorsa M (1980). Toluene-exposed workers and chromosome aberrations. J. Toxicol. Environ. Health. **6**, 775-781.

Mørck HI, Winkel P, Gyntelberg F (1985). Helbredseffekter af toluenudsættelse. Arbejdsmiljøfondet, Copenhagen, 54 pp.

Nakamura S, Oda Y, Shimada T, Oki I, Sugimoto K (1987). SOS-inducing activity of chemical carcinogens and mutagens in Salmonella typhimurium TA1535/pSK 1002: examination with 151 chemicals. Mutat. Res. **192**, 239-246.

Nathwani JS, Phillips CR (1977). Adsorption-desorption of selected hydrocarbons in crude oil on soils. Chemosphere **4**, 157-162.

Nelson PF, Quigley SM (1984). The hydrocarbon composition of exhaust emitted from gasoline fuelled vehicles. Atmos. Environ. **18**(1), 79-87.

Nestmann ER, Lee EGH, Matula TI, Douglas GR, Mueller JC (1980). Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. **79**, 203-212.

Ng TP, Foo SC, Yoong T (1992a). Menstrual function in workers exposed to toluene. British J. of Ind. Med. **49**, 799-803.

Ng TP, Foo SC, Yoong T (1992b). Risk of spontaneous abortion in workers exposed to toluene. British J. of Ind. Med. **49**, 804-808.

Niederlehner BR, Cairns J, Smith EP (1998). Modeling acute and chronic toxicity of nonpolar narcotic chemicals and mixtures to *Ceriodaphnia dubia*. Ecotoxicol. Environ. Saf. **39**, 136-146.

Nielsen GD, Alarie Y (1982). Sensory irritation, pulmonary irritation and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Toxicol. Appl. Pharmacol. **65**, 459-477.

Nielsen HK, Krusell L, Bælum J, Lundqvist G, Omland Ø, Væth M, Husted SE, Mogensen CE, Geday E (1985). Renal effects of acute exposure to toluene. A controlled clinical trial. Acta Med. Scand. **218**, 317-321.

Nielsen IR, Howe P (1991). Environmental hazard assessment; Toluene. UK Department of the Environment, Building Research Establishment.

Nirmalakhandan N, Arulgnanendran V, Monsin M, Sun B, Cadena F (1994). Toxicity of mixtures of organic chemicals to microorganisms. Water Res. **28**(3), 543-551.

Nise G, Attewell R, Skerfving S, Ørbæk P (1989). Elimination of toluene from venous blood and adipose tissue after occupational exposure. Br. J. Ind. Med. **46**, 407-411.

Nise G, Högstedt B, Bratt I, Skerfving S (1991). Cytogenetic effects in rotogravure workers exposed to toluene (and benzene). Mutat. Res. **261**, 217-223.

NL (1999). Comments to draft risk assessment of toluene (draft of 1998-9-18) E-mail of 1999-02-11.

Nomiyama K, Nomiyama H (1974). Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int. Arch. Arbeitsmed. **32**, 75-83.

NORDIG (1996). Reproduktions-epidemiologische Studie Toluol. Abschlussbericht. NORDIG Institut für Gesundheitsforschung, Hamburg.

Nordic Study Group on the Health Risk of Chromosome Damage (1990). A Nordic database on somatic chromosome damage. Mutat. Res. **241**, 325-337.

NOTOX (1996). Assessment of contact hypersensitivity to toluene in the albino guinea pig (maximization-test). NOTOX BV, NOTOX Project 179911, s' Hertogenbosch, The Netherlands.

NRW (1986). Gewässergütebericht '86. Landesamt für Wasser und Abfall. Nordrhein-Westfalen. Düsseldorf 1987.

Nunes P, Benville P (1979). Uptake and depuration of petroleum in the Manila clam, *Tapes semidecursata* Reeve. Bull. Environ. Contam. Toxicol. **21**, 719-726.

Nyegaard (ed.) (1991). Grundvandsovervågning, Danish Geological Survey.

Nylén P, Hagman M, Johnson AC (1994). Function of the auditory and visual systems, and of peripheral nerve, in rats after long-term combined exposure to *n*-hexane and methylated benzene derivatives. I. Toluene. Pharmacology and Toxicology **74**, 116-123.

Nylén P, Hagman M, Johnson AC (1995). Function of the auditory system, the visual system, and peripheral nerve and long-term combined exposure to toluene and ethanol in rats. Pharmacology and Toxicology **76**, 107-111.

Nylén P (1998). Personal communication.

O'Brian ET, Yeoman WB, Hobby JAE (1971). Hepatorenal damage from toluene in a "glue sniffer". Br. Med. J. **2**, 29-30.

Occupational Exposure Limit Values (1993). Statute book of the Swedish National Board of occupational safety and health. Ordinance (AFS 1993:l9).

Ogata M, Miyaka Y (1978). Disappearance of aromatic hydrocarbons and organic sulphur compounds from fish flesh reared in crude oil suspension. Water Res. **12**, 1041-1044.

Ogata M, Fukisawa K, Ogino Y, Mano E (1984). Partition coefficients as a measure of bioconcentration potential of crude oil compounds in fish and shellfish. Bull. Environ. Toxicol. **33**, 561-567.

Oldham P (1953). The nature of the variability of dust concentrations at the coal face. British Journal of Industrial Medicine **10**, 227-234.

Olsen E, Seedorff L. (1990). Exposure to organic solvents-II an exposure epidemiology study. Ann. Occup. Hyg. **34**(4), 379-389.

Olsen E, Laursen B, Vinzents PS (1991). Bias and random errors in historical data of exposure to organic solvents. Am. Ind. Hyg. Assoc. J. **52**(5), 204-211.

Olsen E, Jensen B (1994). On the concept of the "normal" day. Quality control of occupational hygiene measurements. Appl. Occup. Environ. Hyg. **9**(4), 245-255.

Olsen E (1994). Analysis of exposure using a Logbook method. Appl. Occup. Environ. Hyg. **9**(10), 712-722.

Olsen E (1996). Effect of sampling on measurement errors. The Analyst **121**, 1155-1161.

Ono A, Sekita K, Ohno K, Hirose A, Ogawa Y, Saito M, Naito K, Kaneko T, Furuya T, Matsumoto K, Tanaka S, Kurokawa Y (1995). Reproductive and developmental toxicity of toluene I. Teratogenicity study of inhalation exposure in pregnant rats. J. Toxicol. Sci. **20**, 109-134.

Ono A, Sekita K, Ogawa Y, Hirose A, Suzuki S, Saito M, Naito K, Kaneko T, Furuya T, Kawashima K, Yasuhara K, Matsumoto K, Tanaka S, Inoue T, Kurokawa Y (1996). Reproductive and developmental toxicity studies of toluene II. Effects of inhalation exposure on fertility in rats. J. Environ. Pathol. Toxicol. Oncol. **15**, 9-20.

Overcash MR, Weber JB, Miles ML (1982). Behavior of Organic Priority Pollutants in the Terrestrial System: Di-n-butyl phthalate ester, toluene, and 2,4-dinitrophenol. Water Resources Research Institute of the University of North Carolina. Report No. 171.

Palm WU, Zetsch C (1992). OH-radicale in der Troposphaere; Ihre Konzentration und Auswirkung. Frauenhofer-Institute für Toxicologie und Aerosolforschung, Hanover, Germany.

Pancorbo OC, Varney TC (1986). Fate of synthetic organic chemicals in soil groundwater systems. Vet. Hum. Toxicol. **28**(2), 127-143.

Pankow JF, Isabelle LM, Asher WE (1984). Trace organic compounds in rain. 1. Sampler design and analysis by adsorption/thermal desorption. Environ. Sci. Technol. **18**(5), 310-318.

Parpinelli Tecnon (1996). West European Petrochemical Industry. Aromatics Report and Tables, Mailand 1996.

Patel R, Benjamin J (1986). Renal disease associated with toluene inhalation. Clin. Toxicol. **24**, 213-223.

Pearson MA, Hoyme HE, Seaver LH, Rimeza ME (1994). Toluene embryopathy: Delineation of the phenotype and comparison with fetal alcohol syndrome. Pediatrics **93**, 211-15.

Pedersen F, Tyle H, Niemelä J R, Guttman B, Lander L, Wedebrand A (1995). Environmental Classification - Data Collection and Interpretation Guide for Substances to be evaluated for Classification as Dangerous for the Environment (2nd Edition). Nordic Council of Ministers, TemaNord, 581, 166 pp.

Pelclová D, Rössner P, Picková J (1990). Chromosome aberrations in rotogravure printing plant workers. Mutat. Res. **245**, 299-303.

Pickering QH, Henderson C (1966). Acute toxicity of some important petrochemicals to fish. J. Water Poll. Contr. Fed. **38**(9), 1419-1429.

Piotrowski J (1967). Quantitative estimate of the absorption of toluene in people (In Polish with English summary). Med. Pracy **18**, 213-223.

Pitarque M, Vaglenov A, Nosko M, Hirvonen A, Norrpa H, Creus A, Marcos R (1999). Evaluation of DNA damage by the Comet assay in shoe workers exposed to toluene and other organic solvents. Mutat. Res. **441**, 115-127.

Piwoni MD, Wilson JT, Walters DM, Wilson BH, Enfield CG (1986). Behavior of organic pollutants during rapid-infiltration of wastewater into soil. I. Processes, definition and characterization using a microcosm. Haz. Waste. Haz. Mater. **3**, 43-55.

Plappert U, Barthel E, Seidel HJ (1994) Reduction of benzene toxicity by toluene. Env. Mol. Mutagen. **24**, 283-292.

Plenge-Bönig A, Karmaus W (1999). Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. Occup. Environ. Med. **56**, 443-448.

Popp W, Vahrenholz C, Yaman S, Müller C, Müller G, Schmeiding W, Norpoth K, Fahnert R (1992). Investigation of the frequency of DNA strand breakage and cross-linking and of sister chromatid exchange frequency in the lymphocytes of female workers exposed to benzene and toluene. Carcinogenesis **13**, 57-61.

Post W, Kromhout H, Heederik D, Noy D, Duijzentkunst RS (1991). Semiquantitative Estimation of Exposure to Methylene Chloride and Styrene: The Influence of Quantitative Exposure Data. Appl. Occup. Environ. Hyg. **6**(3), 197-204.

