Institute for Health and Consumer Protection

European Chemicals Bureau

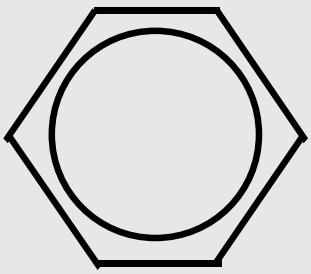
Existing Substances

European Union Risk Assessment Report

CAS No.: 98-82-8

EINECS No.: 202-704-5

cumene



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European Union Risk Assessment Report

CUMENE

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RISK ASSESSMENT

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CUMENE

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RISK ASSESSMENT

Final report, November 2001

Spain

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Final report:	**November 2001**

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.

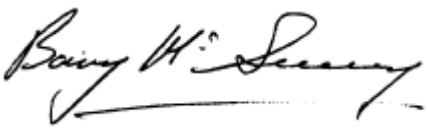
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each 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.

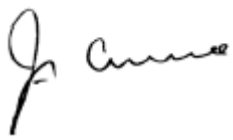
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

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
Joint Research Centre



J. Currie
Director-General
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[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.	98-82-8
EINECS No.	202-704-5
IUPAC name	cumene

Overall results of the risk assessment:

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

This applies to:

Environment

Releases of cumene to the atmosphere, aquatic and terrestrial compartments (including sediments) from the life cycle of cumene production and use, as well as non compartment specific effects relevant to the food chain (secondary poisoning).

Human health

This conclusion applies to the assessment of risk to human health through occupational and consumer exposure as well as indirect exposure via the environment both for toxicological and physico-chemical properties.

This risk assessment only covers the risk associated to the life cycle of produced or imported cumene. The risk associated to the presence of cumene in other substances, particularly petroleum hydrocarbons, is not covered.

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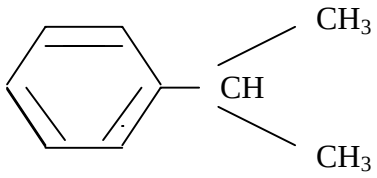
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS – No.: 98-82-8
EINECS – No.: 202-704-5
IUPAC name: Cumene
Molecular formula: C_9H_{12}
Molecular weight: 120.19
Structural formula:



Synonims: Isopropylbenzene, 1-methyl ethylbenzene, 2-phenylpropane, cumol

1.2 PURITY/IMPURITIES, ADDITIVES

Degree of purity: 90 - 99.9%

Identity and percentage of impurities:

Ethylbenzene (< 0,1%)
n-Propylbenzene (< 0,1%)
Butylbenzene (< 0,1%)
t-Butylbenzene (< 10%)
Aliphatic derivatives (< 0,1%)
Benzene (< 0,1%)
Phenol (< 0,1%)

The major amount of cumene production has a degree of purity of 99.9%.

1.3 PHYSICO-CHEMICAL PROPERTIES

Cumene is a colourless and combustible liquid with a strong aromatic odour. It is a compound virtually insoluble in water, although is soluble in ethanol and in many organic solvents. Cumene has been reported to be corrosive to rubber DPIMR (1984). Cumene hydroperoxide may be present in cumene samples that have been exposed to air; this compound is unstable and decomposes below the boiling point of cumene.

1.3.1 Physical state at normal temperature and pressure (ntp)

Cumene is a colourless liquid with a strong aromatic odour.

1.3.2 Melting point

According to Huels (1985 and 08.12.93) this value is –96ºC at 1013 hPa.

1.3.3 Boiling point

Huels (1985) gives the figure 152.7ºC at 1013 hPa, which is identical to Hawley's 1993. Merck Index provides 152-153ºC at 1010.8 hPa.

1.3.4 Relative density

Huels (1985 and 08.12.93) present a density of 0.86 and 0.8615 g/cm3 at 20ºC. Merck Index (11th edition) gives a relative density of d420= 0.862.

1.3.5 Vapour pressure

The value provided by Huels (1985) is approximately 4.96 hPa at 20ºC. This value is an extrapolation of the data given. The validation statement of the value is based on eight experimental data which fit well a linear regression (correlation coefficient = 0.999).

Other data identified has been 4.6 mmHg at 25ºC (cf. Riddick Hohn (1986).

1.3.6 Water solubility

Cumene is practically insoluble in water, screening the literature and according to Huels (1985) data there are two values for water solubility 27 mg/l at 20ºC and 50 mg/l at 25ºC.

An experimental data of 15.3 mg/l at 25ºC was identified (cf. Riddick Hohn (1986). Other data are also available: 82.8 mg/l at 30ºC; 85.5 mg/l at 35ºC; 100.3 mg/l at 50ºC and 161.5 mg/l at 80ºC.

Nevertheless the generally accepted water solubility of cumene is 50 mg/l at 25ºC.

1.3.7 Partition coefficient (log n-octanol/water)

Among the range of log partition coefficients (log n-octanol/water, log Pow) provided in Abernethy (1987), Huels (1989), Church (1979) and Lee (1967), the preferred value is 3.55 at 23ºC obtained via OECD Guideline 107 among the other ones derived following QSAR calculation.

1.3.8 Flash point

Huels (1985 and 08.12.93) present a flash point of ca. 31ºC (closed cup) and Merck Index 39ºC (closed cup). Both values conclude in the same R-phrase.

1.3.9 Autoflammability

National Fire Protection Association (NFPA) (1984) provides a reference of 1984 with a value of 424ºC at 1010 hPa.

1.3.10 Flammability

The result of this test is that cumene is flammable with a lower explosive limit (LEL) of 0.9% in volume and an upper explosive limit (UEL) of 6.5% in volume. These data are obtained from NFPA (1984).

1.3.11 Explosive Properties

IUCLID data present that cumene is explosive under influence of a flame, although no bibliography is given.

1.3.12 Oxidizing properties

According to IUCLID cumene has no oxidizing properties.

1.3.13 Refractive index

According to Merck Index the value is nD20 = 1.4914.

1.3.14 Surface tension

27.5 mN/m at 25ºC (Method "Pure component average" from the Programme PRO/II of simulation SCIENCES INC).

1.3.15 Kinematic viscosity

0.73.10-6 m2/s at 40ºC.

Table 1.1 Physico-chemical properties of cumene

Property	Value	Remarks
Physical state (at ntp)	Liquid	Colourless with strong aromatic odour Exposed to air its hydroperoxide may be present
Melting point °C	-96	At 1013 hPa
Boiling point °C	152,7 152-153	At 1013 hPa At 1010.8 hPa (760 mmHg)
Relative density (d_4^{20})	0.86 0.862 (*)	 Merck Index (*)
Vapour pressure Hpa	ca. 4.96	At 20°C
Water solubility (at 25°C) mg/l	50	Practically insoluble in water Soluble in ethanol and organic solvents
Partition coefficient Log n-octanol/water	3.55	At 23°C OECD Guideline 107
Flash point °C	31 39	Closed cup Closed cup
Autoflammability °C	424	At 1010 hPa
Flammability % in volume	0.9 6.5	Lower explosive limit (LEL) Upper explosive limit (UEL)
Explosive properties		Explosive under influence of a flame.
Oxidizing properties	None	
Refractive Index	1.4914	At 20°C
Conversion factor mg/m^3	4.91	At 25°C
Henry's Law Constant $Pa.m^3/mol$	1010.80	At 20°C
Relative vapour density (air = 1)	4.13	
Surface tension mN/m	27.5	At 20°C
Kinematic viscosity m^2/s	$0.73 \cdot 10^{-6}$	At 40°C

1.4 CLASSIFICATION AND LABELLING

The new classification and labelling was adopted in the 25th ATP[4] according with the proposal of the rapporteur:

R10: Flammable.

Xn; R65: Harmful: may cause lung damage if swallowed.

Xi; R37: Irritating to respiratory system.

N; R51/53: Toxic to aquatic organisms, may cause long-term adverse effect in the aquatic environment.

Labelling

Symbols: Xn, N R-phrases: 10-37-51/53-65

S-phrases: (2)-24- 37-61-62

[4] Commission Directive 98/98/EC of 15 December 1998 adapting to technical progress for the 25 time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

Cumene (iso-propylbenzene) is produced via alkylation of benzene with propene using an acidic catalyst. The product is recovered from high boiling reaction components while non reacted benzene is recycled. From natural sources cumene is manufactured from distillation of coal tar and petroleum fractions.

The compound is manufactured in EU by 8 companies in 7 European countries. Based on IUCLID data, the total EU production volume ranged between 850,000 and 4,100,000 tonnes in 1992/93. (**Table 2.1**.). One country imports this product from outside, but the way of cumene transport is not specified.

Table 2.1 Production of cumene in EU in 1993

Country	Quantity produced Tonnes·10^3/year	Application
Italy[a]	100-500 100-500	Basic industry Synthesis
Germany[a,b]	100-500 100-500	Synthesis
Spain	100-500	Basic industry
The Netherlands	100-500	Basic industry Synthesis
France	100-500	Basic industry Synthesis
UK	50-100	Synthesis
Finland	100-500	Chemical Industry
Total	850-4,100	

[a]Two sites production
[b]1992 data

2.2 USE

Cumene is used in chemical industry in categories 2 (basic chemicals) and 3 (chemical used in synthesis). The compound is mainly used as an intermediate in the production of phenol and acetone (aprox. 95%). It is also a minor constituent of gasolines and solvents, but its presence should not be regarded as an additive but as an integrated ingredient from a petroleum derivative. Therefore, the exposure in these cases should be considered in the risk assessment of petroleum derivatives. As has been reported by the Swedish C.A., the presence of cumene in gasoline and solvents in Sweden 1993 is estimated to be about 40,000 Ton. in gasoline and about 2,400 Ton in solvent naphtha (assuming a percentage of 1% and 3% respectively).

In Spain 99.9% of the production of cumene is used in the manufacture of phenol and acetone, and 0.1% of the production is used in the manufacture of detergents.
In Germany 95% of the production is employed in the manufacture of phenol, acetone, and 2% is used as starting material in the synthesis of detergents. A small amount of 15 tonnes, were used in 1996 as a solvent in staving varnishes for the automobile industry.

Other uses for cumene include:

- The synthesis of alpha-methylstyrene, acetophenone and detergents.
- The manufacture of di-isopropylbenzene.
- The catalyst for acrylic polyester-type resins.
- It is found as an isomer in the general C9 aromatic hydrocarbon content of solvents, particularly those used in the printing industry.

2.3 EXPOSURE CONTROL

The main route of potential worker exposure that exists during manufacture and use of cumene is via inhalation. Respiratory protective equipment and local exhaust ventilation can be used to control inhalation exposure in the maintenance activities manufacturing sector and uses.

Dermal exposure is potential during shutdown activities, but gloves are worn to avoid direct skin contact.

3 ENVIRONMENT RISK ASSESSMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

In the assessment, releases to the environment are considered in various scenarios. These are explained more fully in the Technical Guidance Document. The local environment is considered to be the environment near to a site of release (e.g. a production or processing site). The regional environment is taken to represent a highly industrialised area (size is 200 km by 200 km with 20 million inhabitants) and it is assumed that 10% of the European production or use takes place in this area. The continental environment is the size of the EU and is generally used to obtain "background" concentrations of the substance.

3.1.1.1 Releases into the environment

3.1.1.1.1 Releases from production and use

Cumene is commonly synthesized by alkylation of benzene with propene and mainly used to produce phenol and acetone, although actual figures of production are not included in the IUCLID database. Production and use of cumene is assumed to occur in the same site as a worst case scenario. The use of cumene as a solvent in various formulations is mainly reported by petroleum industry and should be considered in the risk assessment of petroleum products.

Releases to air

The loss of cumene during production has been reported to range between 0.08 to 0.27 kg cumene/tonne, for controlled or uncontrolled production respectively (US EPA, 1980; Bouscaren et al., 1986). A release factor to air of 1.03 kg cumene/tonne phenol from use of cumene in synthesis has also been reported (US EPA, 1988).

Release estimates at production (local and regional situation) for industrial products used as intermediates (use category Ib) are given in the Technical Guidance Document. For these compounds the emissions factors are 0.01% for air and 0.1% for wastewater. Release factors at processing for chemicals used in synthesis (main category Ib; Technical Guidance Document) are 0.001% for air and 0.05% for wastewater. The overall production and processing factors would be 0.011% for air and 0.15% for wastewater. The proportion of cumene released in a wastewater treatment plant, according with the EUSES model, the properties of the molecule and inherently biodegradability in industrial sewage, would be 80% to air. Then, the overall release factor would be 0.131% for air, that corresponds to 1.31 kg/tonne. The release factor for air is similar to that proposed earlier by US EPA considering production and processing. Industry has submitted data for the cumene emissions to atmosphere of 125 tonnes/annum in 1993, which has been reduced to 75 tonnes/annum in 1995, for cumene production. Nevertheless, assuming that this value corresponds to a maximum production volume of 500,000 tonnes/site the emission factor is 0.015% for the lower value (75 tonnes), which is similar to that given in the TGD 0.011% for production and processing. Then, this emission factor will be used in the risk assessment.

Assuming the maximum production at any one site is 500,000 tonnes and a release factor to air of 1.31 kg/tonne, a release of 2,183 kg/day can be estimated for a production site. The total amount for the EU, assuming a maximum production of 4,100,000 tonnes/year, would be 17,903 kg/day.

Release to water

Release estimates to wastewater are, according to the Technical Guidance Document, 0.1% at production and 0.05% at processing. The overall factor for wastewater, including production and processing, is then 0.15%. Assuming a maximum production per site of 500,000 tonnes, 300 days of releases and the release factor of 1.5 kg/tonne a release of 2,500 kg/day to wastewater can be estimated per site. The proportion of cumene released in a waste treatment plant, according to the Simpletreat model, the properties of the molecule and inherently biodegradability in industrial sewage, is 7% to water. Industry has submitted release data for different production/processing sites (**Table 3.3**) and these data will be considered in the exposure of the aquatic compartment.

Release to soil

Releases estimates to soil are, according to the Technical Guidance Document, 0.001% at production and 0.001% at processing, and the overall factor is then 0.002%. Considering 500,000 tonnes, 300 days of production and the overall factor of 0.02 kg/tonne a release of 33.3 kg/day to soil can be estimated per site.

3.1.1.1.2 Releases from disperse sources

Assuming a 0.2% cumene by weight of hydrocarbon losses (Nelson et al., 1983; Verschueren, 1983) and a VOC emission factor of 5 kgVOC/tonne gasoline delivered (average between 4.5 proposed by Bouscaren et al., 1986 and 5.5 of Eggleston, 1987), the cumene emission from one area (UK, $24 \cdot 10^6$tonnes gasoline) would be 240 tonnes/year and 658 kg/day and the overall amount for EU (117,205,000 tonnes) would be 1172 tonnes/year and 3211 kg/day. The regional release, considered as 10% of the continental release, would be 321 kg/day.