Potera GT (1975). The Effects of Benzene, Toluene and Ethylbenzene on several important Members of the Estuarine Ecosystem. Ph.D. dissertation, Lehigh University.

Pozzani UC, Weil CS, Carpenter CP (1959). The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Amer. Ind. Hyg. Assoc. J. **20**, 364-369.

Preller EA, van Amelsfort M, de Pater AJ, Matulessy JH, Leenheers LH. (1998). Exposure to Organic Solvents during Treatment of Metal Objects. Organisation for Applied Scientific Research (TNO), TNO Report, Zeist, The Netherlands.

Price KS, Waggy GT, Comway RA (1974). Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollution Control. Federation **46**(1), 63-77.

Primate Research Institute (1988). Lifetime dermal carcinogenesis/chronic toxicity screening bioassay of refinery streams in C_3H/HeJ mice. AP-135r. Final Report, Lifetime Carcinogenicity Evaluation. Volume 1, 1-31.

Pryor GT, Dickinson J, Howd RA, Rebert CS (1983a). Neurobehavioral effects of subchronic exposure of weanling rats to toluene or hexane. Neurobehav. Toxicol. Teratol. **5**, 47-52.

Pryor GT, Dickinson J, Howd RA, Rebert CS (1983b). Transient cognitive deficits and high-frequency hearing loss in weanling rats exposed to toluene. Neurobehav. Toxicol. Teratol. **5**, 53-57.

Pryor GT, Rebert CS, Dickinson J, Feeney EM (1984). Factors affecting toluene induced ototoxicity in rats. Neurobehav. Toxicol. Teratol. **6**, 223-238.

Pryor GT, Howd RA (1986). Toluene-induced ototoxicity by subcutaneous administration. Neurobehav. Toxicol. Teratol. **8**, 103-104.

Pyykkö K, Tähti H, Vapaatalo H (1977). Toluene concentrations in various tissues of rats after inhalation and oral administration. Arch. Toxicol. **38**, 169-76.

Rappaport SM (1991). Assessment of long-term exposures to toxic substances in air. Ann. Occup. Hyg. **35**(1), 61-121.

Rastogi SC (1992). Organic solvents in shoe- and leather glues. Toxicol. Environ. Chem. **35**, 213-217.

Rastogi SC (1993). Organic solvent levels in model and hobby glues. Bull. Environ. Contam. Toxicol. **51**, 501-507.

Rebert CS, Sorenson SS, Howd RA, Pryor GT (1983). Toluene-induced hearing loss in rats evidenced by the brainstem auditory-evoked response. Neurobehav. Toxicol. Teratol. **5**, 59-62.

Rees DC, Wood RW, McCormick JP, Cox C (1985). Toxicokinetics of toluene in the rat. Scand. J. Work Environ. Health **11**, 301-306.

Regno V, Arulgnanendran J, Nirmalakhandan N (1998). Microbial toxicity in soil medium, Ecotoxicol. Environ. Saf. **39**, 48-56.

Reisin E, Teicher A, Jaffe R, Eliahou HE (1975). Myoglobinuria and renal failure in toluene poisoning. Br. J. Ind. Med. **32**, 163-168.

Rhudy RL, Lindberg DC, Goode JW, Sullivan DJ, Gralla EJ (1978). Ninety-day subacute inhalation study with toluene in albino rats. Abstract. Toxicol. Appl. Pharmacol. **45**, 284-285.

Richer CL, Chakrabarti S, Senécal-Quevillon M, Duhr MA, Zhang XX, Tardif R (1993). Cytogenetic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. Int. Arch. Occup. Environ. Health. **64**, 581-585.

Riihimäki V, Pfäffli P (1978). Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ. Health **4**, 73-85.

Rippen G (ed) (1992). Toluol. Handbuch Umweltchemikalien. Vol.7. 18. Ergänzungslieferung 11/92. Ecomed verl. Landsberg/Lech, Germany, pp.1-42.

Roach S (1992). Health Risks from Hazardous Substances at Work: Assessment, Evaluation and Control. Oxford: Pergamon Press.

Roberts L, Vernot E, Bevan C, Bui Q, Koschier F, Panson R, Brooker A, Harris S (1993). Developmental toxicity of toluene in the rat. Teratology **47**, 434.

Roch F, Alexander M (1997). Inability of bacteria to degrade low concentrations of toluene in water. Environ. Toxicol. Chem. **16**(7), 1377-1383.

Roch F, Védy JC (1999). Modulation of metabolic activity prevents degradation of sorbed toluene. Chemosphere **38**, 1797-1810.

Rodrigue-Arnaiz R, Villalobos-Pietrini R (1985a). Genetic effects of thinner, benzene and toluene in Drosophila melanogaster. 1. Sex chromosome loss and non-dis-junction. Contam. Amb. **1**, 35-43.

Rodrigue-Arnaiz R, Villalobos-Pietrini R (1985b). Genetic effects of thinner, benzene and toluene in Drosophila melanogaster. 2. Sex linked recessive lethal mutations and translocations II-III. Contam. Amb. **1**, 45-49.

Roh J, Moon YH, Kirr KY (1987). The cytogenetic effects of benzene and toluene on bone marrow cells in rats. Yonsei Medical Journal **28**, 297-309.

Rosenbaum AS, Ligocki MP, Wei YH (1999). Modelling Cumulative Outdoor Concentrations of Hazardous Air Pollutants. Systems Applications International Inc., Final Report SYSAPP-99-96/33r2, San Rafael, CA, USA.

Rossi SS, Thomas WH (1981). Solubility behaviour of three aromatic hydrocarbons in distilled water and natural seawater. Environ. Sci. Technol **15**(6), 715-716.

Russ G, Clarkson AR, Woodroffe AJ, Seymour AE, Cheng IKP (1981). Renal failure from glue sniffing. Med. J. Aust. **2**, 121-123.

Römmelt H, Kessel R, Pfaller A (1982). Rückschlüsse auf die Arbeitsplatzbelastung durch die Bestimmung von Lösungsmittelkonzentration im Vollblut. Verh. Dtsch. Ges. Arbeitsmed. **22**, 575-578.

Saeger E De, Gerbola M, Ballesta PP, Amantini L, Payrissat M (1995). Air Quality Measurements in Brussels (1993-1994). NO2 and BTX Monitoring Campaigns by Diffusive Samplers. European Commission, Joint Research Center, Environment Institute, EUR 16310 EN, Ispra, Italy.

Sangster J (1989). Octanol-water partition coefficients of simple organic compounds. J. Phys. Chem. Ref. Data **18**(3), 1111-1229.

Sasa M, Igarashi S, Miyazaki T, Miyazaki K, Nakano S, Matsuoka I (1978). Equilibrium disorders with diffuse brain atrophy in long-term toluene sniffing. Arch. Otorhinolaryngol. **221**, 163-169.

Sato A, Fujiwara Y, Hirosawa K (1972). Solubility of benzene, toluene and m-xylene in blood. (In Japanese with English summary) Jap. J. Ind. health **14**, 3-8.

Sato A, Nakajima T (1977). Vatten/luft, blod/luft, olja/luft, olja/vatten och olja/blod fördelingskoefficientar av några aromatiska kolväten. (Original in Japanese, translated to Swedish). Jap. J. Ind. Health **19**, 132-133.

Sato A, Nakajima T (1978). Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. Br. J. Ind. Med. **35**, 43-49.

Sato A, Nakajima T, Fujiwara Y, Hirosawa K (1974). Pharmacokinetics of benzene and toluene. Int. Arch. Arbeitsmed. **33**, 169-182.

Sato A, Nakajima T, Koyama Y (1980). Effects of chronic ethanol consumption on hepatic metabolism of aromatic and chlorinated hydrocarbons in rats. Br. J. Ind. Med. **37**, 382-386.

Sauter JJ, Pambor L (1989). The dramatic corrosive effect of road-side exposureof aromatic hydrocarbons on the epistomatal wax crystalloids in spruce and fir- and its significance for the 'Waldsterben'. Europ. J. of Forest Pathology **19**, 370-378.

Schmid E, Bauchinger M, Hauf R (1985). Chromosome changes with time in lymphocytes after occupational exposure to toluene. Mutat. Res. **142**, 37-39.

Schnaak WJT (1995). Untersuchungen zum Vorkommen von ausgewählten organischen Schadstoffen im Klärschlamm und deren ökologische Bewertung bei der Aufbringung von Klärschlamm auf boden sowie Ableitung von Empfehlungen für Normwerte. Landesumweltamt Brandenburg, Potsdam, Germany.

Schubert U et al. (1992). Determination of the phytotoxicity of volatile organic compounds by measuring germination arte of tobacco pollen. Plant physiology **99**(1), 147.

Schultz TW, Bryant SE, Kissel TS (1996). Toxicological assessment in *Tetrahymena* of intermediates in aerobic microbial transformation of toluene and p-xylene. Bull. Environ. Contam. Toxicol **56**, 129-134.

Seeber A (1999). Personal communication. Enclosure titled "Hearing capability: Some remarks to the "Responses to comments…."" received with letter of 02.08.99 from Berufsgenossenschaft Druck und Papierverarbeitung, signed Glöckle.

Seedorff L, Olsen E (1990). Exposure to organic solvents-I. A survey on the use of solvents. Ann. Occup. Hyg. **34**(4), 371-378.

Sherwood RJ (1976). Ostwald solubility coefficients of some industrially important substances. Br. J. Ind. Med. **33**, 106-107.

Shigeta S, Aikawa T, Misawa T (1982). Effects of maternal exposure to toluene during pregnancy on mouse embryos and fetuses. Tokai J. Exp. Clin. Med. **7**, 265-270.

Shigeta S, Aikawa H, Misawa T, Yoshida T, Momotani H, Suzuki K (1986). Learning impairment in rats following low-level toluene exposure during brain development - A comparative study of high avoidance rats and Wistar rats. Ind. Health **24**, 203-211.

Sina JF, Bean CL, Dysart GR, Taylor VI, Bradley MO (1983). Evaluation of the alkaline elution/rat hepatocyte as a predictor of carcinogenic/mutagenic potential. Mutat. Res. **113**, 357-391.

Singh HB, Salas LJ, Smith AJ, Shiheishi H (1981). Measurements of some potentially hazardous organic chemicals in urban environments. Atmos. Environ. **15**, 601-612.

Slomianka L, Edelfors S, Ravn-Jonsen A, Rungby J, Danscher G, West MJ (1990). The effect of low-level toluene exposure on the developing hippocampal region of the rat: Histological evidence and volumetric findings. Toxicology **62**, 189-202.

Slomianka L, Rungby J, Edelfors S, Ravn-Jonsen A (1992). Late postnatal growth in the dentata area of the rat hippocampus compensates for volumetric changes caused by early postnatal toluene exposure. Toxicology **94**, 203-208.

Sloof W, Blokzijl PJ (eds.) (1988). Integrated criteria document Toluene. National Institute of Public Health and Environmental Protection (RIVM), RIVM Report 758473010, Bilthoven, The Netherlands.

Sluyter R, Camu A (1999). Air Pollution by Ozone in the European Union. Overview of the Summer Season (April - August). Report to the Commission by the European Environment Agency. European Topic Centre on Air Quality.

Smith JN, Smithies RH, Williams RT (1954). Studies in detoxication. 55. The metabolism of alkylbenzenes. (a) Glucuronic acid excretion following the administration of alkylbenzenes. (b) Elimination of toluene in the expired air of rabbits. Biochem. J. **56**, 317-320.

Smyth HF, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS (1969). Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. **30**, 470-6.

Snyder RD, Matheson DW (1985) Nick translation – a new assay for monitoring DNA damage and repair in cultured human fibroblasts. Env. Mutagen. **7**, 267-279.

Spanggord RJ, Mortelmans KE, Griffin AF, Simmon VF (1982). Mutagenicity in Salmonella typhimurium and structure-activity relationships of wastewater components emanating from the manufacture of trinitrotoluene. Environ. Mutagen. 4, 163-179.

Staples CA, Werner AF, Hoogheem TJ (1985). Assessment of priority pollutant concentrations in the United States using STORET database. Environ. Toxicol. Chem. **4**, 131.

Streicher HZ, Gabow PA, Moss AH, Kono D, Kaehny WD (1981). Syndromes of toluene sniffing in adults. Ann. Intern. Med. **94**, 758-762.

Sugai S, Murata K, Kitagaki T, Tomita I (1990). Studies on the eye irritation caused by chemicals in rabbits - 1. A quantitative structure-activity relationships approach to primary eye irritation of chemicals in rabbits. J. Tox .Sci. **15**, 245-62.

Sullivan MJ, Rarey KE, Conolly RB (1989). Ototoxicity of toluene in rats. Neurotoxicol. Teratol. **10**, 525-530.

Suter GW, Rosen AE (1988). Comparative toxicology for risk assessment of marine fishes and crustaceans. Environ. Sci. Technol. **22**(5), 548-556

Sutton C, Calder JA (1975). Solubility of alkylbenzenes in distilled water and seawater at 25°C. J. Chem. Eng. Data **20**, 320-322.

Svensson BG, Nise G, Englander V, Attewell R, Skerfving S, Möller T (1990). Deaths and tumours among rotogravure printers exposed to toluene. Br. J. Ind. Med. **47**, 372-379.

Svensson BG, Nise G, Erfurth EM, Nilsson A, Skerfving S (1992a). Hormone status in occupational toluene exposure. Am. J. Ind. Med. **22**, 99-107.

Svensson BG, Nise G, Erfurth EM, Olsson H (1992b). Neuroendocrine effects in printing workers exposed to toluene. Br. J. Ind. Med. **49**, 402-08.

Svirbely JL, Dunn RC, Von Oettingen WF (1943). The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. J. Ind. Hyg. Toxicol. **25**, 366-373.

Swedish EPA (1992). Slam. Innehåll av organiske miljöfarliga ämnen. Naturvårdsverket. (Sludge. Content of organic environmental hazardous substances. In Swedish).

Tabak HH, Quave SA, Mashni CI, Barth EF (1981). Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Contr. Fed. **53**(10), 1503-1518.

Taher SM, Anderson RJ, McCartney R, Popovtzer MM, Schrier RW (1974). Renal tubular acidosis associated with toluene "sniffing". New Engl. J. Med. **290**, 765-768.

Taskinen H, Kyyrönen P, Hemminki K, Hoikkala M, Lajunen K, Lindbohm M-L (1994). Laboratory work and pregnancy outcome. J. Occup. Med. **36**, 311-319.

Tátrai E, Rodics K, Ungváry G (1980). Embryotoxic effects of simultaneously applied exposure of benzene and toluene. Folia Morphologica, XXVIII, 286-289.

Taylor JD, Evans HL (1985). Effects of toluene inhalation on behavior and expired carbon dioxide in macaque monkeys. Toxicol. Appl. Pharmacol. **80**, 487-495.

TGD (1996). Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on Risk Assessment of New Notified Substances and The Commission Regulation (EC)1488/94 on Risk Assessment For Existing Substances. European Commission, Joint Research Centre, European Chemicals Bureau, Ispra, Italy.

Tham R, Bunnfors I, Eriksson B, Larsby B, Lindgren S, Ödkvist LM (1984). Vestibulo-ocular disturbances in rats exposed to organic solvents. Acta Pharmacol. Toxicol. **54**, 58-63.

Thiel R, Hartmann J, Gericke C, Webb J, Chahoud I (1993). Untersuchung zur Reproduktionstoxizität von Toluol. Technik + Forschung, Weisbaden III/1993. Bundesverband Druck.

Thiel R, Chahoud I (1997). Postnatal development and behaviour of Wistar rats after prenatal toluene exposure. Arch. Toxicol. **71**, 258-265.

Thomas RE, Rice SD (1979). The effect of exposure temperatures on oxygen consumption and opercular breathing rates of pink salmon fry exposed to toluene, naphthalene and water soluble fractions of Cook Inlet crude oil and No. 2 fuel oil. Mar. Pollut. **79**, 39-52

TNO (1998). Summary by J Marquart. Letter to DEPA of 1998-08-17.

Toutant C, Lippmann S (1979). Fetal solvents syndrome. Lancet **2**, 1356.

Triebig G, Braune U (1983). Neurotoxische Arbeitstoffe: II. Organische Substanzen - Eine Übersicht der Jahre 1970 bis 1982. Zbl. Bakt. Hyg. I. Abt. Orig. B. **178**, 207-258.

Tsuruta H (1982). Percutaneous absorption of organic solvents. III. On the penetration rates of hydrophobic solvents through the excised rat skin. Ind. Health **20**, 335-345.

Tsushima WT, Towne WS (1977). Effects of paint sniffing on neuropsychological test performance. J. Abnorm. Psychol. **86**, 402-407.

UK Environment Agency (1997). Exposure data for toluene. Letter to Danish EPA. October 16, 1997.

Ulfvarson U, Övrum P (1976). Fördelning av lösningsmedel mellan blod och luft. I. Bestämning av fördelningskoefficienten mellan blod och luft för några lättflyktiga lösningsmedel. Arbete och Hälsa **7**, 1-7.

Ungváry G, Tátrai E (1985). On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch Toxicol (suppl.) **8**, 425-430.

Ungváry G, Mányai S, Tátrai E, Szeberényi S, Cseh RJ, Molnár J, Folly G (1980). Effect of toluene inhalation on the liver of rats - dependence on sex, dose and exposure time. J. Hyg. Epidemiol. Microbiol. Immunol. **24**, 242-252.

Ungváry G, Tátrai E, Szeberényi S, Rodics K, Lörincz M, Barcza G (1982). Effect of toluene exposure on the liver under different experimental conditions. Exp. Mol. Pathol. **36**, 347-360.

US EPA (1987). Household solvent products: a National Usage Survey. EPA-OTS 560/5-87-005, Washington, USA.

US EPA (1994). ECOSAR ver. 1.01. A computer program for estimating the ecotoxicity of industrial chemicals based on structure activity relationships. US EPA, Office of Pollution Prevention and Toxics.

US EPA (2001). Personal communication with Joe Ford at the OECD, SIAM 11, Florida, USA 2001.

Van de Meent D, den Hollande HA, Pool WG, Vredenbregt MJ, van Oers HAM, de Greef E, Luijten JA (1986). Organic micropollutants in Dutch coastal waters. Water Sci. Technol. **18**, 73-81.

Van der Heijden CA, Mulder HCM, de Vrijer F, Woutersen RA, Davis PB, Vink GJ, Heijna-Merkus E, Janssen PJCM, Canton JH, van Gestel CAM (1988). Integrated Criteria Document Toluene Effects. National Institute of Public Health and Environmental Protection (RIVM), Appendix to Report 758473010, Bilthoven, The Netherlands.

Van Haut H, Prinz B, Höckel FE (1979). Ermittlung der relativen Phytotoxizität von Luftverunreinigungen im LIS-Kurzzeittest an verschiedenen organischen Komponenten und Ammoniak. Schriftenreihe der Landesanstalt für Immissionschutz des Landes Nordrhein-Westfalen, **49**, 29-65.

Veulemans H, Masschelein R (1978a). Experimental human exposure to toluene. I. Factors influencing the individual respiratory uptake and elimination. Int. Arch. Occup. Environ. Health **42**, 91-103.

Veulemans H, Masschelein R (1978b). Experimental human exposure to toluene. II. Toluene in venous blood during and after exposure. Int. Arch. Occup. Environ. Health **42**, 105-17.

Vincent (1998). Data extracted from the French National Occupational Exposure Database of 1998-08-17.

von Euler G, Ögren SO, Li XM, Fuxe K, Gustafsson JÅ (1993). Persistent effects of subchronic toluene exposure on spatial learning and memory, dopamine-mediated locomotor activity and dopamine D_2 agonist binding in the rat. Toxicology **77**, 223-232.

von Euler G, Ögren S-O, Eneroth P, Fuxe K, Gustafsson S-Å (1994). Persistent effects of 80 ppm toluene on dopamine-regulated locomotor activity and prolactin secretion in the male rat. Neurotoxicology **15**, 621-24.

Vrca A, Bozicevic D, Bozikov V, Fuchs R, Malinar M (1997a). Brain stem evoked potentials and visual evoked potentials in relation to the length of occupational exposure to low levels of toluene. Acta Med. Croatica **51**(4-5), 215-9.

Vrca A, Karacic V, Bozicevic D, Fuchs R, Malinar M (1997b). Cognitive evoked potentials VEP P300 persons occupationally exposed to low concentrations of toluene. Arh. Hig. Rada. Toksikol. **48**(3), 277-85.