Assuming that VOC from motor exhaust of vehicles contains 0.2% cumene and an emission of 617,400 tonnes VOC/year at one area (UK), the release of cumene would be 3,383 kg/day. The overall amount for the EU, considering a population ration of 6, would be 20,298 kg/day. The regional release would be 2,030 kg/day.

Table 3.1 Summary of release estimates

Source	Amount/site kg/day	Amount/regional kg/day	Amount/EU kg/day	Main compartment
Production & use	2,183 2,500 (waste) 33.3	1,790 2,050 (waste) 27.3	17,903 20,500 (waste) 273	Air Water Soil
Disperse sources Gasoline dist. Motor exhaust	 - -	 321 2,030	 3,211 20,298	 Air Air
Total	2,183 2,500(waste) 33.3	4,141	41,412	Air Water Soil

3.1.1.2 Degradation

3.1.1.2.1 Abiotic degradation

Photo-oxidation of cumene has reaction rates of 6.14-7.8 $\cdot 10^{-12}$ $cm^3molec^{-1}sec^{-1}$ with hydroxyl radicals at near 300ºK (Lloyd et al., 1976) and of 5.81 $\cdot 10^{-18}$ $cm^3molec^{-1}sec^{-1}$ for the reaction with ozone at 300ºK (US EPA, 1979a). Using an average ozone atmospheric concentration of $1 \cdot 10^{12}$ molec/cm^3 a half-life of 1.4 days can be calculated. Assuming an atmospheric concentration range of hydroxyl radicals between $5 \cdot 10^5$ and $1 \cdot 10^6$ molec/cm^3, atmospheric half-lives of 1-2.4 days can be estimated.

The photo-oxidation of cumene in natural waters was shown to yield side-chain oxidation products after reaction with RO_2 radicals, i.e. cumene hydroperoxide, cumyl alcohol and acetophenone, while after reaction with OH radicals gave both side-chain and ring oxidation products, including 2- and 4- isopropylphenols (Mill et al., 1980). Half-lives of 0.4-5.1 h have been reported.

3.1.1.2.2 Biodegradation

Table 3.2 shows the biodegradation of cumene.

Large contradictions among the different reports on the biodegradability of cumene have been found. The available data set includes the whole range of possibilities from non-biodegradable to readily biodegradable.

The aerobic biodegradability of cumene has been tested in industrial sewage using the closed bottle test, Directive 84/449/EEC, <20% degradation was observed after 28 days suggesting that the compound can be classified as non biodegradable. By contrast, an unpublished study by Huels AG (1984) using the BODIS test (ISO 10708, in preparation) with non-adapted domestic activate sludge indicated 86% of biodegradation after 28 day, suggesting that the compound should be classified as readily biodegradable, or at least, inherently biodegradable, considering that there is no information about the 10 days window criterion in this tests.

Dow (1985), Price et al. (1974) and Waggy et al. (1974) found degradation values between 60 and 70%, but the 10 days window criterion was not fulfilled.

Additional data have been presented by other authors. An Ecocore Biodegradation Study published by Williams et al. (1993) using undisturbed sediments is presented. Volatilization and biodegradation were the main removal routes. The compound was mineralised up to 47% over 45 days at 2.5 mg/l. Higher initial concentrations showed lower mineralisation percentages. Additional references appear in **Table 3.2**.

Taken into account the disparity of the available data, it seems appropriate to consider some experimental information on this issue. The biodegradation of cumene in *Pseudomona putida* is regulated by a specific plasmid (Eaton and Timmis, 1986). This point is relatively common for Gram negative microorganisms. However, the role of plasmids in the biodegradation of cumene has recently been observed also for Gram positive microorganisms, by the isolation and characterisation of a linear and transmissible plasmid that codifies cumene metabolism in *Rodococcus erythropolis* BD2 (Dabrock et al., 1994), a microorganism that can use cumene as the exclusive source of carbon and energy.

Considering the wide distribution of cumene in the environment, mostly related to gasoline exhausts and other non point pollution sources, and the capability of Gram positive and negative microorganisms to transmit plasmids that codify cumene metabolism, the possibility of gets cumene metabolizing populations from WWTP is relatively high. Thus, the presence of cumene metabolizing plasmids in some non adapted populations can be suggested as a possible explanation for the disparity of the data.

As a conclusion of the biodegradation reports, large contradictions can be found, from 86% degradation in 28 days to 13% in the same period. The validity of the unpublished BODIS Test (Dow Chemical Company, 1985) can be questioned by the lack of information about the 10 days window criterion and on the use of GLPs. It is considered that the criteria for ready biodegradability have not been fulfilled. The weight of evidence on the provided degradation data and the information available for other related chemicals indicate that cumene should be classified as "inherently biodegradable".

The biodegradation of cumene in seawater or under anaerobic conditions must be expected to be lower than for aerobic freshwater conditions.

WWTP populations should be expected to adapt their metabolism to cumene degradation, however, this fact cannot justify the use of biodegradation rate constants higher than the value proposed by the Technical Guidance Document. Nevertheless, the main elimination of cumene in WWTP is due to volatilisation and adsorption, therefore, the use of any specific biodegradation category does not suppose a great difference in PEC calculations.

Table 3.2 Biodegradation of cumene

Sources of Microorganisms	**Test type**	**Comments**	**Duration (Days)**	**% Biodegradation**	**Reference**
Industrial Wastewater	Aerobic biodegradation	Methodology 84/449/ EEC	28	13	Huels AG (1984)
Domestic Wasterwater Non-adapted	Aerobic biodegradation	Methodology ISO10708 BODIS test	28	86	Huels AG (1984)
	Aerobic biodegradation		20	63,6	Dow (1985)
Domestic Wasterwater Non-adapted	Aerobic biodegradation	Standard Methods for the examination of water and wastewater	20	70	Price et al. (1974) Waggy et al. (1974)
Seawater Microorganisms Non-adapted	Aerobic biodegradation	Standard Methods for the examination of water and wastewater	20	2	Price et al. (1974)
	Anaerobic biodegradation		60	No biodegradation	Battersby and Wilson (1989)
Groundwater and Aquifer Material	Anaerobic biodegradation	Laboratory Microcosmos Biodegradation	187	6	Acton et al. (1992)

3.1.1.3 Accumulation

The provided information presents contradictory data on the bioaccumulation potential of cumene. Considering the octanol/water partition coefficient, the P_{ow} of cumene is higher than 3, therefore, a high bioaccumulation potential should be expected. However, Ogata et al. (1984) present a bioconcentration factor of 35.5 for *Carassius auratus*, a figure that could indicate a low potential for bioaccumulation. The discrepancy has been resolved by a careful review of the original paper from Ogata et al. The methodological description in the paper is poor, without definition of the methods and exposure times, but with additional data for other chemicals, some of them with available information on bioconcentration factors calculated under standard protocols. Comparisons among bioconcentration factors presented by Ogata et al. and calculated under ordinary protocols show lower values for the first method; therefore, the data presented for *C. auratus* cannot be considered as an experimental proof of a lower bioaccumulation potential for cumene than that expected according to the P_{ow} value. In fact, Ogata et al. confirm a good relationship between the P_{ow} and the BCF for cumene; thus, the data presented in this paper should be considered as an experimental demonstration that the P_{ow} value is a good parameter for the estimation of the bioaccumulation potential of cumene.

This assumption agrees with the BFC of 224, calculated from the molecular connectivity model by Sabljic (1987), and with the value of 208 calculated by the equation included in the Tecnical Guidance Document.

3.1.2 Aquatic compartment (incl. sediment)

3.1.2.1 Calculation of PEClocal, PECregional and PECcontinental

The PEC_{local} for water has been calculated using the equations given in the Technical Guidance Document, assuming that the amount released/site is released to wastewater and that it enters a wastewater treatment plant with an inflow of 2000m^3/day of water. It is assumed that removal during waste treatment is 93%, according to the emission factors given in the Technical Guidance Document. Other assumptions are a dilution factor of 10 and concentration of suspended matter in surface water of 15mg/l with an organic carbon content of 10%.

$$PEC_{local(water)} = C_{eff}/(1 + Kp_{(susp)} \cdot C_{susp}) \cdot D \quad [g/l]$$

Where

D= dilution factor =10 (default)

$Kp_{(susp)} = K_{oc} \cdot foc,susp = K_{oc} \cdot 0.1 = 884 \cdot 0.1 = 88.4$ l/kg

$C_{susp} = 15$ mg/l $= 15 \cdot 10^{-6}$kg/l

The C_{eff} ((WWTP effluent concentration) is calculated using the following equation:

C_{eff}= W· (100-P)/ 100·Q

Where

W= emission rate kg/day

Q= volume of wastewater = 2000 m^3/day (default)

P= % removal in WWTP= 93%

W = 2,500 kg/day (**Table 3.1**)

C_{eff} = 2,500·7/ 100·2000 = 0.0875 kg/m^3 = 87.5 mg/l

$PEC_{local(water)}$= 87.5 / 10.013 = 8.74 mg/l

Data on the discharge to the aquatic compartment from production and use of cumene have been reported by industry and are shown in **Table 3.3**. These data show a cumene release to water clearly lower than the release calculated using TGD. Nevertheless, the information is not complete considering that data from two sites are lacking, the methodology used is not described and no variability of data is available.

$PEC_{local(water)}$ has been calculated for the two production sites with measured values of C_{eff}, and values lower than 0.14 and 1.04 µg/l have been obtained, **Table 3.3**.

Release to STP has been calculated for six production/processing sites based on actual data reported by industry, ranging from 0.85 to 8.26 kg/day, **Table 3.3**. A value of W = 2.04 kg/day has been selected as a representative release for cumene production/processing more realistic that the one calculated using TGD. Then, the continental release would be 16.7 kg/day.

C_{eff} has been calculated for the six production/processing sites with data on release to STP and ranged from <3 µg/l to <0.5 mg/l, **Table 3.3**

$PEC_{local(water)}$ has been calculated using this representative release of 2.04 kg/day

C_{eff}= 2.04·7/ 100·2000 = $7.14 \cdot 10^{-5}$ g/l

$PEC_{local(water)}$= $7.14 \cdot 10^{-5}$/10.013 = $7.13 \cdot 10^{-6}$ g/l

Therefore the estimated value is: PEC_{local}(water)= 7.13 µg/l

The concentration in water of the sewage treatment plant will be

W/Q = 2.04 kg/day ≅ 2000 m^3/day = 1.02 mg/l.

The PEC_{local}(sediment) can be estimated from the sediment-water partition coefficient using the equations given in the Technical Guidance Document:

$PEC_{local(sed)}=[K_{susp\text{-}water}/RHO_{susp}] \cdot PEC_{local\ water} \cdot 1000$

$K_{susp\text{-}water}=23\ m^3 \cdot m^{-3}$

$RHO_{susp}=1150\ kg \cdot m^{-3}$

$PEC_{local(sed)}=[23/1150] \cdot 7.14 \cdot 1000 = 143\ \mu g/kg$

Table 3.3 Cumene release data for different production/processing sites

Release to STP kg/a mg/l			612	 0.043[a]	 5.9			
Size of STP m^3/d	72,000	16,800	8,400				1,008	54,000
Waste water volume m^3/d				19,752	1,400	6,000		
Release to rec. water kg/a	< 80	22.4					60.48	
Mean flow of rec. water m^3/d	1,589,760	B	B	1,296,000	86,400,000	b	b	
Dilution factor	22.1			65.6	480			
C_{eff}	< 3 ∝g/l	4.45∝g/l	17∝g/l	3∝g/l	<0.5 mg/l		0.2mg/l	
PEC_{local} ∝g/l [c]	< 0.14				< 1.04			
Calculated release to STP kg/day	< 3.81[d]	1.07[d]	2.04[e]	0.85[f]	8.26[g]		2.88[d]	

[a]Concentration of aromatic compounds in untreated wastewater
[b]The receiving water is a sea
[c]Calculated as C_{eff}/dilution factor
[d]Calculated from values of release to receiving water assuming a 93% removal in STP
[e]Calculated from the annual release to STP (612) divided by 300 days
[f]Calculated from the concentration of aromatic compounds (0.043 mg/l), assuming to be cumene as the worst case, and the volume of wastewater (19,752)
[g]Calculated using the highest cumene concentration (5.9 mg/l) and the volume of wastewater (1,400)

The calculation of PECs on a regional and continental scale has been done using EUSES. The quantities used as inputs into the model were the total amount released in a standard region, considered as 10% of the continental release, and the total amount released in the EU (continental), as described in the Technical Guidance Document. A summary of the results obtained using site-specific emissions reported by industry is shown in **Table 3.4** and EUSES report is enclosed in Appendix A.

Table 3.4 Summary of regional and continental modelling

	Regional	Continental
PEC air µg/m³	0.07	0.04
PEC surface water ng/l	0.3	0.09
PEC sediment ng/kg	6.8	2
PEC agricultural soil ng/kg	2.7	1

3.1.2.2 Measured levels

The analysis of cumene in water has been carried out generally by liquid-liquid extraction with methylene chloride or by purge and trap on Tenax followed by gas chromatography determination using a mass spectrometry or a flame ionization detector. Cumene concentrations in wastewater were found in the range of 0.1 to 0.8 µg/l in Sweden and around 0.5 to 5 µg/l in Germany. Levels of cumene in surface water at a contaminated site ranged from 0.01 to 47.3 µg/l in UK, **Table 3.5**. The PEC_{local} calculated for surface water using the default emission factors given in the Technical Guidance Document, 8.74 mg/l, is much higher than measured levels in wastewater or in water from contaminated sites, indicating that default emission factors from TGD overestimate the actual release of cumene. However, the local PEC of 7.13 µg/l, calculated with a representative cumene release of six production/processing sites, based on actual data reported by industry, is of the same order than those measured values in contaminated or wastewater, although the origin of the contamination may be diverse.

Background concentration in surface water along the British North Sea coast in 1986 ranged between <1 ng/l to 69 ng/l, **Table 3.5**. These background levels, which have been measured not far away from contaminated sites, although somewhat higher, are reasonably consistent with regional and continental PECs calculated using EUSES model, 0.3 and 0.09 ng/l, respectively, **Table 3.4.** Cumene was detected in sediment samples from contaminated sites at levels ranging from 0.6 to 11 µg/kg in Japan and from 0.25 to 43.37 in UK. Sediment samples collected from beaches located along shipping lanes have been analysed and cumene concentrations were found in a range from 0.02 to 5.5 µg/kg (US EPA, 1979), **Table 3.5**. The PEC regional for sediment calculated using EUSES model, 0.007 µg/kg, is lower than the cumene levels reported. Nevertheless, the sediment samples analysed came from contaminated sites and therefore the measured levels are not background concentrations.