Vrca A, Bozicevic D, Karacic V, Fuchs R, Prpic-Majic D, Malinar M (1995). Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. Arch. Toxicol. **69**(5) 337-340.

Wagner G (1985). Bemerkungen zum Krebsatlas der Bundesrepublik Deutschland. Sonderdruck aus dem Berichtsband der MEDICINALE XV. Iserlohn 1985 herausgegeben von Graul EH, Pütter S und Loew D (In German).

Wakeham SG, Davis AC, Karas JL (1983). Mesocosm experiments to determine the fate and persistence of volatile organic compounds in coastal seawater. Environ. Sci. Technol. **17**(10). 611-617.

Waldron HA, Cherry N, Johnston JD (1983). The effects of ethanol on blood toluene concentrations. Int. Arch. Occup. Environ. Health **51**, 365-369.

Waldron HA, Cherry N, Venables H (1982). Solvent exposure and liver function. Lancet **2**, 1276.

Wallén M (1986). Toxicokinetics of toluene in occupationally exposed volunteers. Scand. J. Work. Environ. Health **12**, 588-593.

Ward GS, Parrish PR, Rigby RA (1981). Early life stage toxicity tests with a saltwater fish: effects of eight chemicals on survival, growth and development of sheepshead minnows (*Cyprinodon variegatus*). J. Toxicol. Environ. Health **8**, 225-240.

Watson JM (1979). Glue sniffing: two case reports. Practitioner **222**, 845-847.

Weast RC (ed) (1977). CRC Handbook of Chemistry and Physics. 58th edition. The Chemical Rubber Company. CRC Press. Boca Raton, Florida.

Weinstein S, Scottolini AG, Bhagavan NV (1985). Low neutrophil alkaline phosphatase in renal tubular acidosis with hypophosphatemia after toluene sniffing. Clin. Chem. **31**, 330-331.

Weisenberger BL (1977). Toluene habituation. J. Occup. Med. **19**, 569-570.

WHO (1999). Overview of the Environment and Health in Europe in the 1990's. Background document for the Third Ministerial Conference on Environment and Health. Action in Partnership. London 1999. http://WWW.WHO.DK/London99/

Wiebelt H, Becker N, Holzmeier S (1996). Kohortenstudie zur Mortalität in einer toluolexponierten Berufsgruppe (Tiefdrucker) und einer Vergleichsgruppe aus der papierverarbeitenden Industrie (Hygieneartikel). Abschlussbericht. Deutsches Krebsforschungszentrum, Abteilung Epidemiologie, Heidelberg.

Wiebelt H, Becker N (1999). Mortality in a cohort of toluene exposed employees (Rotogravure printing plant workers). J. Occup. Environ. Med. **41**(12) 1134-39.

Will AM, McLaren EH (1981). Reversible renal damage due to glue sniffing. Br. Med. J. **283**, 525-526.

Williams RT (1959). Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and other Organic Compounds. 2nd Ed. Chapman and Hall Ltd, London.

Wilson JT, Enfield CO, Dunlap WJ, Cosby RL, Foster DA, Baskin LB (1981). Transport and fate of selected organic pollutants in a sandy soil. J. Environ. Qual. **10**(4), 501-506.

Winchester RV, Madjar VM (1986). Solvent effects on workers in the paint, adhesive and printing industries. Ann. Occup. Hyg. **30**(3), 307-317.

Winneke G, Krämer U, Kastka J (1976). Zur Beeinflussung psychomotorischer Leistungen durch Alkohol und durch verschiedene Lösungsmitteldämpfe. **In**: Horváth M (ed) Adverse effects of environmental chemical and psychotropic drugs. Vol. 2. Elsevier Scientific Publishing Company, Amsterdam.

Winston S, Matsuhita, T (1975). Permanent loss of chromosome initiation in toluene-treated Bacillus subtilis cells. J. bacteriol. **123**, 921-927.

Withey RJ, Hall JW (1975). The joint toxic action of perchloroethylene with benzene or toluene in rats. Toxicology **4**, 5-15.

Woiwode W, Drysch K (1981). Experimental exposure to toluene: further consideration of cresol formation in man. Br. J. Ind. Med. **38**, 194-197.

Woiwode W, Wodarz R, Drysch K, Weichardt H (1979). Metabolism of toluene in man: Gas-chromatographic determination of o-, m- and p-cresol in urine. Arch. Toxicol. **43**, 93-98.

Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F (1956). Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health **14**, 387-398.

WRC (1991). The effect of toluene on early life stages of rainbow trout (*Oncorhynchus mykiss*). Report No. DoE 2943, UK.

Zahlsen K, Eide I, Nilsen AM, Nilsen OG (1992). Inhalation kinetics of C6 to C10 aliphatic, aromatic and naphthenic hydrocarbons in rat after repeated exposures. Pharm. Toxicol. **71**, 144-149.

Zarani F, Papazafiri P, Kappas A (1999). Induction of micronuclei in human lymphocytes by organic solvents in vitro. JEPTO **18**, 21-28.

Zoeteman BCJ, de Greef E, Brinkmann FJJ (1981). Persistency of organic contaminants in groundwater, lessons from soil polution incidents in the Netherlands Sci. Total. Environ. **21**, 187.

Ørbæk P, Nise G (1989). Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers. Am. J. Ind. Med. **16**, 67-77.

Åstrand I (1975). Uptake of solvents in the blood and tissues of man. A review. Scand. J. Work Environ. Health, **1** 199-218.

Åstrand I, Ehrner-Samuel H, Kilbom Å, Övrum P (1972). Toluene exposure I. Concentration in alveolar air and blood at rest and during exercise. Work Environ. Health **9**, 119-30.

ABBREVIATIONS

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

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

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

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

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

Appendix A Sources of toluene exposure

Other existing chemicals/preparations, which contain toluene and which are not covered by this risk assessment contribute to the environmental and human exposure to toluene:

- emission from motor vehicles and aircraft exhaust,
- losses during gasoline marketing activities,
- mixtures containing toluene,
- spills,
- cigarette smoke,
- processes in which toluene containing products are used.

Toluene source

An "overview" of the toluene molecule existence and formation in the EU based on information from the main manufacturers is presented below.

Table A.1 Toluene existence and formation in the EU

	kTonnes
In crude oil	2,900
From coal	100
From pyrolysis/reformation	13,600
Imports	200
Diesel engine exhaust	200
Fires, vulcanos, tobacco smoke, etc.	?
Total	17,000

Toluene products

Toluene products and toluene molecule containing products in theEU are presented below.

Table A.2 Toluene and toluene containing substances in the EU

	kTonnes
Toluene commercial product	2,800
Gasoline	14,000
Diesel engine exhaust	200
Total	17,000

The risk assessment report is concerned with the isolated toluene (the commercial product). Assuming the import to be 200 kTonnes/year (worst case) the total consumption in the EU would be 2,800 kTonnes which is used in the EUSES model calculations.

Crude oil and coal component

The toluene content in crude oil is measured in 4 crude oils to be 0.4, 0.4, 0.66 and 1.24 wt% (CONCAWE report 1998/52). The same report shows EU refinery annual intake of crude oil to be 526,000-580,600 kTonnes in the period 1991-1996. Assuming an average of 0.5% toluene and 580,000 kTonnes crude oil yields 2,900 kTonnes toluene in crude oil.

Toluene produced from coal is reported to amount to approximately 73 kTonnes (Parpinelli Technon, 1995). This number has been rounded to 100 kTonnes.

The volume of toluene formed through pyrolysis and reformation is based on a calculated material balance: Toluene in gasoline + commercial toluene - toluene from crude oil - toluene from coal - toluene from imports = 13,600 kTonnes.

Gasoline

Traffic is the main source of toluene emitted into the environment.

Release from gasoline and diesel

The emission from automobile engine exhaust of toluene is calculated using 8.6% content in gasoline to 350 mg/m^3 equivalent to 370 mg/km according to ECE-test (Häsänen et al., 1981). Diesel fuel contains 0.02 to 0.7% by wt of toluene depending of diesel type and use (IPCS, 1996). In diesel exhaust, the amount of released toluene is 190 mg/kg used (burned) diesel (Rippen, 1992). Toluene release from diesel engines has been measured in 8 diesel types to be 2 to 9 mg/km; average 4.3 mg/km (Beije, 1993). IPCS (1996) has found the emission to be <1 to 2 mg/km for light-duty vehicles (weight below 3.5 t or 5 t) and 2-32.5 mg/km for heavy-duty vehicles (weight >5 t).

The traffic volume in Western Europe in 1992 was estimated to be $2.2 \cdot 10^{12}$ km (Styrene Risk Assessment report, 1996). Using this figure will overestimate toluene emission as it includes diesel vehicles. The content in diesel is considerably lower than in gasoline (<0.2%, Ripppen,1992).

The estimated emissions for Western Europe are $2.2 \cdot 10^{12} \cdot 370 \cdot 10^{-9}$ = 814,000 tons/year. Taking 10% of this for the regional release gives 81,400 t/yr (223,000 kg/day)

To compensate for the reduced release from diesel engines the value is estimated to be divided by a factor 2. This would result in the continental release of 417,000 t/yr, which is close to the value of 404,500 t/yr. estimated by Sloof and Blokzijl (1988). Thus the regional release would be estimated to be 41,700 t/yr. (or 114,000 kg/d).

This estimate is close to the estimate from Section 2.3.3 where 13.7 million tonnes were estimated to remain in the gasoline and 3.3% to be expelled as unburned toluene in the exhaust gasses. These assumptions would result in a continental emission of 451,000 tonnes/year to air.

The emission of toluene into air in the EU has been estimated in Sloof and Blokzijl (1988). The emissions resulting from road traffic are determined by the toluene content in petrol. The total use of solvents in the industrialised countries was estimated at approx. 12 kg per inhabitant per year and the share of toluene at about 5% of this amount, i.e. 0.6 kg/inhabitant/year. “Other emissions” have been estimated by using an emission factor per inhabitant derived from the situation in The Netherlands (at about 0.26 kg/inhabitant/year), cf. **Table A.3** below.