Table 3.5 Levels of cumene in water and sediment

Country	Location/Sample	Method[a]	Concentration
Germany	River Rhine	GC-FID	0.028 µg/l
	Lake Constance[b]	GC-MS	0.006 - 0.028 µg/l
	Waste water	GC-MS	0.5 - 5 µg/l
Italy	Groundwater (underground solvent storage tanks)[c]	GC-FID	1,581 µg/l
Japan	Surface water[d]		0.09 - 0.44 µg/l
	Sediment[d]		0.6 - 11 µg/kg
Spain	River Gallego	GC-MS	<0.001 ng/l
Sweden	Waste water-Göteborg	GC-MS	0.1 - 0.8 µg/l
UK	Solent estuary	GC-ITD	0.01 - 47.3 µg/l
	British North Sea[e]	GC-MS	0.001 - 0.069 µg/l
	Ground water-East Anglia (near an airfield)[f]		1 - 30 µg/l
	Sediment-Southampton[g]	GC-ITD	0.25 - 43.37 µg/kg
USA	River Brazos-Texas[h]		0.006 - 0.017 µg/l
	Ground water-Wyoming (under-ground coal gasification plants)[i]		19 - 54 µg/l
	Sediment- Strait of Juan de Fuka, Alaska[j]		0.02 - 5.5

[a]GC-FID= gas chromatography with flame ionization detection; GC-MS= GC with mass spectrometry detection; GC-ITD= GC with ion trap detection
[b]Jüttner, 1988
[c]Botta et al., 1984
[d]Office of Health Estudies, 1991
[e]Hurford et al., 1989, 1990
[f]Tester and Harker, 1981
[g]Bianchi et al., 1991
[h]Mc Donald et al., 1988
[i]Stuermer et al., 1982
[j]US EPA, 1979b

3.1.3 Terrestrial compartment

3.1.3.1 Calculation of PEC local, PECregional and PECcontinental

Cumene has a low water solubility and moderate vapour pressure. No occurrences of cumene in rainwater have been reported and its removal from atmosphere in rainfall is unlikely. The main source of soil contamination is from point emissions caused by other uses like garage spills or petrol stations. These facts suggest that the calculation of a local PEC is not required. Nevertheless, the PEC_{local} for soil can be calculated using model EUSES and a concentration of 0.18 mg/kg for agricultural soil was found using site-specific emissions (Appendix A).

Predicted concentration of cumene in soil on a regional and continental scale has been calculated using EUSES model. The $PEC_{regional}$ obtained for soil was 2.7 ng/kg and the $PEC_{continental}$ was 1 ng/kg, **Table 3.4**. PEC_{soil}, pore water was calculated using the model EUSES and found to be 0.2 ng/l and 0.07 ng/l for regional and continental level respectively (Appendix A).

3.1.3.2 Measured levels

Cumene levels measured in soil from contaminated sites in Netherlands ranged from 12 to 20 μg/kg. In other study, cumene was found in soils contaminated by garage spills at levels ranging from 10 to 305 mg/kg (Kliest et al., 1989).

3.1.4 Atmosphere

The bulk of cumene release to the atmosphere is attributable to disperse sources (gasoline marketing, distribution and use) and the highest levels of cumene are recorded in industrial and urban areas.

3.1.4.1 Calculation of PEC_{local}, $PEC_{regional}$ and $PEC_{continental}$

PEC local for air at a distance of 100 meters from a point source can be estimated using the equation given in the Technical Guidance Document:

$C_{air} = \text{Emission} \cdot C_{std\ air}$

Where

C_{air}= air concentration at 100m from a point source [$kg.m^{-3}$]

Emission= emission rate to air [$kg.s^{-1}$]

$C_{std\ air}$= standard concentration in air at source strength of

$$1\ kg.s^{-1} = 24 \cdot 10^{-6}\ kg.m^{-3}$$

Direct emission from production and use, calculated using emissions factors given in TGD, was 0.011% of 500,000 tonnes/year = 55,000 kg/year or 183.3 kg/day. From a waste treatment plant, the emission was 0.80 · 0.15% of 500,000 tonnes/year = 600,000 kg/year or 2,000 kg/day.

The air concentration of cumene produced by these two sources will be:

$C_{air1} = (183.3/24 \cdot 60 \cdot 60) \cdot 24 \cdot 10^{-6} = 0.05\ mg/m^3$

$C_{air2} = (2000/24 \cdot 60 \cdot 60) \cdot 24 \cdot 10^{-6} = 0.55\ mg/m^3$

The maximum from the two concentrations is used as the PEC_{local}

$PEC_{local} = 0.55\ mg/m^3$, calculated using TGD emission factors.

Industry has submitted data for release into the atmosphere and to STP. A figure of 75 tonnes/annum was provided for atmospheric emissions during cumene production and a value of W = 2.04 kg/day was selected as a representative release to wastewater as indicated above.

The air concentration of cumene produced by those sources will be:

$C_{air\ i1} = (75{,}000/300 \cdot 24 \cdot 3600) \cdot 24 \cdot 10^{-6} = 0.07\ mg/m^3$

$C_{air\ i2} = (0.77 \cdot 2.04/24 \cdot 3600) \cdot 24 \cdot 10^{-6} = 0.44 \cdot 10^{-3}\ mg/m^3$

Then, $PEC_{local} = 0.07\ mg/m^3$, based on data submitted by industry for cumene production.

Regional and continental calculations have been done by means of EUSES model. Results obtained with this model, shown in **Table 3.4**, are $PEC_{regional} = 0.07\ \mu g/m^3$ and $PEC_{continental} = 0.04\ \mu g/m^3$ (Appendix A).

3.1.4.2 Measured levels

Levels of cumene in air have been measured in urban, industrial and rural areas of European countries (**Table 3.6**.) and of other countries (**Table 3.6. continued**).

Table 3.6 Levels of cumene in the European atmosphere

Country	Location/Sample	Method[a]	Concentration µg/m³
France	Grenoble area[b]		0.9 - 7.45
Germany	Urban air[c]		6 - 9
	Hamburg- Major road tunnel[d]		3 - 3.8
Italy	Rome- Urban air	GC - FID, MS	1.1
	Milan- Urban air	GC - MS	1.1 - 1.8
Sweden	Near factory[e]		4.5
	Göteborg[e]		0.6
	Rural sample[e]		0.02
The Netherlands	Urban air[c]		0.3
	Rural air[c]		0 - 5
	Delft ambient air[f]		<0.49 - 1.96
	Ambient air[g]		0.49 - 34.79
	Rotterdam and Ede-Near homes[h]		0.3
UK	Urban air[c]		1 - 20
	Gatwick airport-ambient air[i]		1.6 - 12
	London- urban air[i]		5
	Southampton estuary-ambient air	GC - ITD	0.6 - 410
Former USSR	Leningrad- urban air[j]		0.98 - 11.76

[a]GC-FID= gas chromatography with flame ionization detection; GC-MS= GC with mass spectrometry detection; GC-ITD= GC with ion trap detection
[b]Foster et al., 1991
[c]Bouscaren et al., 1986
[d]Danneker et al., 1990
[e]Peterson, 1982a
[f]Bos et al., 1977
[g]Guicherit and Schulting, 1985
[h]Lebret et al., 1986
[i]Tsani-Bazaca et al., 1982
[j]Isidorov et al., 1983

Table 3.6 continued

Country	Location/Sample	Concentration μg/m³
Nepal	Mount Everest	0.07
USA	Houston, Texas- Urban and industrial areas[a]	0 - 42.2
	St. Petersburg, Florida- Urban air[b]	0.83 -1.29
	Miami, Florida- Urban air[b]	1.11 - 2.59
	Rio Blanco Country, Colorado[c]	1.57
	Great Smoky Mountains,Tennessee[c]	0.28 - 0.65
	Chicago, Illinois[d]	0.59 - 1.1
	Boston, Massachusetts[d]	0.1
	Houston, Texas[d]	0.14 - 0.81
Taiwan	Urban air, near heavy traffic[e]	0.6 - 0.9
	Urban air, away from heavy traffic[e]	0.5

[a]US EPA, 1979c
[b]Lonneman et al., 1978
[c]Arnts and Meeks, 1981
[d]US EPA, 1986
[e]Hung and Liao, 1991

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

Considering low environmental levels and assuming that the oral toxicity of cumene on mammals is moderate, the suggestion is that secondary poisoning should not be relevant. Nevertheless a preliminary assessment (see 3.2.4.) has been included in the report.

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

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Aquatic organisms

The IUCLID data base (August 23, 1995) includes: seven values regarding on the acute toxicity of cumene for five fish species (four freshwater species and one marine fish); 19 figures on acute toxicity for aquatic invertebrates, involving crustacean (fresh and saltwater species) and molluscan (two freshwater gastropods); the result of one test on algae growth inhibition for *Selenastrum capricornutum*, and two additional effects on algae photosynthetic activity (after 3 hours of exposure) for other algae species.

The provided information includes a set of data on the acute toxicity of cumene for aquatic organisms. These data have been summarized in **Tables 3.7** to **3.10**. A statement on the quality of each value has been included. For some data included in IUCLID, the original publications were not provided. In these cases, the cross reference between IUCLID and other reports, particularly the UK hazard assessment report, was searched and it is mentioned in the tables. The validity of the most significant data could be contrasted with original references. As expected for

this compound, data of low quality, and specifically those reporting nominal concentrations, showed, in general, higher L(E)C_{50} values than those considered appropriate for the evaluation. Thus, and taken into account that this assessment uses the lowest end of the toxicity range, the lack of validation for some data of low or no relevance does not affect the outcome of the final assessment. The selected data are considered valid for the PNEC calculation.

The lowest figure is the 72h EC_{50} for *Radix peregra*, with a value of 0.01 mg/l; in addition, there is a 24h EC_{100} for *Asellus* sp. of 0.5 mg/l. In both cases, these values are referred to papers from Erben and Beader (1983a; 1983b) cited in Environmental Hazard Assessment: Cumene, UK Department of the Environment (1994). The original papers confirmed that these entries present erroneous figures due to confusion in the units (% versus mg/l). Thus, the real LC_{50}s have been calculated using probit analysis on the original data, after transformation into mg/l. These figures have been incorporated in **Tables 3.10** and **3.8** respectively. The corrected figures are higher than 5 mg/l and therefore, do not represent the lowest end of the acute toxicity range for aquatic organisms.

A peer review of **Tables 3.7** to **3.9** shows that the lowest individual values have been reported for crustaceans; although fish and algae data are in the same range. The lowest individual data is a 48h EC_{50} on *Daphnia magna* of 0.6 mg/l, but there are additional reliable values for the same species, all higher than 1 mg/l. The TGD gives the possibility of using the arithmetic mean to solve these situations, but it is not possible to use this approach because one of the validated figure, 1.4, was reported for 24 instead of 48h. Taking into account the 96h EC_{50} on *Mysidopsis bahia*, reported as 1.3 mg/l we can conclude that the "weight of evidence" suggest that the best estimation for the available data set is to set 1 mg/l as the lowest end of the acute toxicity range for aquatic organisms.

Following the indications of the TM, additional information on the chronic toxicity of cumene for aquatic organisms was required for the refinement of the environmental risk of cumene. Taking into account the available information, the request included chronic studies on invertebrates and algae. Two chronic studies, on *Daphnia magna* and *Scenedesmus subspicatus* respectively, were presented in July 1998. These studies have been conducted under GLP following the OECD 211/draft of December 1996 and the Algae growth inhibition test complying with Directive 92/69/EEC guidelines respectively. The effects of cumene on the reproduction of *Daphnia magna* were assessed under semistatic exposure, sealed flasks, and individual culture conditions. The effects on algae were also assessed using sealed vessels. Real concentrations were significantly lower than nominal in both cases, therefore real concentrations (geometrical mean of fresh and old analytical mean values) have been used. After a peer review of the presented reports, both tests have been considered valid.

Table 3.10 summarizes the results of the chronic toxicity of cumene for aquatic organisms. The lowest chronic NOEC was 0.22 mg/l. Taking into account that cumene is considered as a non polar narcotic and the similar range of the acute toxicity data observed for fish, invertebrates and algae, it was previously accepted by the TM that, in order to reduce testing with vertebrates, the chronic toxicity studies should be conducted only with *Daphnia* and algae, while QSAR calculations should be employed for the estimation of the chronic toxicity on fish after checking the validity of this approach. Chronic NOECs for fish and Dapnia have been calculated by the rapporteur following the QSAR equations for non polar narcosis included in the TGD. The results are 0.38 and 0.32 mg/l for fish and *Daphnia* respectively.

The comparison between the QSAR estimation (0.32 mg/l) and the measured (0.35 mg/l) chronic toxicity of cumene on *Daphnia magna* clearly indicate the validity of this approach for cumene, therefore the QSAR estimated NOEC for fish will be used in the assessment. In addition, the chronic NOEC for *Daphnia magna* and *Scenedesmus subspicatus* are in the same range confirming the similar toxicity of this chemical for the different taxonomic groups employed for the PNEC estimation.

As a conclusion, the algae NOEC of 0.22 mg/l, represents the lowest chronic toxicity value for cumene. The data set includes fish (QSAR estimation), *Daphnia* and algae and therefore a factor of 10 has been used for the PNEC estimation.

$$PNEC_{aquatic\ organisms} = \text{lowest NOEC}/10 = 22\ \mu g/l$$

The data set includes both, fresh and saltwater species. The available data on saltwater species are in the same range than those regarding on freshwater organisms, therefore, the above PNEC can be used for both, freshwater and marine environments.