Table A.3 Emissions of toluene into air in the EU12 in kTonnes, 1982 (Sloof and Blokzijl, 1988)

Country	Road traffic	Solvent use	Solvent range	Process emissions	Other emissions	Total
Belgium	11.0	6.0	4-8	0	2.4	19.4
Denmark	6.5	3.0	2-4	0	1.3	10.8
France	86.5	31.0	22-40	0.1	13.3	130.9
Germany (BRD)	81.0	35.0	25-45	0.2	15.2	131.4
Greece	7.5	4.5	4-5	0	2.4	14.4
Ireland	4.0	1.5	1-2	0	0.9	6.4
Italy	50.0	33.5	23-44	0.4	14.1	98.0
Luxemburg	0.5	0.2	0.1-0.3	0	0.0	0.7
The Netherlands	18.0	5.8		0.1	2.9	26.8
Portugal	12.5	4.3	4-4.5	0.1	2.5	19.4
Spain	47.5	17.5	15-20	0.1	9.3	74.4
United Kingdom	79.5	31.5	23-40	0.1	13.7	124.8
Total	404.5	173.8	130-220	1.1	78.0	657.4

Emission to air and water in the Netherlands

Toluene emission to air and water in the Netherlands for 1995 has been estimated by Dutch authorities (Emissieregistratie, 1997).

Table A.4 Toluene emission to air and water in the Netherlands, 1995 (t/y)

Source	Air	Water
Refineries	418	3.5
Energy sector	2,130	0.03
Chemical industry	850	3.8
Other industry	7,650	1.5
Waste	146	0.5
Agriculture	47	0
Traffic	8,840	431
Construction	1,390	0
Consumers	1,100	248
Services	702	5
Drinking water production	0.06	0
WWTP	0.05	0
Nature	0	0
Total	23,300	693

From **Table A.4** it can be concluded that emission to air by far exceeds those to water by a factor of approximately 3. Generally, the Dutch data support the RAR employed emission scenarios according to the realistic worst case. The Dutch data indicate that the contribution from traffic is approximately 38% of the total air emission and 62% of the total release to water.

The RAR only includes the emissions estimated from production and use of isolated toluene and not traffic etc. Therefore, the Dutch values are not directly comparable to the RAR values.

Appendix B Exposure assessment by the main manufacturers

An exposure assessment has been performed by the main manufacturers and their assessment has been included as an appendix.

Production facilities - characteristics

The data from producers with regard to production volumes, process type, wastewater and sludge treatment, volumes of wastewater and dilution in receiving water are summarised below in **Table B.1**.

There were 25 facilities reporting production volumes of toluene in pure form, with a total annual volume of 2,591 kTonnes (kt). Six sites reported production of toluene in refinery streams with a volume of 936 kt. Of these sites, only one also reported production of pure toluene at a volume of 13 kt. The occurrence in refinery streams at this site was 23 kt yearly. The occurrence of toluene in refinery streams was not included further in the consideration of toluene emissions at the production stage.[9] The mean production of pure toluene at these 26 sites was 199 kt, with a median value of 60.5, and a 90 percentile value of 206. These production volumes were primarily from 1995, with 3 unspecified as to year and 3 for 1994.

Regarding the general nature of production and wastewater treatment processes: All responders (23 of 25) indicated that production is in closed systems and is continuous. The majority (18) indicated that production was a dry process (no contact with wastewater) and 5 reported a wet process. Although the typical process is dry, a wet process may be considered a worst case. Regarding wastewater treatment systems, 19 responded and of these, 18 indicated that wastewater was treated and 2 that it was not. This amounts to about 90% with treatment and 10% without. The TGD assumes that 20% of the wastewater is untreated. Seventeen (17) responders gave further details of the wastewater treatment plant (WWTP). Sludge from WWTP was incinerated at 15 of these, landfilled at 1, and applied to agricultural soil at 1. The receiving water was rivers in 16 instances, the sea 4, an estuary 1, and a lake 1.

Details of the flows are given in **Table B.1**. The mean river flow was 586 m^3/sec, with a median of 125 and a 90 percentile of 23. The dilution into oceans is theoretically much larger due tides and ocean volume but not considered. The instance of a reported flow into a lake is atypical and not considered. Six respondents reported WWTP influent concentrations and 9 reported effluent concentrations. The mean influent concentration of toluene was 2.3 mg/l and the effluent was 0.02 mg/l. The median effluent concentration was 0.01 mg/l and the 90 percentile was 0.05 mg/l.

[9] Toluene occurs naturally in crude oil and additional amounts are produced during refining (catalytic reformation). The toluene containing refinery streams (light aromatic naphthas) are blended with other naphthas to produce gasoline. In general, it is not economic to isolate toluene from these streams only to add it back to the final gasoline mixture. The component naphthas in gasoline and gasoline itself are substances separate from toluene, having their own EINECS numbers. These substances must be assessed for risk separately from toluene.

Table B.1 Mass flows and concentrations of toluene at production sites

Type of flow or concentration	No. Reporting	Mean Value	Median Value	90%-ile
Production volume (kTonnes/yr.)	25	199	60.5	206
Wastewater flow (m^3/day)	17	45,200	19,200	4,800
Receiving water flow (m^3/sec)	14	586	125	23
Dilution (calculated)	-	1,120	562	414
WWTP influent toluene (mg/L)	6	2.3	1.2	6 a)
WWTP effluent toluene (mg/L)	9	0.02	0.01	0.05 a)
Receiving water toluene (calc. μg/L)	-	0.018	0.018	0.12

a) worst case

These data cannot be fully compared with those from the Emission Scenario Document for IC-3 in the TGD since the wastewater flows section is under preparation. The Document does treat river flows and lists the 90 percentile flow from such plants at 60 m^3/sec, somewhat higher than the value of 23 above. The default wastewater treatment flow from the TGD is for municipal plants serving 10,000 inhabitants and is a flow of 2,000 m^3/day.

The use of these parameters in assessing environmental concentrations is given an order of preference in the TGD (Chapter 3, 2.3.3.3). This is:

- specific information for a given substance (e.g. from producers.),
- specific from the emission scenario documents,
- emission factors as included in the release tables in Appendix I [of the TGD].

The information given in **Table B.1** uses the same approach as the Emission Scenario Documents, namely, rank ordering the available data from numerous sites and calculating the 90 percentile as a "reasonable worst case". The calculated concentrations presented in **Table B.1** probably are not considered by themselves to establish a local PEC, since they are from a minority of producers (9 of 25) and since no information on the sampling and analysis program is provided. They are used to check the model-calculated values as discussed in the TGD. However, the wastewater treatment flows and the receiving water flows are representative of the industry and ought to be used in preference to the default tables in Appendix I of the TGD.

Emissions data were reported from a few of the producers. Six reported emissions to water, 3 in kt/year and 3 in concentration units. Four producers reported annual emissions to air. These data are insufficient to represent the industry and the values from the Emission Scenario Documents should be used. Where available, the Emission Scenario Documents should be used for calculation of emissions at formulation and processing as well.

Processing facilities - characteristics

The data collected by APA included information from sites which combined production and processing and from others which only reported processing. There were 11 facilities reporting processing and they processed a total of 1,252 kt/year, or nearly half of total toluene production. The reported process used was again as an intermediate (84%) and as a basic chemical (11%). Of the 11 sites, 6 gave details of the process. All 6 were continuous and closed processes. Of the 6, 3 were dry and 3 wet, so wet represents the worst case for emissions to water.

The characteristics of wastewater treatment were described for 8 of the processors and all of these directed wastewater to treatment facilities. The sludge from these WWTPs were incinerated in 3 cases and landfilled in 4. No application to soil was reported. The receiving water for these WWTPs was rivers in 8 instances, the sea in one and an estuary in one.

Details of the mass flows and concentrations reported for processing site WWTPs are given in **Table B.2**. The average amount processed per site was 114 kt/year. And the 90 percentile was 206. Wastewater flows were somewhat lower than at production sites with a median flow of 2,440 m^3/day. Due to the small number of sites reporting, the 90 percentile was also the worst case or lowest flow of 1.4 m^3/day. River flows were lower than for production facilities with a median flow of 50 m^3/sec and a worst-case low flow of 1.4 m^3/sec. Thus, the worst-case dilution is calculated as 30-fold. Effluent toluene concentrations were reported for 5 sites and the highest of these (worst case) was 0.42 mg/l, giving a river concentration of 14 μg /l.

Table B.2 Mass flows and concentrations of toluene at processing sites

Type of flow or concentration	No. Reporting	Mean Value	Median Value	90%-ile
Process volume (kTonnes/yr.)	11	114	20	206
Wastewater flow (m^3/day)	8	74,628	24,400	4,020 a)
Receiving water flow (m^3/sec)	7	229	50	1.4 a)
Dilution (calculated)	-	265	177	30 a)
WWTP influent toluene (mg/L)	1	-	0.06	0.06 a)
WWTP effluent toluene (mg/L)	5	0.096	0.01	0.42 a)
Receiving water toluene (calc. μg/L)	-	0.36	0.056	14 a)

a) worst case

Calculation of Predicted Environmental Concentrations (PECs) from toluene production, production + processing and processing sites

The measurements and EUSES calculation have been performed for production sites, sites with combined production and processing and 6 processing sites. The data are presented in Tables B.3 and B.4.

There are two different scenarios for production sites, those in which toluene is produced as a chemical intermediate and processed elsewhere and those in which toluene is produced and processed as a chemical intermediate on the same site. Production is continuous in closed systems using dedicated equipment. Off-site processing as a chemical intermediate accounts for a remaining 53.5% (total = 73.5%) of the use as an intermediate.