Table 3.7 Acute toxicity of cumene to fish

Species	Test type	Comments	Duration	Toxicity endpoint (mg/l)	Data quality	Reference
Cyprinodon variegatus (marine)	Dynamic	GLP measured concentration	96 hour	LC_{50} = 4,7 NOEC = 2,9	OK	Springborn Laboratories Inc., 1990a
Oncorhynchus mykiss (fresh water)	Dynamic	GLP measured concentration	96 hour	LC_{50} = 4,8 NOEC = 1,9	OK	Springborn Laboratories Inc., 1990b
Poecilia reticulata (fresh water)	semi-static closed bottles	methodology OECD 203	96 hour	LC_{50} = 5,1	OK	Galassi et al., 1987; 1988
Salmo gairdneri (estuary, fresh water)	semi-static closed bottles	methodology OECD 203	96 hour	LC_{50} = 2,7	OK	Galassi et al., 1987; 1988
Leuciscus idus (fresh water)	Static	methodology DIN 38412	48 hour	LC_{50} = 22,5	Quality not valuable	Huels study unpublished, 1984
Leuciscus idus melanotus (fresh water)	Static	methodology DIN 38412	48 hour	LC^{50} = 47	Low quality	Juhnke et al., 1978 (cited in UK report)
Pimephales promelas (fresh water)	Static	Nominal concentration	96 hour	LC_{50} = 20	Low quality	Dow Chemical USA, 1975

Table 3.8 Acute toxicity of cumene to crustacea

Species	Test type	Comments	Duration	Toxicity endpoint (mg/l)	Data quality	Reference
Artemia salina (marine)	Static		24 hours	EC_{50}=110		Price et al., 1974 (cited UK report)
Artemia salina (marine)	Static using WSF	Measured	48 hours	EC_{50}=7.4 LC_{50}=7.3	Low relevance	UB/TIB (Mc Lean et al., 1989)
Artemia salina (marine)	Static	Nominal	24 hours	EC_{50}=13.7		Abernethy et al., 1986 (cited UK report)
Asellus sp	Static		96 hours	LC_{50}=15.2	Low quality	Erben and Beader, 1983a
Daphnia magna (fresh water)	Static closed bottles	OECD Guideline 202, part 1	24 hours	EC_{50}=1.4	OK	Galassi et al., 1987; 1988
Daphnia magna (fresh water)	Static using WSF	Measured	48 hours	EC_{50}=10.8 LC_{50}=25.2	Low relevance	UB/TIB (McLean et al., 1989)
Daphnia magna (fresh water)	Static	Nominal	48 hours	EC_{50}=0.6		Abernethy et al., 1986 (cited UK report)
Daphnia magna (fresh water)	Dynamic	GLP measured concentration Acute immobilization and mortality test	48 hours	EC_{50}=4 NOEC=1.5	OK	Springborn Laboratories, 1990c
Daphnia magna (fresh water)		Methodology DIN 38412	24 hours	EC_{50}=2	Quality no valuable	Huels, 1988a (report unpublished)
Daphnia magna (fresh water)	Static		24 hours	EC_{50}=91		Bringmann et al., 1982 (cited UK report)
Gammarus fossarum (fresh water)	Static		96 hours	LC_{50}=11.6	Low quality	Erben and Beder, 1983a
Mysidopsis bahia (marine)	Dynamic	GLP measured concentration	96 hours	LC_{50}=1.3	OK	Envirosystems study number 9019-CMA (1990)

Table 3.8 bis Acute toxicity of cumene to other aquatic invertebrates

Species	Duration	Toxicity endpoint (mg/l)	Data quality	Reference
Radix peregra (fresh water snail)	96 hour	LC_{50} = 6.1	Low quality	Erben and Beader, 1983b
Lymnea stegnalis (fresh water snail)	96 hour	LC_{50} = 10.5	Low quality	Erben and Beader, 1983b
Dicranophorus forcipatus	24 hour	EC_{50} = 172		Erben, 1978

Table 3.9 Acute toxicity of cumene to algae

Species	Comments	Duration	Toxicology endpoint mg/lReference	Data quality	Reference
Chlorella vulgaris (fresh water)	Photosynthetic CO_2 uptake	3 hour	EC_{50} = 21.27		Hutchinson, et al., 1980 (cited in UK report)
Chlamydomonas angulosa (fresh water)	Photosynthetic CO_2 uptake	3 hour	EC_{50} = 8.8		Hutchinson et al., 1980 (cited in UK report)
Selenastrum Capricornotum (fresh water)	Methodology OECD 201, modified growth inhibition	72 hour	EC_{50} = 2.6	OK	Galassi et al., 1987; 1988

Table 3.10 Chronic toxicity of CUMENE to aquatic organisms

Species	Duration	Toxicity endpoint (mg/l)	Data quality	Reference
Daphnia magna	21 days	Reproduction rate or survival of parent animals: NOEC = 0.35	Valid	Huels Infracor. Final report DL - 172 (1998)
Scenedesmus subspicatus	72 hours	Growth rate: NOEC = 0.22	Valid	Huels Infracor. Final report AW –469 (1998)
Brachydanio rerio *P. promelas* QSAR CALCULATION	28-32 days	QSAR NOEC = 0.38	Following TGD	Calculated by the rapporteur

3.2.1.2 Effects on microorganisms

The provided information does not include enough information to assess the potential effects of cumene on the microbial activity of WWTPs. Available data are: a 24h EC_{10} of 211 mg/l for *Pseudomona putida*; a 16h LOEC of 31 mg/l for a sublethal parameter (ATP content) on a consortia of microorganisms isolated from ground waters; and three toxicity tests on protozoa, one of them highly sensitive, but without relation with the activity of WWTPs. The value for *Pseudomona putida* corresponds to an unpublished study reporting nominal concentrations above the water solubility limit of cumene. Neither GLPs nor analytical monitoring were employed. Thus, it is considered unappropriated to derive a PNEC value from this particular figure.

Due to the lack of specific information, the data on biodegradation can be considered at this point. Particular relevance must be recognized to those results that may suggest the emergence, or not, of inhibitory mechanisms in the biodegradation of the chemical at higher concentrations. However, there are large differences in the presented data set. Results range from ready biodegradable to lack of degradation under test conditions. There are two data regarding on degradation by non-adapted microorganisms from domestic sewage plants; in both cases, more than 70% of cumene was degraded and there are not indications of inhibitory effects at concentrations up to 1 mg/l. Monitoring data for cumene concentration in the receiving water of WWTP have been presented for two production sites in the UE, reported data were always below 0.5 mg/l. However, the C_{eff} estimated according to the TGD is 87.5 mg/l, suggesting that this limit can be overpassed in some plants. This suggestion is confirmed by the effluent concentrations included in the US Hazardous Substances Database (reported form the Shackelford WM et al., 1988 paper). The included figures indicated that although all mean values are below 1 mg/l, peak values could be as high as 17.9 mg/l.

Table 3.11 Toxicity of cumene to microorganisms and protozoa

Species	Comments	Duration	Toxicity endpoint (mg/l)	Reference
Pseudomonas putida	Methodology DIN 38412	24 hour	EC_{10} = 211	Huels, 1984
Ground water microorganisms	ATP level test	16 hour	LOEC = 31	Dippel et al., 1991
Colpidium colpoda	Toxicity threshold for cessation of ciliary movement	18 hour	TT = $12 \cdot 10^{-3}$	Rogerson et al., 1983
Tetrahymena elliozzi	Toxicity threshold for cesation of ciliary movement	24 hour	TT = $3017 \cdot 10^{-3}$	Rogerson et al., 1983

3.2.1.3 Effects assessment for the sediment

The available data set does not include a single data on the effects of cumene on sediment organisms. In the absence of any ecotoxicological data for sediment-dwelling organisms, the PNEC may provisionally be calculated using the equilibrium partitioning method with the PNEC for aquatic organisms and the sediment/water partitioning coefficient.

The conditions assumed when this method is employed are clearly stated in the Technical Guidance Document. The P_{ow} of cumene is about 3.5, therefore, this approach seems to be appropriate. The Ksed-water value for cumene is 22.9 m^3/m^3, being RHOsed 1300 kg/m^3.

$$PNECsed=(Ksed\text{-}water/RHOsed)\cdot PNECaquatic\ organisms\cdot 1000$$

$$= (22.9/1300)\cdot PNECaquatic\ organisms\cdot 1000 = 388\ \mu g/kg\ wwt$$

3.2.2 Terrestrial compartment

The available data set includes three toxicity tests on plants (*Phaseolus aureus, Sorghum bicolor* and *Helianthus annuus*) using the OECD guideline 208 with soil exposures for 21 days; toxicity was not detected even at the highest concentrations. Results can be summarized by expressing both toxicity parameters, 21 days CL_{50} and NOEC, as higher than 1000 mg/kg soil d.w.

The information includes some toxicity data on birds and mammals, but does not present toxicity data on soil organisms other than the above mentioned test on plants.

Following the technical guidance document, if only one terrestrial test is available, the risk assessment should be performed based on both, the terrestrial test and the aquatic toxicity data as an indication of the risk to soil organisms.

Starting with the PNEC derivation form the plant toxicity data; for this particular case, the use of an assessment factor of 1000 on the reported EC_{50} value, >1000mg/kg, is not appropriated because of this value correspond, in fact, to the highest tested concentration, and did not produce any effect. The $PNEC_{soil}$ can be calculated applying a factor of 100 to the 21 days NOEC for plants, the result is a $PNEC_{soil}$ of 10 mg/kg dw. The use of this applying factor can be also justified by considering a factor of 10 between a concentration that does not produce any effect on three different species, and the EC_{50} value. Nevertheless, the sensitivity of plants to cumene is so low that the use of applying factors of 1000 or 100 does not produce any effect in the risk characterisation.

The risk assessment for terrestrial compartment should include the estimation of the PNEC for terrestrial organisms using the equilibrium partitioning method. Due to the low sensitivity of plants, this ratio will become the essential instrument in the risk characterisation of cumene for soil organisms. In the absence of enough ecotoxicological data for soil organisms, the equilibrium partitioning method should be applied in order to identify the potential risk to the soil compartment. Considering the P_{ow} of cumene this "screening approach" may be acceptable, but only due to the lack of available data. The additional level of uncertaintyproduced by this approach should be considered in the risk assessment, however, a direct increment by a factor of 10 of the PEC/PNEC ratio is not required.

The PNEC for soil dwelling organisms has been calculated by EUSES program using the equilibrium partitioning method.

$$PNEC_{terrestrial\ organisms} = 0.347\ mg/kg\ wwt$$

Table 3.12 Toxicity of cumene to terrestrial plants

Species	Comments	Duration	Toxicity endpoint (mg/kg)	Reference
Sorgum bicolor (Monocotyledon)	Methodology OECD 208	21 day	EC_{50} > 1000 NOEC > 1000	Windeatt et al., 1990
Phaseolus aureus (Dicotyledon)	Methodology OECD 208	21 day	EC_{50} > 1000 NOEC > 1000	Windeatt et al., 1990
Helianthus annus	Methodology OECD 208	21 day	EC_{50} > 1000 NOEC > 1000	Windeatt et al., 1990

3.2.3 Atmosphere

According to the Technical Guidance Document, for the risk assessment of the air compartment, biotic and abiotic effects shall be considered.

3.2.3.1 Biotic effects

The provided information does not present the set of data required for a full assessment of the potential environmental effects of cumene on biota directly exposed via air (gaseous or deposited).

There are no data on the toxicity of cumene on insects (i.e., honeybees) or plants (other than by soil exposure). The only available data are those reported on the inhalation toxicity and skin irritation in mammals. These data do not allow to derive a PNEC value, however, the figures, and particularly those related to medium-long exposure periods, would provide a very useful information in the risk process. A full description of the available data and their quality appears in the human toxicity section; thus, an additional report is not required here.

3.2.3.2 Abiotic effects

Considering the low atmospheric half-lives of cumene, a global warming potential is not expected for this chemical. The molecular structure of cumene does not include Cl, Br, F, N or S; therefore impacts on the stratospheric ozone layer and/or acidification are not expected.

Regarding the production of tropospheric ozone, the photochemical ozone creation potential, POCP, of cumene has been estimated by Derwent (1991, personal communication), giving a value of 74.4 relative to ethylene which has a POCP of 100.

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

According to the Technical Guidance Document, the risk characterisation for secondary poisoning is required if three specific criteria are fulfilled. These criteria can be summarized as:

- Indirect exposure likely

- Indication of bioaccumulation potential, and

- Mammalian toxicity risk

Therefore, the available information on the accomplishment of these criteria appears as the starting point of this topic.

Indirect exposure - The evaluation of the environmental exposure conditions suggests indirect exposure of ecosystems is likely to occur. In fact, cumene has been detected not only in air, water, soil and sediment samples, but also in aquatic organisms. Data on monitoring programs included in IUCLID, displayed the detection of cumene in vertebrate (rainbow trout, *Oncorhynchuss mykiss*) and invertebrate (mussel, *Mytilus edulis*) aquatic organisms. Thus, the criteria of potential indirect exposure must be considered fulfilled.

Bioaccumulation potential.- According to the explanation reported in point 3.1.0.3, the $P_{ow} > 3$ indicates a bioaccumulation potential for cumene.

Mammalian toxicity - The oral toxicity of cumene on mammals is moderate, suggesting that secondary poisoning should not be relevant. To check this hypothesis, a "screening" assessment has been done, estimating the PNECoral from mammalian data on oral repeated exposures.

$PNEC_{oral}$ estimation - The data set includes a single study that can be used to estimate the $PNEC_{oral}$ for secondary poisoning. Wolf et al. (1956) reported a 6 months NOAEL in rats for cumene administered in olive oil by gavage of 154 mg/kg b.w.d.; a further description of the study has been presented under the regarding point of the human toxicity assessment. The transformation of this figure according to the appendix VIII gives a final value of 3080 mg/kg food. An assessment factor of 30 has been considered appropriate. The use of an additional correction factor of 3 to consider the difference in caloric content of the diet of the laboratory animals and the diet of fish-eating birds or mammals produces a final $PNEC_{oral}$ value of 34 mg/kg food.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

Taken into account the available data, and the release estimates described in 3.1.1.1, local PECs have been calculated for both, water and sediments. In addition, the Mackay´s model has been used to estimate regional and continental PECs for surface water and sediment.

The PNEC for aquatic organisms has been estimated from the new chronic toxicity data. The lowest chronic NOEC is 0.22 mg/l, found in the growth rate inhibition test on *Scenedesmus subspicatus*. The NOEC for *Daphnia magna* reproduction is in the same range, 0.35 mg/l, as was expected from the similitude between the acute toxicity of cumene for the different taxonomic groups and the consideration of cumene as a non polar narcotic. The chronic toxicity of cumene for fish has been estimated by QSAR, the calculated NOEC is 0.38 mg/l. The validity of QSAR estimations has been checked comparing the measured (0.35 mg/l) and calculated (0.32 mg/l) chronic toxicity of cumene for *Daphnia magna*. The available information includes chronic toxicity data on fish (QSAR estimation) *Daphnia* and algae supporting the use of a factor of 10 for the calculation of the PNEC. Applying an assessment factor of 10 to this value produces a PNEC for aquatic organisms of 22 µg/l.

The lack of data on sediment-dwelling organisms forces the estimation of the PNEC value for these organisms by the equilibrium partitioning method. Thus, an additional level of uncertainty must be considered when using this figure.

A clear disagreement between PEC_{local} values estimated according to the TGD and those calculated from the monitoring data provided by the industry was observed. The difference, four orders of magnitude, is mostly explained by discrepancies in the emission rates. However, the information provided by the industry is incomplete, and in same cases unconvincing, and only allows the estimation of reliable PEC_{local} data for two (25%) production sites located in the EU. These two sites do not represent the "Worst case scenario" and therefore cannot be used as the basis for the assessment.

However, industry data allows the estimation of reliable emission rates for six (75%) production sites. These data demonstrate that the TGD default values overestimate the release of cumene to the WWTP.

The most appropriate solution is to calculate the PCE_{local} values for the aquatic compartment using the average release estimations provided by monitoring data and the TGD default values for all other parameters. The obtained value, 7.13 ug/l, will be used for the risk characterisation.

The PEC/PNEC ratios have been summarized in **Table 3.13**. All PEC/PNEC ratios are lower than 1, suggesting a low environmental concern of cumene releases from the activities covered by this assessment.

The available toxicity data set also covers marine organisms. In fact, a similar acute toxicity range for fresh and salt water organisms can be observed. Thus, a similar level of hazard may be expected for discharges into fresh water bodies and estuaries, with risk assessments specifically based on the expected environmental concentrations, predicted as functions of emission/dilution values.

Result

For production and subsequent use in phenol and acetone production and for the emission from disperse sources

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

For WWTP the available information do not allow a quantitative estimation of a PNEC value although the data suggest that no inhibitory effects should be expected at concentrations up to 1 mg/l. Monitoring data presented for two production sites in the UE and those included in the US Hazardous Substances Database indicate that although mean values of cumene in the effluents are expected to be always below this limit, peak values can be as high as 17.9 mg/l. Thus, although in general a low risk for WWTP should be expected, a potential risk for episodic problems should be considered.

Table 3.13 PEC/PNEC ratios for the aquatic compartment

Scenario	PEC/PNEC ratio
$PEC_{local\ (water)}$ 7.13 µg/l	0.32
$PEC_{local\ (sed)}$ 143 µg/kg	0.37
$PEC_{regional\ (water)}$ 0.3 ng/l	0.00001
$PEC_{regional\ (sed)}$ 6.8 ng/kg	0.00002
$PEC_{continental\ (water)}$ 0.09 ng/l	0.000004
$PEC_{continental\ (sed)}$ 2 ng/kg	0.000005

3.3.2 Terrestrial compartment

Regional and continental PECs for the soil have been calculated. The produced figures are $PEC_{soil/regional}$ 0.0027 µg/kg and $PEC_{soil/continental}$ 0.001 µg/kg. The local PEC value for agricultural soil has also be estimated. In addition, local soil contaminations not related to the life-cycle of cumene have also been observed (i.e., due to garage spill or in waste dump sites), representing an additional potential risk that cannot be adequately estimated is this assessment, but should be considered in the risk assessment of petroleum products.

The toxicological information includes a single data on plants exposed via soil with EC_{50} and NOEC values higher than the maximum tested concentration (1000 mg/l). There are not studies available on earthworms or other soil-dwelling organisms. Therefore, the risk assessment should be based on the equilibrium partitioning method, the estimated PNEC value is 0.347 mg/kg soil wwt.

The value obtained for these ratios are included in **Table 3.14**.

Table 3.14 PEC/PNEC ratios for the terrestrial compartment

Scenario	PEC µg/kg soil	PEC/PNEC
Local (agricultural soil)	181	0.52
Regional	0.0027	0.000008
Continental	0.001	0.000003

Result

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

This conclusion applies to local, regional and continental scenarios associated to the production and use of cumene.

At the local scale, soil pollution by cumene is expected to be mostly associated to the use of other substances, particularly petroleum products, which are not related to the life cycle of cumene. Thus, the local risk for soil organisms should be additionally assessed when considering petroleum products.

3.3.3 Atmosphere

The bulk of cumene release to the atmosphere is attributable to disperse sources (gasoline marketing, distribution and use). Regional and continental PECs can be calculated according to Mackay´s fugacity model. The following figures, $PEC_{air/regional}$ 0.17 μg/m^3 and $PEC_{air/continental}$ 0.02 μg/m^3, are produced.

A PNEC value cannot be produced due to lack of information. There are no studies available on the toxicity of cumene on insects (i.e., honeybees) or plants (other than by soil exposure). The only available data are those reported on the inhalation toxicity and skin irritation in mammals. The NOAEL values for mammals are several orders of magnitude higher than the PEC at the regional and continental levels. Thus, effects on mammals are not likely expected, while the risk for insects and plants cannot be assessed due to lack of data.

Available information suggests that probably cumene has not a significant impact on global warming, the stratospheric ozone layer, or acidification. However, the POCP of cumene is 74.4 relative to ethylene, which has a POCP of 100, and may contribute to the formation of tropospheric ozone.

Result

For regional and continental exposures of mammals

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

This assessment does not include neither local exposures nor effects on invertebrates and plants.

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

According to the Technical Guidance Document, the risk characterisation for secondary poisoning is required if three specific criteria are fulfilled. These criteria can be summarized as:

- Indirect exposure likely

- Indication of bioaccumulation potential, and

- Mammalian toxicity risk

The exposure and bioaccumulation criteria are fulfilled. Exposure is suggested by the available information and confirmed by monitoring data on fish and mussels. The P_{ow} of cumene indicates a potential for bioaccumulation.

However the oral toxicity of cumene on mammals is moderate, suggesting that secondary poisoning should not be relevant. To check this hypothesis, a "screening" assessment has been done, estimating the $PNEC_{oral}$ from the mammalian data on oral, repeated doses, toxicity.

Applying an assessment factor of 30 to the data reported by Wolf et al. (1956) produces a $PNEC_{oral}$ value of 34 mg/kg food. The reported data is a 6 months NOAEL in rats for cumene

administered in olive oil by gavage of 154 mg/kg b.w.d.; the transformation of this figure according to the appendix VIII gives a value of 3080 mg/kg food. The PNEC estimate includes an additional correction factor of 3 to consider the difference in caloric content of the diet of the laboratory animals and the diet of fish-eating birds or mammals.

The association of calculated PEC_{water} with the BCF, estimated from the P_{ow}, would produce provisional PEC_{oral} values several orders of magnitude lower than the PNEC figure. Therefore, the risk of secondary poisoning in birds and mammals, based on existing information, would appear to be low. However, the potential to enter the food chain has been revealed. Thus, if additional information became available indicating that cumene is more toxic to mammalian or avian species that presently thought, then the risk of secondary poisoning would have to be reassessed.

Result

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

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

The lack of human data is surprising for cumene, a common commodity chemical. Cumene is well absorbed through the lungs and, by analogy with toluene and xylene, it is assumed to be absorbed through the skin, although no satisfactory study is available to demonstrate this.

Cumene has been reported to be ubiquitously present in the breath and blood of hospital and chemical workers not occupationally exposed to cumene.

4.1.1.2 Occupational exposure

During cumene's manufacture and primary use, the number of workers exposed is around 200. These will be shift operators, foremen, maintenance fitters and quality control personnel, together with others such as delivery drivers. Further exposures during loading and unloading of road tankers and ships can occur, but this work is not continuous and may be carried out by a few number of workers. There are also possibilities for exposure arising from minor applications and the handling of materials in which it is a common constituent like solvents.

The different systems of limit values are summarized in the **Table 4.1**.

Table 4.1 Occupational exposure limit in different countries

Country	OEL-Occupational Exposure Limit (TWA 8 h)		STEL-Short Term Exposure Limit		Skin notation
	ppm	mg/m³	ppm	mg/m³	
U.S.A. (A.C.G.I.H)	50	245			YES
U.S.A (O.S.H.A.)	50	245			YES
AUSTRIA	50	245			YES
BELGIUM	50	246			YES
DENMARK	50	245			YES
FINLAND	25	120	60	300	YES
FRANCE	50	245			YES
GERMANY	50	245			YES
NETHERLANDS	25	120	70	370	YES
SWEDEN	25	120	35	170	YES
UNITED-KINGDOM	25	120	75	370	YES

1ppm = 4,96 mg/m³

4.1.1.2.1 Manufacture

In the manufacture of cumene the number of workers potentially exposed within the E.U. is about 110 - 200 workers.

The production of cumene involves the use of closed systems. One company has reported that contact is limited to:

- Collection of samples for analysis. This operation is made one time per eight-hour shift (three times per day).

- During loading of tankers (never more than four tankers per year).

- During the technical shutdown of the plant. The frequency is once 11 per year and usually last 25 days. The exposure is a consequence of the cleaning and maintenance activities.

Due to the volatility of cumene, the main route of potential exposure is inhalation.

Other manufacturers transport the cumene via rail or sea for further chemical conversion. Consequently their usage would be termed non-dispersive.

The Workplace Exposure Model predicts that inhalation exposure to gas or vapour (process temperature: 200ºC) used in a closed system will be in the range of 0-0.1 ppm. The model also predicts that, in these conditions, dermal exposure will be very low.
For sampling, maintenance, tanker loading operations and cumene transport, the next choices have been made:

- Non dispersive pattern of use.

- Low tendency to become airborne.

- Dilution ventilation.

The estimated exposure level is, therefore, 10-50 ppm (8 hour-TWA). Furthermore, regarding the batch production methods employed, these concentrations will be received as brief and intermittent exposures, rather than over a full workshift.

However, 1993 data from seven European Companies shows that exposure levels are, in general, below 1 ppm (8 hour-TWA), across all job categories. The range of data is from 0.05 ppm to a maximum of 4.46 ppm (all activities combined).

Typically the mean range values from individual companies was 0.1-0.65 ppm (8 hour-TWA).

Individual data from a cumene producing plant confirm that workplace exposure is below 1ppm. This value refers to 8 hours shifts. Personal air samplers were collected from the following job categories: Runner, Filling station attendant, Laboratory co-worker, Chemical technology co-worker.

Another company had reported that 40-50 samples were taken in 1991 to asses the manufacture long-term exposure to cumene. The exposure level was less than 0.1 ppm (8 hour-TWA). No respiratory protection was worn (on special tasks only).

Cumene is produced, stored and converted in closed systems. Regarding the information provided at the beginning of this section potential contacts could occur during sampling (1 time per 8-hour shift), loading of tankers (never more than 4 tankers per year) and during the shutdown activities (once per year, lasting 25 days). The Workplace Exposure Model predicts that dermal exposure will be in the range of 0-0.1 mg/cm^2 /day (non dispersive use, incidental contact). On most days no such accidental contacts will occur and exposure will be towards the bottom of this range. Therefore, dermal exposure will be low. On the other hand, exposure to cumene is strictly controlled since it is manufactured from benzene and is used to produce phenol. Companies have reported that gloves are worn to avoid direct contact, so in practice this low dermal exposure will be negligible.

4.1.1.2.2 End uses

The major part of cumene is used as raw material for the production of phenol and the associated products, acetone and alpha-methylstyrene.

There are no cumene specific exposure data available for phenol production. Some manufacturers use cumene in a totally closed system where there is on site phenol production.

One company has reported that 99.9% of cumene total production is consumed by the own company in the manufacture of phenol and acetone in a closed system. In these cases we can assume the same range of exposure data (0.05-4.46 ppm 8 hours-TWA) and the same approach that in the manufacture scenario.

The 8 hour workplace exposure in a plant processing cumene was determined in 1990. In a first series of 18 measurement few values were above 2 ppm. In a second series of 18 analysis, the situation had improved and all concentrations were below 2 ppm. No details about the job categories were reported.

Cumene is found as a minor constituent in gasolines and solvents. It also has limited use as a laboratory chemical.

Cumene is found as an isomer in the general C_9 aromatic hydrocarbon content of many solvents, particularly those used in the printing industry.

The number of persons potentially exposed to cumene due to its presence in solvents can not be estimated.

Measured exposures to cumene from solvents was carried out by U.K. (H.S.E., 1994). In all cases monitoring for cumene was undertaken as it was held to be representative of the C9 aromatic content (small and not quantified) of the solvent. Results indicated levels of cumene up to 0.6 ppm.

Data collected in Germany stem from construction engineering, paints lacquers and varnishing industry, metal working industry and mechanical engineering are summarized in the **Table 4.2**.

Table 4.2 Data collected in Germany - Processing types

	No. of results	90% value	
		mg/m³	ppm
Production of paints	125	4.0	0.8
Surface treatment, manual (painting, paint rolling)	255	16.9	3.4
Surface treatment, manual (spraying)	300	5.0	1.01
Surface treatment, mechanical	84	4.0	0.8

-Data period: 1991 - 1995.
-Sampling type: 75% personal samples remaining stationary.
-Exposure duration: 1h (shift averages)

In the worst case (surface treatment, manual) the exposure level is 3.4 ppm. In the same period the short term exposure (≤1h) resulted in a 90% value of 2.23 ppm (11 mg/m^3) for total types of processing.

In the same way, Germany has sent additional exposure data from different processes, **Tables 4.3** and **4.4**.

Table 4.3 Measured 8 h-TWA exposure data ppm

Work area	Number	Range (max-min)
Offset printing works	17 person-related measurement	0.1-1.3
Painting of signs using lacquering machines	2 person-related measurement	0.2

Table 4.4 Short term (10-20 min or 20-30 min) exposure data ppm

Work areas	Number	Range (max-min)
Car repair work (using manual compressed-air spray guns in spray booths)	8 person related measurement	1.9 - 6.7

Considering the use of solvents in the industry we can assume a non dispersive pattern of use and local exhaust ventilation or in the worst case dilution ventilation. Due to cumene's moderate tendency to become airborne (aerosol formation expected), the Model predicts that inhalation exposure will be in the range of 10 - 50 or 100 - 200 ppm. Regarding dermal exposure, the TGD predicts that it will be in the range of 0.1-1 mg/cm^2/day (intermittent contact level). However, if we consider that cumene is a small part of the total C_9 aromatic content of the solvent (small and not quantified), the potential exposure (inhalation and dermal) will be not relevant.

There are no cumene exposure data available for gasoline products. Following HSE, a survey of exposures to gasoline vapour was carried out in 13 European countries during 1984/85 and showed that exposures were below the occupational exposure standard for a variety of occupations involving gasoline handling and movement.

Literature data

Cocheo et al., (1983) measured volatile pollutants produced from several rubber goods manufacturing processes. A total of 35 samples were collected in the vulcanization areas of a shoe-sole factory, a tire retreading operation and also in the extrusion areas of the retreading operation and an insulated cable manufacturer. The sampling time was limited to 30 minutes. One of the pollutants found was (cumene). The results are presented in the **Table 4.5**.

Table 4.5 Measured exposure data for cumene for several rubber goods manufacturing processes

		Sampling site			
		A	**B_1**	**B_2**	**C**
Number of samples		13	6	6	10
Cumene observed concentration range	($\mu g/m^3$)	60 - 250	2 - 200	0 -10	ND
	($\mu g/m^3$)				
	(ppm)	0.012 - 0.05	0.0004 - 0.04	0 - 0.002	

A = Shoe-sole factory, vulcanization area.
B_1 =Tire retreading factory, vulcanization area.
B_2 =Tire retreading factory, extrusion area.
C = Electrical cables insulation plant, extrusion area.

Scheffers (1985) have investigated the exposure to solvent vapours. The actual health-related hazard was investigated in a small random sample of 45 maintenance painters at 23 different job locations spread over 12 projects. Results obtained by personal air sampling to cumene ranged from 0-4 mg/m^3 (0-0.81 ppm) (8 hours-TWA), all the project locations included.

4.1.1.3 Consumer exposure

No quantitative data have been obtained for the evaluation of consumer exposure.

Information from all the European manufacturers of cumene have reported that there is no use of cumene in any consumer's product.

Therefore, cumene is not of concern for consumers.

On the other hand, consumer's exposure to cumene respecting its use as constituent of gasolines has not been evaluated here, since it should be assessed when a petroleum products risk assessment report will be elaborated.