Table B.3 Calculation of PECs at production sites

Site		P1 [1]	P2	P3	P4	P5	P6	P7	P8	P9
Tonnage	Amount produced (1,000 tonnes)	1.5	81.3	180	13	36.7	103	75	100	240
	Amount imported from outside EU (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount bought in from EU (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount processed (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount formulated (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount sold on for processing/formulation elsewhere (1,000 tonnes)	1.5	81.3	180	13	36.7	103	75	100	240
Site	Type	Production	Production	Production	Production	Production	Production	Production	Production	Production
Specific	Main use category	1c	1c	1c	1c	1c	1c	1c	1c	1c
Data	Industry category	3	3	3	3	3	3	3	3	3
	Use category	33	33	33	33	33	33	33	33	33
Fate of Sludge		incinerated	incinerated	incinerated	landfilled	incinerated			landfilled	incinerated
Release fractions:		Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)
	- to air	0.01	0.01	0.01	**8.8E-05**	0.01	**7.282E-06**	**0** [2]	0.01	**0.0002**
	- to water	0.003	**0.00082**	**0.00002**	0.003	0.003	**3.136E-05**	0.003	0.003	0.003
Emissions	- to air (kg/day)	41.10	2227.40	4931.51	3.13	1005.48	2.05	0	2739.73	131.51
	- to water (kg/day)	12.33	**8.8**	9.86	106.85	301.64	8.85	0.3727	821.92	1972.60
WWTP	Size of WWTP (m^3/day)	**12,772**	**3,000**	**4800**	2000	**19200**	2000	**1133**	**60000**	**840**
	Influent concentration (mg/l)	**5.10** [3]	2.93	2.05	53.42	15.71	4.42	0.33	**1.44**	**5.00**
	WWTP removals (%-calc)	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421
	Effluent concentration (mg/l)	0.30	0.17	**0.005** [4]	**0.050**	0.910	0.256	**0.01** [5]	**0.013**	0.290
	Dilution (-)	**28.6** [6]	**150.00**	**36000.00**	**25.00**	**22.50**	**44929.00**	**4320.00**	**3333.30**	**82,285.71**
	Basis of Dilution	low flow	unspecified	unspecified	unspecified	unspecified	10^{th}%ile	average	unspecified	10th%ile
Water	Concentration (mg/l): measured									
	Concentration (mg/l): calculated	$1.03 \cdot 10^{-2}$	$1.1 \cdot 10^{-3}$	$1.39 \cdot 10^{-7}$	$2.00 \cdot 10^{-3}$	$4.04 \cdot 10^{-2}$	$5.70 \cdot 10^{-6}$	$2.31 \cdot 10^{-6}$	$3.90 \cdot 10^{-6}$	$3.52 \cdot 10^{-6}$
Air	Concentration at 100m (mg/m^3): measured		**0.010**							
	Concentration at 100m (mg/m^3): calculated	0.011	0.619	1.371	0.0144	0.2795	0.0012	$5.04 \cdot E-05$	0.7616	0.267
Soil										
Local	Concentration calculated (mg/kg dry) (air deposition only)	$2.223 \cdot 10^{-4}$	$1.054 \cdot 10^{-2}$	$2.330 \cdot 10^{-2}$	$2.599 \cdot 10^{-4}$	$5.439 \cdot 10^{-3}$	$3.000 \cdot 10^{-5}$	$8.55 \cdot 10^{-7}$	$1.482 \cdot 10^{-2}$	$5.146 \cdot 10^{-3}$
Agric	Concentration calculated (mg/kg dry) (air deposition only)	$2.223 \cdot 10^{-4}$	$1.054 \cdot 10^{-2}$	$2.330 \cdot 10^{-2}$	$2.599 \cdot 10^{-4}$	$5.439 \cdot 10^{-3}$	$3.000 \cdot 10^{-5}$	$8.55 \cdot 10^{-7}$	$1.482\ 10^{-2}$	$5.146 \cdot 10^{-3}$
Grassland	Concentration calculated (mg/kg dry) (air deposition only)	$1.146 \cdot 10^{-4}$	$5.432 \cdot 10^{-3}$	$1.202 \cdot 10^{-2}$	$1.340 \cdot 10^{-4}$	$2.804 \cdot 10^{-3}$	$1.547 \cdot 10^{-5}$	$4.41 \cdot 10^{-7}$	$7.641 \cdot 10^{-3}$	$2.654 \cdot 10^{-3}$

1) Production stopped 1998
2) As provided by the company
3) 90%percentile of monthly means of daily monitoring during production period. Previous data given refer to cleaning operations of tanks containing products containing non-isolated toluene.
4) Limit of detection
5) 90%percentile at DL: 322 < DL at 0,01; 15 at mean 0,029
6) Effluent is diluted by a factor of 2.86 (35%) before being discharged. Assuming default TDG dilution of 10 this yields a minimum combined site-specific dilution factor of 28.6

Table B.3 continued overleaf

Table B.3 continued Calculation of PECs at production sites

Site		P10	P11	P12	P13	P14	P15	P16	P17	P18
Tonnage	Amount produced (1,000 tonnes)	8.065	66	116.6	170	24.8	55	25	41	43
	Amount imported from outside EU (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount bought in from EU (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount processed (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount formulated (1,000 tonnes)	0	0	0	0	0	0	0	0	0
	Amount sold on for processing/formulation elsewhere (1,000 tonnes)	8.065	66	116.6	170	24.8	55	25	41	43
Site	Type	Production	Production	Production	Production	Production	Production	Production	Production	Production
Specific	Main use category	1c	1c	1c	1c	1c	1c	1c	1c	1c
Data	Industry category	3	3	3	3	3	3	3	3	3
	Use category	33	33	33	33	33	33	33	33	33
Fate of Sludge		resued onsite	incinerated	incinerated			incinerated		incinerated	landfilled
Release fractions:		Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)
	- to air	**0.00023**	0.01	0.01	0.01	0.01	**$1.111 \cdot 10^{-6}$**	**0.0000004**	**$1.22 \cdot 10^{-6}$**	**$1.163 \cdot 10^{-6}$**
	- to water	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
Emissions	- to air (kg/day)	5.08	**25.0**	**43.84**	4,657.53	679.45	0.17	0.03	0.14	0.14
	- to water (kg/day)	66.29	542.47	35.20 [1]	**0.00** [2]	203.84	452.05	205.48	336.99	353.42
WWTP	Size of WWTP (m^3/day)	**360**	**6,340**	**4,168**	2,000	2,000	**27,000**	**24,000**	**28,800**	**7,700**
	Influent concentration (mg/l)	184.13	85.56	**8.45**	0.00	101.92	16.74	8.56	11.70	**1.00**
	WWTP removals (%-calc)	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421
	Effluent concentration (mg/l)	**0.010**	**$5.00 \cdot 10^{-4}$** [3]	**$3.65 \cdot 10^{-4}$** [4]	0.000	5.900	**0.020**	**0.005**	**0.010**	**0.050**
	Dilution (-)	**5,555.56**	**120,000**	10.00	10.00	10.00	**$1.00 \cdot 10^{+6}$**	**150.00**	**$1.00 \cdot 10^{+6}$**	**$1.68 \cdot 10^{+3}$**
	Basis of Dilution	unspecified	unspecified	TGD default	TGD default	TGD default	unspecified	unspecified	unspecified	10^{th}%ile
Water	Concentration (mg/l): measured					**n.d.** [5]				
	Concentration (mg/l): calculated	$1.80 \cdot 10^{-6}$	$4.17 \cdot 10^{-9}$	$3.65 \cdot 10^{-5}$	0	$5.90 \cdot 10^{-1}$	$2.00 \cdot 10^{-8}$	$3.33 \cdot 10^{-5}$	$1.00 \cdot 10^{-8}$	$2.97 \cdot 10^{-5}$
Air	Concentration at 100m (mg/m^3): measured	**0.00023** [6]		**0.004** [7]	**53.6** [8]					
	Concentration at 100m (mg/m^3): calculated	0.0014	0.0733	0.0047	1.2948	0.1889	0.0611	$2.78 \cdot 10^{-2}$	$4.55 \cdot 10^{-2}$	$4.78 \cdot 10^{-2}$
Soil										
Local	Concentration calculated (mg/kg dry) (air deposition only)	$1.761 \cdot 10^{-4}$	$1.363 \cdot 10^{-3}$	$2.877 \cdot 10^{-4}$	$2.199 \cdot 10^{-2}$	$3.675 \cdot 10^{-3}$	$1.038 \cdot 10^{-3}$	$4.716 \cdot 10^{-4}$	$7.738 \cdot 10^{-4}$	$8.115 \cdot 10^{-4}$
Agric	Concentration calculated (mg/kg dry) (air deposition only)	$1.761 \cdot 10^{-4}$	$1.363 \cdot 10^{-3}$	$2.877 \cdot 10^{-4}$	$2.199 \cdot 10^{-2}$	$3.675 \cdot 10^{-3}$	$1.038 \cdot 10^{-3}$	$4.716 \cdot 10^{-4}$	$7.738 \cdot 10^{-4}$	$8.115 \cdot 10^{-4}$
Grassland	Concentration calculated (mg/kg dry) (air deposition only)	$9.079 \cdot 10^{-5}$	$7.026 \cdot 10^{-4}$	$1.484 \cdot 10^{-4}$	$1.134 \cdot 10^{-2}$	$1.895 \cdot 10^{-3}$	$5.352 \cdot 10^{-4}$	$2.431 \cdot 10^{-4}$	$3.990 \cdot 10^{-4}$	$4.184 \cdot 10^{-4}$

1) Calculated from Ceffl and STP flow
2) As provided by the company
3) < 0.5 mg/m^3 = A.M. of D.L. 1 sample per month 1997-1999
4) A.M. n = 63
5) No other information is provided other than conc in receiving water are below detection
6) Maximum estimated concentration at 50 meters from source based on atmospheric dispersion modleing for this site
7) Mean of 4 measurement points at 50-200 m distance from site border
8) Maximum measured value - no indication of location where sampling took place - suspect data point

Table B.3 continued Calculation of PECs at production sites and combined production and processing sites