4.1.1.4 Indirect exposure via the environment

Cumene is manufactured almost exclusively for the production of phenol and acetone. Other uses are as a minor constituent in gasolines, solvents and detergents.

In spite of the fact that some derivatives obtained by sulfonation of cumene are used for the manufacturing of detergents. Consequently, no pure cumene in detergents is left.

The main source of exposure of humans via the environment is likely to be via food and, to a lesser extent, drinking water.

The concentration of a substance in food is correlated to its concentration in water, soil and air and is also dependent on its bioacumulation behaviour.

The indirect exposure is assessed estimating the total daily intake of a substance by consumption of food, water and inhalation of air. This estimation is based on the predicted environmental concentrations in all compartments.

The EUSES model has been used (Appendix A). Some values are reproduced in **Table 4.6**.

Model predictions suggest that by far the greater amount of human exposure via the environment will be from the air, contributing some 97% of the intake. For the propose of risk assessment, intakes of 0.11 mg/kg/day and $1.45 \cdot 10^{-5}$ mg/kg/day for the local and regional exposure levels respectively will be used.

Table 4.6 Estimated human daily intake of cumene

Source	Local	Regional
Air (mg/kg/day)	0.107	$1.43 \cdot 10^{-5}$
Drinking water (mg/kg/day)	$1.19 \cdot 10^{-4}$	$4.87 \cdot 10^{-9}$
Fish (mg/kg/day)	$2.01 \cdot 10^{-3}$	$9.8 \cdot 10^{-8}$
Leaf crops (mg/kg/day)	$5.92 \cdot 10^{-4}$	$7.9 \cdot 10^{-8}$
Root crops (mg/kg/day)	$7.93 \cdot 10^{-4}$	$3.24 \cdot 10^{-8}$
Meat (mg/kg/day)	$2.43 \cdot 10^{-5}$	$3.23 \cdot 10^{-9}$
Milk (mg/kg/day)	$1.43 \cdot 10^{-5}$	$1.91 \cdot 10^{-9}$
Total human dose (mg/kg/day)	0.11	$1.45 \cdot 10^{-5}$

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

4.1.2.1 Toxico-kinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

In vivo studies

A study about metabolism, disposition and pharmacokinetics of cumene in F-344 rats following oral, i.v. administration or nose-only inhalation exposure was carried out by Research Triangle Institute in 1989.

Male and female Fischer F-344 7-9 weeks old rats were used. During experiments, animals were housed individually in metabolism chambers for collection of urine, faeces, CO_2, and expired volatiles. [^{14}C]cumene oral doses were given by intragastric intubation and i.v. doses were administered as bolus doses into one of the lateral tail veins. The [^{14}C]cumene atmosphere was available into the chamber. The doses used were: 33 mg/kg for single intravenous dose, single oral gavage dose and oral gavage dose, daily for 8 days; 1350 mg/kg for single oral gavage dose and 100, 500 and 1500 ppm for single nose only inhalation exposure, 6 hours.

[^{14}C]cumene was absorbed rapidly and nearly completely from the stomach although absorption may have been delayed slightly at the highest oral dose. [^{14}C]cumene was also absorbed rapidly through the lung with detectable levels of [^{14}C]cumene found to be present in the blood within 5 min of the beginning of the exposure.

In general, very similar rates and routes of elimination were observed for oral dosing and inhalation studies. Urine was the major route of elimination following oral dosing and inhalation exposure. A minimum average of 70% of the dose was excreted in the urine. At lower doses or exposure levels of [^{14}C]cumene, relatively little radioactivity was excreted in the expired breath or in the faeces while almost all of the dose was eliminated in the urine. With increasing doses of exposure levels, great amounts of radioactivity appeared in the expired breath and, to a much smaller extent, in the faeces.

Analysis of tissue distribution data indicated that several tissue types had elevated tissue to blood ratios (TBR) for total radioactivity following administration of [^{14}C]cumene by all routes. Adipose tissue was observed to have elevated TBR following all doses and routes. This observation is consistent with the known lipophilicity of parent cumene and was not totally unexpected. Liver and kidney tissues were also observed to have elevated TBR in most studies. These tissues are responsible for the bulk of oxidative metabolism in mammals and as such are likely to have higher concentrations of cumene metabolites than other tissues. In addition, the kidney is also the major excretory organ for cumene and its radiolabeled metabolites. Contamination of kidney tissue with residual urine could also be expected to raise the concentration of radiolabel in this tissue.

Elimination of radiolabel from the blood of rats given an i.v. bolus of cumene was described by a two compartment pharmacokinetic model. The fit of this model to the observed data was excellent. This indicates that the disappearance of radiolabel from the blood is, in all likelihood a biexponential process. For all other studies that employed radiolabel it was necessary to fit the data to a one-compartment model. This was necessary due to the lack of blood samples timed appropriately to yield information regarding the rates of absorption of radiolabel and distribution to the tissues. Without this information the early (fast) phase of the biexponential process cannot be defined. The results of using a one-compartment model to simulate what is probably a two-compartment process are first, a model with less than optimum ability to predict the concentrations of radiolabel in the blood as a function of time and second, an estimated distribution half-life (THALF1) for the single exponential phase that is actually a combination of the fast phase and the slow phase of the biexponential process. This causes the value of THALF1 to be larger than the true value for the fast, early phase and somewhat smaller than the true value for the slower terminal phase. A number of additional blood samples during the period up to 8 h following dosing would be required to avoid this problem and allow development of the two-compartment model for all routes and doses.

After i.v. dose of 33 mg/kg, pharmacokinetic variables were calculated using a two compartment open model. For [^{14}C]cumene, the distribution half-life (THALF1) was calculated to be 0.21 h for males and 0.27 h for females. The elimination (terminal) half-life (THALF2) was calculated to be 8.6 h for males and 7.3 h for females.

Conjugated metabolites of cumene were excreted in the urine. The radiolabeled metabolites of cumene excreted in urine and breath were studied using reversed phase HPLC. Based upon retention times, the six radiolabeled metabolite peaks observed in urine following i.v. administration of cumene are the same six observed following oral dosing and inhalation exposure. In general over all doses and routes we conclude 50%, or more, of urinary excretion was accounted for by 2-phenyl-2-propanol and its glucuronide and/or sulphate conjugates. The balance of excretion in urine was accounted metabolites 1, 4 and 5 were all converted to free 2-phenyl-1,2-propanediol. Unknown urine metabolite 6 was found to have been converted to 2-phenyl-2-propanol and urine metabolite 2 which was unaffected by treatment with the deconjugating enzymes ß-glucuronidase and sulfatase and thereby retained the same retention time. The effect of enzyme treatment on urine metabolite 3 is equivocal, possible no change but difficult interpret due to the minor nature of the metabolite. In addition, small amounts of the free, unconjugated cumene metabolites 2-phenyl-1,2-propanediol, 2-phenyl-2-propanol and 2-phenylpropionic acid were detected.

In conclusion, it was shown that cumene is well absorbed by oral administration or nose-only inhalation exposure. Following its absorption, cumene is extensively metabolized and excreted. No evidence for the accumulation of cumene following high doses or repeated administration was observed.

During studies of the metabolism and pharmacokinetics of cumene in rats several urinary metabolites remained unidentified (Research Triangle Institute, 1992). One of these metabolites, Metabolite 2, comprised between 3 and 40% of the radioactivity that was excreted in the urine. The fraction excreted as Metabolite 2 varied directly with the dose. Since the urine was the major route for the elimination of cumene and its radiolabeled metabolites, accounting for greater than 70% of the administered dose, the identity of this metabolite was of significant interest. The current document reports the results of studies conducted to determine the chemical identity of Metabolite 2.

Pooled composite urine obtained from animals which had received 1.35 g cumene/kg *per os* during the course of previous studies was used as the source of Metabolite 2 during the current studies. Frozen storage of this pooled urine since the end of the previous studies in 1989 was shown not to have affected the qualitative or quantitative composition of radiolabeled metabolites as determined by HPLC. Enzyme treatment and multiple chromatographic steps were used to prepare an enriched, partially purified sample of Metabolite 2. Analysis of this sample using two different analytical HPLC methods indicated radiochemical homogeneity.

Analysis using ^{13}C and ^{1}H-NMR spectroscopy gave results indicating the presence of at least two compounds. Careful comparison of spectrometric results indicates that the identity of one of the two components may be phenylmalonic acid. This dicarboxylic acid can be predicted to be an oxidative metabolite of cumene. Attempts to achieve co-chromatography of Metabolite 2 with phenylmalonic acid yielded conflicting results in two different chromatography systems. HPLC-MS of the partially purified metabolite gave no useful information due to the presence of at least 2 different compounds in the sample.

Subsequently, using a normal phase HPLC system, two radiolabeled components were resolved from the partially purified Metabolite 2 sample that had been studied spectrometrically. Further studies are necessary to unambiguously elucidate the identity of these two compounds. Current evidence is not inconsistent with one of the two components being phenylmalonic acid (2-phenylpropane-1,3-dicarboxylic acid).

Percutaneous penetration of cumene has frequently been claimed to occur at a rate similar to that obtained for benzene, toluene and p-xylene based on one early investigation (Valette and Calver, 1954). In this study, conducted in the rat, each of cumene or the other solvents was used as a vehicle for eserine application. The authors measured the biological activity of eserine as the endpoint.

The metabolism of cumene was studied by Robinson et al. (1954), when 2 ml (1720 mg) cumene were given to rabbits by gavage; 40% of the administered dose were metabolized to 2-phenylpropan-2-ol and 25% each to 2-phenylpropan-1-ol and alpha-phenylpropionic acid, which were excreted as conjugated glucuronic acids, triacetyl methyl ester.

van Doorn et al. (1981), studied the excretion of cumene. After a single i.p. administration of 120.2 mg cumene/kg b.w. to male Wistar rats 73 ± 6 mmol SH/mol creatinine were found in the urine compared to 6 ± 2 mmol SH/mol creatinine in the untreated control; 3.4 mmol SH/mol creatinine of these urinary thio compounds had been excreted as mercapturic acid.

4.1.2.1.2 In *vitro* studies

In an earlier experiment 200 mg/l cumene were metabolized *in vitro* by a rabbit liver soluble enzyme fraction, 1hr incubation at 37ºC and pH = 7.4, yielding 2-phenylpropan-1-ol (0.04-0.07 mol/min/g liver), 2-phenylpropan-2-ol (0.17-0.35 mol/min/g liver) and 2-phenylpropionic acid (0.03-0.05 mol/min/g liver). Metabolites were identified by gas-liquid chromatography with a FID detector. Detection limit was 0.01 g/metabolites (Chakraborty and Smith, 1967).

Pyykkö in 1986 studied *in vitro* inhibition of Cytochrome P-450 dependent monooxygenases by cumene: aryl hydrocarbon hydroxylase (AHH), IC_{50} = 564,9 mg/l, 7-ethoxy-coumarin O-deethylase (ECD), IC_{50} = 132.2 mg/l; rat hepatic microsome preparation; 10 min incubation; 0.08 mM (AHH) or 0.1 mM (ECD) enzyme substrate.

Sato and Nakejime (1987) studied the mean rates of *in vitro* metabolism of cumene in rat liver: 12.3 µg/min (2.6 nmol/nmol cytochrome P-450 (min), in rat lung: 17.3 µg/g/min (42.4 nmol/nmol cytochrome P-450/min).

4.1.2.1.3 Studies in humans

In several non-occupational exposure studies, cumene has been reported to be associated with human metabolism and found as an organic constituent present in expired air of non-smoking normal healthy urban (man and women) population with a mean concentration about 0.35 ng/l (one sigma limit 0.25-0.45 ng/l) (Conkle et al., 1975; Krotoszynski et al., 1977).

In a study (Parbellini et al., 1988) for the determination of 13 industrial solvents in blood, alveolar air and urine the concentration of cumene was measured in 49 Italian blood donors. For a geometric mean environmental air concentration of 6 ± 2 ng cumene/l (range 1-2 ng/l), the results found in the specimens analyzed were as follows: alveolar air, geometric mean 3 ± 2 ng/l

(range 1-14 ng/l), blood, geometric mean 199 ± 2 ng/l (range 17-963 ng/l) and urine, geometric mean 202 ± 2 ng/l (range 20 - 1190 ng/l).

Alveolar and blood cumene concentrations were measured in 58 hospital employees (geometric mean environmental concentration 6.4 ± 2.4 ng/l, range 2-36 ng/l) and in 28 chemical workers, benzene manufacturing plant, (geometric mean environmental concentration 10.7 ± 5.6 ng/l, range 1-279 ng/l) (Brugnone et al., 1989). The alveolar concentrations did not differ significantly between hospital staff and chemical workers. No correlation was found between smokers and non-smokers. The alveolar concentrations were correlated significantly to environmental concentrations measured in the hospital and in the plant infirmary ($p<0.001$). The alveolar cumene retention ranged from between 70.4% in the hospital staff to 77.8% in the workers. The blood cumene level was significantly lower in the hospital staff than in the chemical workers ($p<0.002$). The smoking habit did not influence the blood level in both employee groups. Only in the chemical workers significant correlations were found between blood and alveolar cumene concentrations and blood and environmental concentrations ($p<0.001$).

Experiments on the absorption of cumene and the excretion of dimethylphenylcarbinol (2-phenylpropan-2-ol) were made on 10 healthy volunteers (5 men and 5 women aged between 20 and 35 years) exposed to 49, 98 or 147 ppm (240, 480 or 720 mg/m3, respectively) under controlled conditions for 7 hours using head-only inhalation exposure (Senczuk and Litewka, 1976). Retention of cumene vapours in lungs during exposure decreased from 64% at 0.5 h of exposure to 45% at the end of each exposure. The urine was collected for examination during and after exposure (2.5-48 h after the exposure began) and dimethylphenylcarbinol, in the extracts was determined. Maximum excretion was observed after 6-8 h of exposure, diminishing after cessation of exposure approaching zero after 48 h. The average percentage yield of the conversion of cumene into 2-phenylpropan-2-ol was 35%.

4.1.2.1.4 Summary of toxicokinetics

In studies in animals cumene is rapidly absorbed following inhalation exposure and is also absorbed from the gastrointestinal tract. In humans cumene is associated with the human-metabolism found as an organic constituent present in blood, alveolar air and urine with a significant correlation between blood and alveolar cumene concentrations. One study in humans suggests that 50% of the cumene inhaled was taken up by the lungs; other study calculated alveolar cumene retention to 77.8%. No satisfactory studies of dermal absorption are available. Cumene and/or its metabolites are distributed widely following inhalation exposure or oral administration to animals, the highest tissue levels being found in body fat.

A great part of radiolabelled cumene is excreted over 72 hours, mainly as conjugated metabolites in the urine (70% or more of the administered dose). In animal studies the faeces and expired breath are minor routes of excretion. 2-phenylpropan-2-ol is a major metabolite in both animals and man.

Other urinary metabolites are 2-phenylpropane-1,2-diol and 2-phenylpropionic acid.Very similar toxicokinetics are observed when single and repeated oral dose animal studies are compared.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Oral

There are six references in the IUCLID dealing with acute oral toxicity. All studies are done in rats.

In a study done by Dow Chemical Company (1948) it was reported the value 1400 mg/kg as the largest dose letting all rats survive. The cumene was administered in single doses to rats. The smallest dose killing all rats was 5000 mg/kg.

Smyth et al. (1951) reported an estimated LD50 of 2910 mg/kg in a range finding study in male rats by gavage administration.

Wolf et al. (1956) determined on 20 young adult Wistar rats the toxicity of cumene. The material was introduced into the stomach by means of a stomach tube. The cumene was undiluted or in olive oil solution. All the surviving rats were observed until recovery was assured (usually about two weeks). An LD50 value of approximately 1400 mg/kg was reported. When the rats were autopsied, slight liver changes and, in some instances some kidney involvement of questionable significance were observed. Isopropyl benzene appeared to cause some irritation to the stomach and intestine.

Gerarde and Linden (1959), studied the acute toxicity giving a single dose of 2.5 ml of a mixture of cumene in olive oil 1:1 v/v to fasted rats weighing approximately 250 g. Surviving animals were observed for three weeks after dosing for evidence of abnormality in behaviour and activity. Cumene caused mortality in 6 out of 10 rats. The LD50 established was an approximate value of 4000 mg/kg (on the basis of the dilution). This report was conducted on several alkylbenzenes. Symptoms of toxicity included central nervous depression. Post-mortem examination revealed that the principal cause of death from these compounds was chemical pneumonitis with pulmonary oedema and haemorrhage.

A more recent study (Monsanto, 1985) reported a value of LD50= 2700 mg/kg. Five Sprague Dawley Albino rats by dose were treated with cumene undiluted at doses levels of 2000, 2510, 3160 and 3980 mg/kg. Signs of intoxication were: weight loss (one to three days in survivors), increasing weakness, ocular discharge, collapse and death. Gross autopsy in decedents showed haemorrhagic lungs, liver discoloration and acute gastrointestinal inflammation. Viscera appeared normal in survivors (14 days).

In a test reported in Dow Chem Company (1985) a single oral dose of 3980 mg/kg body weight of cumene was quoted as the LD50 value for rats. Death occurred after 2.5 hours and followed respiratory distress, the onset of which was observed immediately after dosing. No lethal effects were observed in rats dosed at 2000 mg/kg cumene, although both groups displayed slight liver and kidney injury at necropsy.

Dermal

Smyth et al., (1951) reported a dermal LD50 of 10600 mg/kg b.w. (12.3 ml/kg b.w.); in a range-finding study, following application of single occluded doses levels of 4310, 8620 and 17420 mg/kg at male albino rabbits. An observation of 14 days post treatment was done.

In a more recent study, Monsanto (1985), reported a value of LD50 >3160 mg/kg. New Zeland albino rabbits were treated with cumene undiluted at dose levels of 2000, 3160, 5010 and 7940 mg/kg for 24 hours exposure.

Signs of intoxication included weight loss, increasing weakness, collapse, and death. Gross autopsy of decedents revealed haemorrhagic areas of the lungs, liver discoloration, enlarged gall bladder, darkened kidneys and spleen and gastrointestinal inflammation.

Inhalation

Studies in rats

There are several references about acute toxicity in rats:

Smyth et al., (1951) reported a concentration of 8,000 ppm (40 mg/l) cumene to cause 4 deaths in a group of 6 rats within 14 days after 4 hours exposure. The exposure for 1 hour resulted in no deaths.

In a study deaths were reported to occur during higher exposure levels, 814 ppm (4 mg/l) and 1,323 ppm (6.5 mg/l), killed the rats within 16 h of exposure; these rats displayed impaired locomotion, incoordination, and somnolence (Fabre et al., 1955).

Two references are dated in 1949; a concentration of 40 mg/l cause 4 deaths of 6 rats after 4 hours exposure; 20 mg/l did not cause any deaths at a similar exposure period. (Smyth et al., 1951; Union Carbide Corporation, 1985).

Monsanto (1985), reported a dose > 17.6 mg/l causes no mortalities after 6 hours (OECD protocols for acute inhalation are for 4 hour exposures). Six Sprague-Dawley Albino male rats were used. No toxic signs were showed. In gross autopsy, visceras appeared normal after 14 days.

Gerarde (1960) described the principal causes of death in acutely exposed animals as respiratory paralysis, pulmonary oedema and haemorrhaging, lung haemorrhage being associated with further haemorrhage in the thymus, bladder and adrenals. Liver hypertrophy was also described as resulting from compensation for metabolic stress caused by the compound, as were observed splenic deformities; 20 to 25 mg/l cumene cause prostration and loss of reflexes.

The effects of single inhalation exposure to cumene vapour on behavioural function in rats were evaluated by the examination of a range of parameters, including tremors, righting reflexes, gait, startle response, activity, salivation and rectal temperature (Bushy Run Research Centre, 1989a). After nose-only exposure of groups of 10 rats of each sex to 0, 490 (100 ppm), 2450 (500 ppm) or 5880 mg/m3 (1200 ppm) cumene for 6 hours; gait abnormalities, decreased rectal temperature and increased activity were observed in the groups exposed to the two highest levels. The effects were observed at 1 hour after exposure, but not after 6 or 24 hours. No treatment-related effects were seen at 490 mg/m3 cumene.

Studies in mice

Lazarew (1929) noted a narcotic effect in white mice over 2 hours exposure to 20 mg/l cumene (i.e. the mice were observed lying on their sides). At an exposure level of 25 mg/l cumene, loss of reflexes were observed in the mice (quoted by Nielsen et al., 1994).

Werner et al., (1944), reported a value LC50 of 2000 ppm (10 mg/l, when young, mature white mice (average weight 21 g) were exposed to cumene during 7 hours. This experiment, in mice, demonstrated that the toxicity of a cumene fraction of petroleum is similar to that of pure cumene. Both cumene and the technical product have a potent narcotic action characterised by a slow induction and a long duration. Cumene toxicity was also observed to be age dependent to a small extent, as "older" mice (average weight 27 g) exposed to cumene for 7 hours had an LC50 of 11.5 mg/l. From extrapolation of the dose-mortality curve given in this paper (using 80 old mice), it can be seen that only a few of the mice dying during or shortly after exposure to cumene (6-8 hours). In general, most deaths observed occurred 8-24 hours after the start of the 7 hours exposures, although a few deaths were seen up to 1-3 days after exposure. Signs of toxicity included narcosis, ataxia, loss of reflex, unconsciousness and depression of respiration leading to death. Only twenty-two of the mice dying during or shortly after exposure to the cumene vapour were selected for histopathological study. The twenty-two mice exposed seven hours to technical or pure cumene showed essentially similar significant pathologic changes in the liver, kidneys and spleen. All of the twenty-two mice showed small to moderate amounts of fat in the liver and a few showed fat in the kidneys. Slight to marked phagocytosis of nuclear fragments was found in the follicles of all of the nineteen spleens examined.

Similar effects were also noted in the mouse by Izmerov et al. (1982) who described the toxic effects of cumene as being similar to those of benzene and toluene, but being slower to take effect and more persistent. Izmerov et al., reported and LC50 value for cumene of 121 mg/l and an NC50 value (the concentration causing 50% narcosis in exposed animals) of 53.35 mg/l over 2 hours exposure (quoted by Nielsen et al., 1994).

The results of experiments on mice reported by Dow Chemical Company (1948); using single 7-hour exposures indicated that cumene concentration producing 50% kill is 10 mg/l. Excessive exposures resulted in some pathological changes in liver, kidney and spleen, but the principal action, and the alone causing death, was the anaesthetic action (depression of the central nervous alone system).

Tegeris and Balster (1994) evaluated the acute neurobehavioral effect of cumene after 20 min inhalation exposures to 2000, 4000 and 8000 ppm using a functional observational battery (FOB). The lowest concentration tested (2000 ppm) (10 mg/l) produced significant effects on rearing measured during the exposure, thus the minimally effective concentration could not be ascertained. Concentration range of 2000 to 8000 produced a nearly identical profile of effects, a profile that was also produced by 5, 10, 20, 30 and 40 mg/kg i.p. administration of the CNS depressant drug pentobarbital.

These effects included changes in posture, decreased arousal and reaming, increased ease of handling, disturbances of gait, mobility, and righting reflex, decreased forelimb grip strength, increased landing foot splay, and impaired psychomotor coordination. These acute effects were short-lived, with recovery beginning within minutes of removal from exposure.

This experiment points out that cumene produces a profile of neurobehavioral effects similar to that of pentobarbital.

4.1.2.2.2 Study on mechanisms of toxicity

Pyykkö et al. (1987) studied the effects of cumene on cytochrome P-450 concentration and on three monooxygenase activities, as well as on two microsomal enzymes independent of cytochrome P-450, in the rat liver and lungs. The cumene was dissolved in corn oil (2 M) and given by an intraperitoneal injection of 5 mmol/kg. Animals were sacrificed after 24h; no signs of general toxicity were found at a dose of 600 mg/kg b.w.

Cumene increased by 20-50% the cytochrome P-450 concentration in rat liver microsome. In lung microsomes the situation was quite the opposite; decreased the cytochrome P450 concentration to 40-60% of that in the microsomes of control rats.

The effect of cumene on the aryl hydrocarbon hydroxylase activity in the liver was the same as to that on cytochrome P-450 concentration. The increasing effect of cumene on the activities of liver 7-ethoxycoumarin O-deethylase and 7-ethoxyresorufin O-deethylase was much stronger then that on cytochrome P-450 concentration on aryl hydrocarbon hydroxylase activity.

In the lungs, the activity of 7-ethoxycoumarin O-deethylase decreased; the aryl hydrocarbon hydroxylase activities were unchanged and were not decreased of 7-ethoxyresorufin O-deethylase activity.

About the effect on cytochrome b5 and NADPH-cytochrome c reductase; cumene slightly increased the concentration of cytochrome b5 on liver. In the lung no significant changes were seen. NADPH-cytochrome c reductase was increased in the liver microsome to 20-40% above the controls.

The end conclusion is that this study shows the destructive effect of cumene on the pulmonary cytochrome P-450 y 7-ethoxycoumarin O-deethylase.

The main metabolic route of alkylbenzenes in mammals goes via side chain oxidation to aryl alcohol, which is further oxidated to aryl aldehyde and then to an acid which conjugates with and endogenous acid. The aldehyde is rapidly metabolized by aldehyde dehydrogenase but not in the lungs, where aldehyde dehydrogenase is deficient; this could be the mechanism of cytochrome P-450 destruction where aldehyde or some other active intermediate is formed.

4.1.2.2.3 In vitro studies

Holmberg et al. (1974) studied the acute cytotoxicity of 33 organic solvent using Ehrlich-Landchütz diploid (ELD) ascites tumour cells during short-time in vitro incubations. A dye exclusion test was used for estimating the frequency of cells in a stage of irreversible cell injury leading to cell death.

Ascites tumour cells with 50 and 100 mg cumene/l caused a cell mortality of 5 and 18% respectively after 5 hours of incubation (in the control incubation the dead cells was of 4.2%).

Ascites sarcoma BP 8 cells, cultured in suspension in vitro were used as a general toxicity test system for cumene. The toxic effect was measured as the capacity of the studied compound to

inhibit the growth rate of a cell culture. The results obtained with 1 mM cumene for 48 h caused 100% inhibition of growth rate cell; 0.1 mM cumene caused 3% inhibition (Pilotti et al., 1975).

Thelestam et al. (1980) studied the ability of 464 compounds to increase the permeability of the membranes of human diploid embryonic lung fibroblasts (line MRC-5) by measuring the release of an intracellular marker after short term exposure (30 min). The method used is based on the simple principle that leakage of intracellular substances indicates damage to the plasma membrane and that the molecular size of the leaked material serves as an indicator of the degree of membrane damage in terms of the size of the "holes" induced by the test compounds.

A short exposure time were employed to achieve high sensibility and avoid secondary effects arising from cytotoxic damage. The degree of membrane damage caused with 25 mM cumene was 84% nucleotide release. This membrane damage was classified as high.

The effect on cell metabolism of 320 individual smoke component have been investigated by measuring their inhibition of noradrenaline induced respiration in isolated hamster brown fat cells. The test substances, 1 mM dissolved in ethanol or dimethyl sulfoxide, were incubated with the cells for 5 min during which period the oxygen consumption was registered. After this preincubation, noradrenaline was added and the oxygen consumption of the cells was registered for a further 5 min. The noradrenaline concentration was 1 µM, which is approximately twice the dose known to induce maximal respiratory rate.

The toxicity of a substance is determined by comparing the noradrenaline induced oxygen consumption in the presence of the test compound to that observed for the control. The cumene caused 73% inhibition of noradrenaline induced respiration. This effect was considered moderate (Pettersson et al., 1980).

Pettersson et al. (1982b) studied the ciliotoxicity of 316 compound, between them the cumene, by exposing embryo chicken trachea in vitro, 5 mM cumene at 37ºC caused inhibition of ciliary activity after 11 min of exposure. The effect was considered toxic. The inhibition of the ciliary activity reduces the clearance capacity, which allows airborne particles to remain in the air-passages and increases the risk of acute and chronic damages.

4.1.2.2.4 Studies in humans

No information is available.

4.1.2.2.5 Summary of single exposure studies

Due to the volatility of this compound, the bulk of the available acute toxicity data concerns exposure via inhalation.

Cumene has a low acute toxicity in animals. Based on observations that 17.6 mg/l causes no mortalities after 6 hour exposure (OECD protocols for acute inhalation are for 4 hour exposures) and the subsequent observation that 40 mg/l cause deaths in 2/3 rats after 4 hour exposure; a LC50 value in rats >17.6 mg/l could be established. The principal causes of death in acutely exposed animals was respiratory paralysis, pulmonary oedema and haemorrhaging associated with further haemorrhage in the thymus, bladder and adrenals.

An inhalation LC50 value of approximately 2000 ppm (10 mg/l) for a 7 hour exposure has been reported for mouse. Deaths were observed at 1425 ppm the lowest exposure level used. Death is caused by respiratory failure due to CNS depression. Increased activity and gait abnormalities have been observed in rat at 500 and 1200 ppm (2.5 and 6 mg/l) but not at 100 ppm (0.5 mg/l) in a behavioural study following a 6 hour exposure to cumene.

A dermal LD50 value >3160 mg/kg in rabbits has been reported. Signs of toxicity included weight loss, increasing weakness, collapse and death were observed. Gross autopsy showed haemorrhagic areas of the lungs, liver discoloration, darkened kidneys and spleen and gastrointestinal inflammation.