Site		P19	PP1	PP2	PP3	PP4	PP5	PP7
Tonnage	Amount produced (1,000 tonnes)	700	8.5	49	206	35	194	16
	Amount imported from outside EU (1,000 tonnes)	0	0	0	0	0	0	0
	Amount bought in from EU (1,000 tonnes)	0	0	111	0	0	0	0
	Amount processed (1,000 tonnes)	0	2.6	158	206	0	123	3.9
	Amount formulated (1,000 tonnes)	0	5.9	2	0	17.5	0	0
	Amount sold on for processing/formulation elsewhere (1,000 tonnes)	700	0	0	0	17.5	71	12.1
Site	Type	Production	Prod+Proc	Prod+Proc	Prod+Proc	Prod+Proc	Prod+Proc	Prod+Proc
Specific	Main use category	1c	1b	1b	1b	1c	1b	1b
Data	Industry category	3	3	3	3	3	3	3
	Use category	33	33	33	33	33	33	33
Fate of Sludge		landfilled	incinerated	incinerated			incinerated	
Release fractions:		Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)
	- to air	**0.0035**	**0.0012**	**$1.09 \cdot 10^{-5}$**	**0.000149**	0.01	**$1.55 \cdot 10^{-7}$**	0.001
	- to water	0.003	0.003	0.003	**$4.85 \cdot 10^{-6}$**	0.003	0.003	0.003
Emissions	- to air (kg/day)	6712.33	27.95	1.47	84.11	958.90	0.08	10.68
	- to water (kg/day)	5753.42	69.86	402.74	2.74	287.67	1,594.52	32.05
WWTP	Size of WWTP (m^3/day)	**6,000**	**72,000**	**410400**	2,000	2,000	**52,800**	**67,200**
	Influent concentration (mg/l)	958.90 [1]	0.97	0.98	1.37	143.84	30.20	**0.006**
	WWTP removals (%-calc)	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421	0.9421
	Effluent concentration (mg/l)	**0.420**	**0.003** [2]	0.057	0.079	8.330	**0.010**	$3.47 \cdot 10^{-4}$
	Dilution (-)	**50**	**22.00**	**154.00**	**154.00**	10.00	**$1.00 \cdot 10^{+6}$**	**$6.53 \cdot 10^{+1}$**
	Basis of Dilution	unspecified	10th %ile	10th %ile	unspecified	TGD default	unspecified	unspecified
Water	Concentration (mg/l): measured	**0.0014** [3]						**< 0.002** [4]
	Concentration (mg/l): calculated	$8.40 \cdot 10^{-3}$	$1.36 \cdot 10^{-4}$	$3.69 \cdot 10^{-4}$	$5.15 \cdot 10^{-4}$	$8.30 \cdot 10^{-1}$	$1.00 \cdot 10^{-8}$	$5.32 \cdot 10^{-6}$
Air	Concentration at 100m (mg/m^3): measured							**0.045** [5]
	Concentration at 100m (mg/m^3): calculated	1.87	0.0094	0.0544	0.0234	0.2666	0.215	$4.33 \cdot 10^{-3}$
Soil								
Local	Concentration calculated (mg/kg dry) (air deposition only)	$4.489 \cdot 10^{-2}$	$2.922 \cdot 10^{-4}$	$9.309 \cdot 10^{-4}$	$4.033 \cdot 10^{-4}$	$5.187 \cdot 10^{-3}$	$3.659 \cdot 10^{-3}$	$1.240 \cdot 10^{-4}$
Agric	Concentration calculated (mg/kg dry) (air deposition only)	$4.489 \cdot 10^{-2}$	$2.922 \cdot 10^{-4}$	$9.309 \cdot 10^{-4}$	$4.033 \cdot 10^{-4}$	$5.187 \cdot 10^{-3}$	$3.659 \cdot 10^{-3}$	$1.240 \cdot 10^{-4}$
Grassland	Concentration calculated (mg/kg dry) (air deposition only)	$2.314 \cdot 10^{-2}$	$1.507 \cdot 10^{-4}$	$4.800 \cdot 10^{-4}$	$2.080 \cdot 10^{-4}$	$2.674 \cdot 10^{-3}$	$1.886 \cdot 10^{-3}$	$6.393 \cdot 10^{-5}$

1) This concentration exceeds water solubility by a factor 2 and is unlikely since free product would be removed via oil-water separator in pre-treatment to WWTP
2) Limit of detection
3) As provided by the company
4) Measurement showed < limit of determinaion (0.002 mg/l)
5) Maximum fenceline concentrations based on 4-6 measurements per year between 1998 and 1999

Table B.4 Calculation of PECs at processing sites

Site			PC1	PC2	PC3	PC4	PC5	PC6
Tonnage	Amount produced (1,000 tonnes)		0	0	0	0	0	0
	Amount imported from outside EU (1,000 tonnes)		0	0	0	0	0	0
	Amount bought in from EU (1,000 tonnes)		<1	0.225	33	20	0.45	0.16
	Amount processed (1,000 tonnes)		1 [1]	0.225	0	20	0.45	0.16
	Amount formulated (1,000 tonnes)		0	0	0	0	0	0
	Amount sold on for processing/formulation elsewhere		0	0	0	0	0	0
Site	Type		Processing	Processing	Processing	Processing	Processing	Processing
Specific	Main use category	Defaults [2]	3	3	3	3	1b	1b
Data	Industry category		3	3	3	3	3	3
	Use category		33	33	33	33	33	33
Fate of sludge					incinerated		landfilled	landfilled
Release fractions:			Default values	Default values	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)	Default values (except bold font)
	- to air		0.025 [3]	0.025	0.025	0.00013	0.0017	0.00001
	- to water		0.003 [3]	0.007	0.007	0.007	0.003	0.003
Emissions	- to air (kg/day)		68.49	15.41	2260.27	6.85	2.10	4.38E-03
	- to water (kg/day)		8.22	4.32	632.88	0.69 [4]	3.70	1.32
WWTP	Size of WWTP (m^3/day)		2000	2000	2000	4020	21600	3,000
	Influent concentration (mg/l)		4.11	2.16	316.44	0.17 [4]	0.17	0.44
	WWTP removals (%-calc)		0.9421	0.9421	0.9421	0.9421	0.9421	0.9421
	Effluent concentration (mg/l)		0.24	0.12	18.322	0.010 [5]	0.01 [6]	0.025 [6]
	Dilution (-)		10.00	10.00	10.00	31.09 [7]	7.80	1870
	Basis of Dilution		TGD default	TGD default	TGD default	10th %ile	low flow	low flow
Water	Concentration (mg/l): measured						< 0.01 [8]	< 0.2 [9]
	Concentration (mg/l): calculated		$2.38 \cdot 10^{-2}$	$1.25 \cdot 10^{-2}$	1.83	$3.22 \cdot 10^{-4}$	$1.28 \cdot 10^{-3}$	$1.36 \cdot 10^{-5}$
Air	Concentration at 100m (mg/m^3): measured			0.010			0.043 [10]	
	Concentration at 100m (mg/m^3): calculated		0.019	0.00428	0.6284	0.0019	$5.83 \cdot 10^{-4}$	$1.78 \cdot 10^{-4}$
Sludge	Concentration calculated (mg/kg dry)		1817	954	not applic.	154	not applic.	not applic.
Local	Concentration calculated (mg/kg dry) (air deposition only)		$3.422 \cdot 10^{-4}$	$8.265 \cdot 10^{-5}$	$1.212 \cdot 10^{-2}$	$3.393 \cdot 10^{-5}$	$1.838 \cdot 10^{-5}$	$3.085 \cdot 10^{-6}$
Soil	Concentration calculated (mg/kg dry) (air deposition + sludge)		0.467	0.245		0.039		
Agric	Concentration calculated (mg/kg dry) (air deposition only)		$3.422 \cdot 10^{-4}$	$8.265 \cdot 10^{-5}$	$1.212 \cdot 10^{-2}$	$3.393 \cdot 10^{-5}$	$1.838 \cdot 10^{-5}$	$3.085 \cdot 10^{-6}$
Soil	Concentration calculated (mg/kg dry) (air deposition + sludge)		0.080	0.042		0.007		
Grassland	Concentration calculated (mg/kg dry) (air deposition only)		$1.764 \cdot 10^{-4}$	$4.262 \cdot 10^{-5}$	$6.250 \cdot 10^{-3}$	$1.749 \cdot 10^{-5}$	$9.477 \cdot 10^{-6}$	$1.566 \cdot 10^{-6}$
Soil	Concentration calculated (mg/kg dry) (air deposition + sludge)		0.032	0.017		0.003		

1) Highest tonnage used
2) Use defaults because nature of processing unclear
3) Use categories unclear, so typical default values used
4) Calculated from Ceffl, STP removal and STP flow
5) Based on 7 24h samples below D.L. of 0.010 mg/l
6) Limit of determination
7) Dilution based on 10% flow
8) Measurement showed < limit of determination (0.01 mg/l)
9) Measurement showed < limit of determination (0.2 mg/l)
10) Maximum air concentration reported from measurements in 1998 and 1999

Appendix C BAuA model accounting for the vapour pressure of highly volatile substances in dermal exposure assessment

The German competent authorities for Existing Substances (BAuA) proposed to incorporate a method to account for the vapour pressure of highly volatile substances in dermal exposure assessment (BAuA, 2000). The method includes the following steps:

1. estimating dermal exposure to a substance during a certain scenario in mg/cm^2 using EASE 1.0 (TGD, 1996).
2. determining the evaporation time (in seconds) in which the amount of a substance (mg) evaporates from a certain area of the skin (cm^2). To do so an equation based on the EASE-estimate, physical properties of the substance and a coefficient of mass transfer (between liquid and vapour) is used.
3. calculating the amount of substance being absorbed (using the skin absorption rate (mg/s) of the substance) during the evaporation time.

Step 1, estimate dermal exposure

This has been done using EASE in Section 4.1.1. For instance, the upper value of the EASE estimate is 1 mg/cm^2 when input parameters are non-dispersive use and intermittent contact level, and 5 mg/cm^2 when input parameters are non-dispersive use with an extensive contact level or wide dispersive use with an intermittent contact level.

Step 2, determination of evaporation time

The German proposal (BAuA, 2000) includes the following algorithm:

$$t_{(s)} = \frac{m \cdot R \cdot T}{M \cdot \beta \cdot p \cdot A} \cdot K$$

where,
t: time [s]
m: mass, EASE estimate, [mg]
R: gas constant: 8.314 $J \cdot K^{-1} \cdot mol^{-1}$
T: skin temperature [K]
M: molar mass: 92,1 $g \cdot mol^{-1}$
β: coefficient of mass transfer in the vapour phase [m h^{-1}], for calculation:
$\beta = 8.7$ $m \cdot h^{-1}$, see below
p: vapour pressure of the pure substance [Pa]
A: area, EASE: 1 cm^2
K: conversion factor: $3.6 \cdot 10^4$

Skin temperature (T)

The skin temperature amounts normally to 28–32°C (ambient temperature: 20–22°C). In the equation, the reduction of the skin temperature and accordingly of the vapour pressure caused by the evaporation process is not considered. This could be taken into account by choosing a lower mean temperature for the evaporation process (BAuA, 2000). For illustrative purposes the calculations in Table 1 are performed using 20°C and 30°C, respectively.

Vapour pressure (p)

The vapour pressure at 20°C and 30°C is 2,780 and 4,520, respectively (BAuA, 2000).

Coefficient of mass transfer (β)

For the coefficient of mass transfer β only little knowledge is available. It is assumed that the mass transfer during evaporation occurs until a state of equilibrium is achieved and that the main influence on evaporation is the transfer through the interface. Based on measurement results a relationship for the calculation of mass transfer coefficients has been derived:

$$\beta = (0.0111 \cdot v^{0.96} + D_g^{0.19}) / (\nu^{0.15} + X^{0.14})$$

D_g : coefficient of diffusion, gas phase
v: velocity of air [$m \cdot h^{-1}$]
ν: kinematic viscosity [$m^2 \cdot h^{-1}$]
X: length of the area of evaporation in the direction of the air stream [m]

For many organic solvents, D_g is approx. 0.05 $m^2 \cdot h^{-1}$. The velocity of the air (v) is often between 720 $m \cdot h^{-1}$ and 2,520 $m \cdot h^{-1}$. In this, β is about 8.7 $m \cdot h^{-1}$ for low air velocities and 15.9 $m \cdot h^{-1}$ for high air velocities. For a conservative approach, a value of β = 8.7 $m \cdot h^{-1}$ could be used (BAuA, 2000).

The calculated evaporation time for 1 and 5 mg/cm^2, at a skin temperature of 20 or 30 °C, is shown in **Table C.1.**

Table C.1 Calculated evaporation times for T = 20°C and T = 30°C

Skin temperature [°C]	Vapour pressure [Pa]	Evaporation time [s] (m = 1 mg/cm^2)[1)]	Evaporation time [s] (m = 5 mg/cm^2)[2)]
20	2,780	39	197
30	4,520	25	125

1) Upper value of EASE estimate: non dispersive use, contact level: intermittent
2) Upper value of EASE estimate: non dispersive use, contact level: extensive or wide dispersive use, contact level: intermittent

Step 3, calculate the amount of substance being absorbed during the evaporation time

This step depends on the dermal absorption rate of toluene. There are, however, no reliable data which give an estimate of the skin absorption rate of toluene in humans.

If the skin absorption rate of toluene, determined in rat skin, of 0.78 µg/cm^2/min is used (Tsuruta, 1982), the proposed method leads to the results presented in **Table C.2**, under the assumption that pure toluene is used.

Table C.2 Calculated amount of toluene absorbed in evaporation time for toluene at 20 degrees Celsius

EASE estimate [mg/cm²]		Evaporation time [s]	Skin absorption rate [mg/cm²/min]	Amount of toluene absorbed in evaporation time [mg/cm²]
1	20	39	0.00078 1)	0.0005
	30	25		0.0003
5	20	197		0.0026
	30	125		0.0016

1) Skin absorption rate determined in rat skin (Tsuruta, 1982)

According to the Aromatics Producers Association toluene is estimated using the model Skinperm to penetrate undamaged human skin with a rate of 0.05 mg cm^{-2} h^{-1} (APA, 1998b). If this value is used, the proposed method leads to the results presented in **Table C.3**, under the assumption that pure toluene is used.

Table C.3 Calculated amount of toluene absorbed in evaporation time for toluene at 20 degrees Celsius

EASE estimate [mg/cm²]		Evaporation time [s]	Skin absorption rate [mg/cm²/min]	Amount of toluene absorbed in evaporation time [mg/cm²][5]
1	20	39	0.05 1)	0.03
	30	25		0.02
5	20	197		0.16
	30	125		0.10

1) Estimated rate of toluene penetration through undamaged skin (APA, 1998b)

Limitations of the model and the input parameters.

The proposed method certainly gives good opportunities to make a more realistic estimate of actual dermal exposure for highly volatile substances. There are, however, a number of issues which need to be taken into consideration or need clarification before this model can be used in dermal exposure assessment of existing substances:

It should be noted that the model gives an estimate of the evaporation time. The use of this model for estimating the amount of toluene absorbed through the skin is thus highly dependent on reliable data on the skin absorption rate. This is not available for toluene.

The equation used to calculate the evaporation time contains parameters on which very limited knowledge is available. As recognised by the BAuA, there is only little knowledge on the mass transfer coefficient. There is a need for more information on the actual variation in the mass transfer coefficient between different substances and on how "worst case" the suggested default are. Similar questions (variation, degree of conservatism) need to be answered for the parameters that are used to calculate the suggested mass transfer coefficient, such as: the coefficient of diffusion (Dg), the air velocity, the relevant length of the evaporation path (length of the pool in the direction of the airflow and the air speed.

As already stated by the BAuA, the model is not suitable for use of mixtures. Evaporation of a substance in mixtures depends on the properties of other substances in the mixture. For Toluene (and most other existing substances) dermal exposure is expected during the use of products

containing toluene (such as paint and inks). The proposed method cannot be used for these scenarios. Other models have been developed which account for the interaction of substances in mixtures to determine evaporation (e.g. Subtec) that could be used in these cases. Clarification on the significance of this model (and others), in accounting for highly volatile substances in mixtures in dermal exposure assessment is necessary. Anyhow, the use of more complicated models will require relatively extensive knowledge on the composition of the mixtures.

It should also be noted that the skin absorption rate might also be different for mixtures than for pure substances. More information on this is also needed for interpretation of the results.

Conclusion

As outlined above there are a number of issues, which need to be taken into consideration or need clarification. From **Tables C.2** and **C.3** above where the amount of toluene absorbed in the evaporation time is calculated using the proposed model it is clear that the great uncertainty related to the input parameters (i.e. skin temperature, mass transfer, and dermal absorption rate) strongly influences the outcome. Before the proposed method, to account for highly volatile substances in dermal exposure, can be incorporated in the process of exposure assessment the items mentioned above should be clarified.

It is however clear that evaporation, to some extends, lowers the actual amount of toluene, which is available for dermal absorption. This may however not be the case for spray painting scenarios, which are considered to describe steady state processes. Further it is clear that the dermal absorption rate may be low. Assuming that 100% of the toluene, which is deposited on the skin, is absorbed is therefore clearly an overestimate, but the degree of the overestimation is not known. At present the most appropriate way of dealing with this is in the risk characterisation when evaluation the MOS. Lower MOS's could therefore be accepted for all dermal exposure scenarios, however for scenarios describing spray painting evaporation may have less influence on the amount of toluene which is available for absorption, as spray painting is considered a steady state process.

Appendix D Notes to the human health effect assessment and risk characterisation

Note 1

mg% is understood as mg per 100 ml.

Note 2

Regarding the outcome of the water maze test in the Hougaard study, the UK CA considers that there is no evidence of an effect in males. In the memory test, the male latency was marginally greater for the treated group on the first 2 days of testing, but similar to controls on the third day. However, there were no clear and consistent differences during the learning, reversal learning or new learning phases; in the absence of effects in the other phases of the study the view of the UK CA is that it is not possible to interpret the marginal differences in the memory test as an adverse effect on cognitive ability in males. Female latency during the reversal learning and new learning was increased for the treated group. The greatest differences occurred during the first two trials when in the view of the UK CA chance factors have their greatest influence; by the fourth trial there were no differences between the control and treated groups.

Note 3

Though very well conducted, in the opinion of the UK CA a design limitation of both the Hougaard and Hass studies is that only one exposure level was investigated. Thus, it is not possible to assess the presence or absence of consistent dose-response relationships within each study. Such information is an important consideration when arriving at a conclusion as to whether or not observed intergroup differences could be causally related to treatment.

Overall, the UK CA concludes that the Hougaard and Hass studies provide clear evidence of developmental toxicity, manifested as a reduction in birth weight in the absence of maternal toxicity, seen in both studies. In the view of the UK CA these studies also provide weak evidence that toluene may elicit developmental neurotoxicity, manifested as differences in water maze performance and open field activity. The UK CA agree that concerns for developmental neurotoxicity should be addressed in the risk characterisation, but view the conclusion that toluene is a developmental neurotoxicant to be a tentative one with uncertainties remaining to be addressed, a factor which should be considered within the risk characterisation.

Note 4

The UK CA does not agree with the interpretation of this study, believing that there are flaws with the analysis of the results. The most surprising finding was the low rate of spontaneous abortion reported for the “low exposure” group. There were differences between the three study groups in the extent to which verification of circumstances from medical records was applied. Overall, in the opinion of the UK CA the results of this study are not convincing. The rapporteur has contacted Dr. Ng to obtain further information, which is included in the revised text.

Note 5

Because of the concerns that the UK CA have over the quality of the Ng study (see note 4), the UK CA does not agree that this should be used as a basis for risk characterisation of developmental toxicity in humans.

Appendix E Calculation of total systemic dose for workers

For workers the total systemic exposure has been calculated as the sum of the values chosen to represent the realistic worst case for full-shift inhalation and dermal exposures assuming 100% dermal absorption.

Exposure concentrations in mg/m^3 have been converted to mg/kg/d by the multiplying the air concentration by:

$$\frac{\text{minute volume (l/min)} \cdot \text{work exposure time (minutes/day)} \cdot \text{percentage absorption}}{1{,}000\ l/m^3 \cdot \text{body weight (kg)}}$$

The following values have been used:

minute volume:	40 l/min[1)]
work exposure time:	480 min (for workers full shift)
body weight:	70 kg
Percentage absorption:	100%

1) A standard minute volume has been used for all scenarios

The value chosen for workers is the mean (40 l/min) of values normally accepted for light work (20 l/min) and heavy physical work (60 l/min)

European Commission

EUR 20539 EN **European Union Risk Assessment Report toluene, Volume 30**

Editors: B.G. Hansen, S.J. Munn, R. Allanou, F. Berthault, J. de Bruijn, M. Luotamo, C. Musset, S. Pakalin, G. Pellegrini, S. Scheer, S. Vegro.

Luxembourg: Office for Official Publications of the European Communities

2003 – X pp., 308 pp. – 17.0 x 24.0 cm

Environment and quality of life series

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

The evaluation considers the emissions and the resulting exposure to the environment and the human populations 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. For human health 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 for toluene concludes that there is at present concern for workers, consumers and for humans exposed via the environment. The environmental risk assessment for toluene concludes that there is at present concern for the atmosphere, the aquatic ecosystem, the terrestrial ecosystem and for microorganisms in the sewage treatment plant.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) No. 793/93.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, private or national.

European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

toluene

CAS No: 108-88-3 EINECS No: 203-625-9

Series: 2nd Priority List Volume: 30