Acute oral LD50: 1,400-4,000 mg/kg has been reported in rats. Symptoms of toxicity included central nervous depression. Post mortem examination showed haemorrhagic lungs, liver discoloration and acute gastrointestinal inflammation.

These studies were performed without GLP information. All these studies suggest that cumene is of low acute toxicity by inhalation or dermal routes. Our proposal of classification is R65 (Harmful: may cause lung damage if swallowed) attending the cumene's low viscosity (0.73.10-6 m2/s) as well as the post-mortem examination after acute oral toxicity assay which revealed pulmonary oedema and haemorrhage.

One study on mechanisms of toxicity reported that the main metabolic route of alkylbenzenes in mammals goes via side chain oxidation to aryl alcohol, which is further oxidated to aryl aldehyde.

On the other hand data obtained in vitro show that cumene:

a) Inhibit the growth rate cell when it is incubated for a long time (48 h).

b) It produces high membrane damage when it is incubated with human diploid embryonic lung fibroblasts and

c) It causes inhibition of ciliary activity in incubation of chicken trachea segments.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Respiratory tract

Irritation of the respiratory tract by cumene vapour has been reported in two studies with mice. In one study sensory irritation was observed in mice at 2058 ppm within the first 2 min. depressing the respiratory rate by 50% due to the effect in the upper respiratory tract. The pulmonary irritation response is weak (Kristiansen et al., 1986).

In another study the concentration necessary to depress the respiratory rate by 50% (RD50) due to sensory irritation of the upper respiratory tract was 2490 ppm. A rapid decrease not obvious until 2900 ppm in the respiratory rate was observed in normal mice and was not followed with an extensive fade in the response (Nielsen and Alarie, 1982).

In a sighting study carried out prior to pharmacokinetics studies (Research Triangle Institute, 1989) reported the respiratory frequency in groups of three male and three female rats exposed at cumene vapour concentrations of 0, 580 and 1480 ppm. The respiratory frequency of the rats that were not exposed to cumene (0 ppm) was used as the control group. Begining 3 h after the start of the exposure to 1480 ppm cumene vapour for male rats and 5 h after the start of the exposure in female rats, there was a significant depression of respiratory frequency at the 95% confidence level (Student's t-distribution). Severe motor impairment and narcosis were also noted in both male and female rats immediately after the 6 hour termination of the exposure to 1480 ppm. After exposure to 580 ppm cumene vapour, no respiratory frequency depression was observed.

Skin

Data sheet IUCLID includes 6 studies of skin irritation 5 of them in rabbit and one in cow.

There are not data if these studies have been conducted according to GLP.

They are reported by Huntingdon Research Center (1979), report unpublished, Union Carbide Corporation (1985), Smyth et al. (1951), Wolf et al. (1956), Monsanto Company (1985) and Turner et al. (1962). All results, coincide in slightly irritating except the study done in cow and the reported by Wolf et al. (1956) which result was moderate irritating. This study following repeated application of cumene; 10-20 applications of undiluted material were made to the ear and a like number bandaged onto the shaved abdomen over a period of two to four weeks; animals showed definite erythema and development of a thin layer of devitalized tissue which resulted in exfoliation.

In the more recent study (Monsanto Company, 1985), application of 0.5 ml undiluted cumene; 24 h exposure; the mean irritation score was: 1.9 (24, 72 h average); slight defeating effect-skin flaked off in seven to ten days, but there was no injury in depth.

Eye

Data sheet includes 5 studies of eye irritation. Huntingdon Research Center (1979), unpublished report, Union Carbide Corporation (1985), Smyth et al. (1951), Wolf et al (1956) and Monsanto Company (1985). All of them, using rabbit and all results coincide in the EC classification as not irritant.

Two studies, Wolf et al. (1956) and Monsanto Company (1985) coincide in the result slightly irritant.

Wolf et al. (1956), tested the cumene by introducing two drops of liquid onto the right eye ball. Visual observations of irritation and corneal injury (both internal and external) were made upon the treated eye at the following times after treatment: three minutes, one hour, and one, two and seven days. A 5% water solution of fluorescein dye was used to stain and render visible the external injury of the cornea in all observations after the first (three minutes). The response of rabbit's eyes to cumene caused perceptible irritation of the conjunctival membranes but no corneal injury.

In the more recent study (Monsanto Company, 1985), application of 0.1 ml undiluted cumene, mean irritation score was 7.6 of 110 (24, 48, 72 h average), at 120 h the score was 0 of 110.

4.1.2.3.2 Studies in humans

The use of isopropylbenzene as a solvent involving exposures over a period of 1 to 2 years, it was found that no toxic injury resulted from daily exposures to those concentrations of vapour that could be readily tolerated. For most persons, the vapours became painful to the eyes and upper respiratory passages in the concentration range of 300 to 400 ppm although some persons readily tolerated concentrations considerably in excess of 400 ppm.

Experience in handling and using cumene has revealed no unusual hazard of dermatitis. It apparently resembles benzene and toluene in its action on the skin (Dow Chemical Company, 1948).

4.1.2.3.3 Summary of irritation

Limited information in humans indicates that cumene vapour concentrations greater than about 400 ppm become very painful to the eyes and upper respiratory passages. Experience in handling and using cumene has revealed a slight hazard of dermatitis.

The information available from studies in mice indicate that cumene vapour produce irritation in the upper respiratory tract depressing the respiratory rate by 50% in the range of 2058-2490 ppm.

Other study concluded that exposure to cumene vapour at a level of 1480 ppm for a period of 6 h causes a toxic response in both male and female rats, a significant depression respiratory frequency, severe motor impairment and narcosis were observed.

The pulmonary irritation response is weak. Cumene is not a skin irritant and not eye irritant in terms of EU classification. However, one published study indicates that more pronounced skin irritation could occur following repeated application of cumene.

The safety phrase S24 (Avoid contact with skin) was proposed and agreed (see section 1.4).

4.1.2.4 Corrosivity

The studies in animals and humans in 4.1.2.3 indicate that cumene is not corrosive to the skin or eyes.

4.1.2.5 Sensitisation

Only there is a study reported in the IUCLID. This is an unpublished study (cf. Huels Report, 1988b).

The method followed has been OECD Guideline 406 Guinea Pig Maximisation Test; the study demonstrated that cumene is not a sensitising.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Dermal

In a published study of Wolf et al. (1956) the effect of cumene upon the skin of white rabbits have been reported. Routinely 10 to 20 applications of unstated amounts of undiluted cumene were made to the ear and a like number bandaged onto the shaved abdomen over a period of two to four weeks. The animals were observed daily and were weighed weekly. As judged by the gross appearance, behaviour and body weight of rabbits during the treatment there was no indication that cumene were absorbed through the skin in acutely toxic amounts. However, the repeated application of cumene caused a moderate irritation (definite erythema) and a development of a thin layer of devitalized tissue, which resulted in exfoliation.

In an unpublished study, Procter and Gamble (1985) applied a mixture containing 30% cumene at a level of 2 ml/kg body weight/day, 5 days/week for 28 days to the backs of New Zealand white rabbits, with topical application areas no less than 10% of the total surface area of the rabbit. No systemic toxicological effects were observed either during the experiment or at necropsy. The test animals exhibited skin oedema, fissuring and moderate to severe erythema. Macroscopically and microscopic investigation revealed dermatitis and other cellular dermal effects (quoted in Environmental hazard assessment: Cumene).

Oral

A study reported by Wolf et al. (1956), groups of 10 rats/dose were administered: 0, 154, 462 and 769 mg/kg b.w./day. Cumene in olive oil by gavage, once per day, 5 days/week during 6 months. A group of 20 rats feeding with doses of 2.5 ml of olive oil served as control. Haematology parameters were evaluated at several intervals, including total erythrocytes and leukocytes, haemoglobin content and differential blood cell count. Other evaluations included body weights, food consumption, observations of appearance and behaviour, mortality macroscopic and microscopic evaluation and organ weights for the lungs, heart, liver, kidneys, spleen and testis. Microscopic examination was also made of the adrenals pancreas, and femoral bone marrow; 462 mg/kg b.w./day had a slight effect and 769 mg/kg b.w./day had a moderate effect on average kidney weight. No effect upon kidney weight was observed at 154 mg/kg/day. There were no effects on the haematopoietic system and no histopathological findings following examination of lungs, heart, liver, kidneys, spleen, testes, adrenals, femoral bone marrow or pancreas. A NOAEL of 154 mg/kg b.w./day and a LOAEL of 462 mg/kg b.w./day were established.

Inhalation

In a 91 days subchronic study (Cushman et al., 1995) performed according to GLP, male and female Fischer 344 rats (20/group) were exposed to cumene vapour at 0, 100, 500 and 1200 ppm for 6 h. per day, 5 days per week, for 13 weeks a satellite group received a single 6h exposure at the same concentrations and a subsequent 13 week study with a 4 weeks recovery period was conducted at 0, 50, 100, 500 and 1200 ppm (Cushman et al., 1995).

Animals were observed for signs of toxic effects preceding, during and following each exposure.

There were no exposure related deaths during either subchronic study. Clinical observations included ataxia at 1200 ppm following the first 2-3 weeks in the first study and increased incidences of periocular tissue swelling, urine stains, urogenital area wetness and/or perinasal encrustation, primarily in the 500 and 1200 ppm groups.

In the first study, rats in the 1200 ppm group appeared hypoactive, exhibited blepharospasm, and showed a delayed or absent startle reflex. Rats in the 500 ppm group were hypoactive during exposure.

Tone-pip auditory brain stem responses (ABR) were measured during postexposure week 1 of the second subchronic study, ten rats per sex per group were randomly selected from the test groups. ABRs were collected at 4, 8, 16 and 30 KHZ at 50dB above ABR threshold. No changes in the auditory functions of cumene-exposed animals were found. The ABR response to 50dB above ABR threshold at 4, 8, 16 and 30 KHZ was unchanged.

In the first study, total motor activity was decreased at week 13 in male rats exposed to 500 or 1200 ppm, ambulatory activity was statistically decreased at weeks 4, 9 and 13. These findings were not replicated in the second subchronic study.

No differences were seen in body weights. In the first study food consumption was decreased at week 1 for the female rats and 500 and 1200 ppm. A consistent increase in water consumption was observed in the male rats in the 500 and 1200 ppm groups for weeks 2 through 13.

Food and water consumption was not measured in the second subchronic study.

At the end of the first subchronic study cataracts were observed in both the control and treated group in 14-55% of the animals per sex. Because a high incidence of cataracts (19% of male and female rats combined) were observed in the control animals, the cataracts in the exposure groups in the first study were considered uninterpretable. At the end of the second study, two veterinary ophthalmologists independently reading the eyes for possible adverse findings, concluded that there were no cumene-related ophthalmologic findings. This conclusion was supported by the lack of significance when the cataract date was analyzed statistically.

Changes in several haematological and clinical chemistry parameters were observed in the 500 and 1200 ppm groups; increases in total leukocytes, lymphocytes and platelets. Increases in total protein, albumin, globulin, calcium and phosphorus were observed in both male and female rats; primarily of the 1200 ppm group. Female rats of the 500 and 1200 ppm groups had lower serum glucose values compared with the control group.

There were no exposure related effects on spermatogenesis. There were statistically significant increases in the weights of three organs: liver, kidneys and adrenal glands of both male and female rats of the 1200 ppm groups in one or both subchronic studies. In the 500 ppm group, the weight of the liver was increased for male and female rats, and female rats had a mild increase in kidney weight in the first study. Male rats had a mild increase in adrenal gland weight. The were no cumene related differences in weights of lungs, testes, ovaries or brain at any exposure level. There were no organ weight changes for rats of the 100 ppm group. There were no differences between cumene-exposed and air only control rats for weight, length or width of excised brains following perfusion-fixation procedures. There were no cumene-related microscopic alterations in the tissues of the peripheral and central nervous system. For the remaining extraneuronal tissues and organs, the only cumene exposure-related finding was in the kidneys of the male rats.

Renal proximal tubular cell hypertrophy hyperplasia and hyaline drop formation were observed in the male rats at 500 and 1200 ppm. However, this effect is considered to be a male rat specific effect and of no relevance to human health.

In conclusion, exposure to cumene vapour for 6 h per day, 5 days per week for 13 weeks caused mild toxicity in Fischer 344 rats at 1200 ppm minimal effects at 500 ppm and no observable effects at 50 and 100 ppm. Cumene vapour exposure was neither neurotoxic nor ototoxic in this study. A NOAEL: 100 ppm and a LOAEL: 500 ppm were established.

A long-term inhalation screening studies of cumene on experimental animals was conducted by Jenkins et al. (1970). Rats, guinea pigs, monkeys and dogs were exposed to 244 ppm cumene, 8 h a day, 5 days a week for a total of 30 exposures. Body weights were measured and a limited range of haematological parameters and organs (at necropsy) were studied.

A marked reduction in body weight gain was observed in guinea pigs. No other treatment-related effects were reported. In the same study rats, guinea pigs, dogs and monkeys were exposed to 0, 3.7 and 30 ppm cumene for 90 days continuously, no treatment-related toxic effects were observed on body weights gain or in limited haematological or histopathological examinations, in rats, guinea pigs or dogs. However one rat was reported to have died on day 11 at the 3.7 ppm exposure level. No effect upon body weight gain was observed in monkeys following exposure to the same regime.

An inhalation study was well conducted according to GLP by Gulf Oil Corporation (1985a). Rat Fischer 344 at 0, 2000 and 5000 ppm doses cumene 6h/day during 5 days, 15 rats/sex/dose group were exposed.

All of the animals in the high-dose group (5000 ppm) died after two 6 hour exposures to cumene. Congestion of many tissues, abnormal contents in the intestines, excessive ocular and nasal accumulations, and red fluid-filled bladders were seen at the necropsy of these rats. No mortality occurred in the low-dose group (2000 ppm) following 5 exposures to cumene, although the animals in this group exhibited laboured respiration, lethargy and similar clinical observations as those found in the high-dose group, but at a much lower incidence.

In a study by Fabre et al. (1955) rats and rabbits have been exposed to different concentrations of cumene during 130-180 days, 8 hours/day, 6 days/week. There were a decrease in body weight gain limited to the initial part of study and congestion of the lung, liver, spleen, kidney and adrenals in rats exposed to 509 ppm. In rabbits, the same group found than 1323 ppm no produced changes in behaviour or body weight gain.

Branch and Ribelin (1985) reported an unpublished study with Sprague-Dawley rats exposed at 0, 105.1 ± 2.5, 300.1 ± 3.5 and 599.3 ± 6.7 ppm doses cumene 6h/day, 5 days/week/during 28 days. No animals died during the study; hypoactivity occurred during exposure and a slight irritant response to nose, eyes and mouth was seen; absolute and relative liver and/or kidney weights were increased with and unknown significance; no changes in mean body weights; no clinical, gross and microscopic pathology findings.

4.1.2.6.2 Studies in humans

In the use of isopropylbenzene as a solvent involving exposure over a period of 1 to 2 years, it was found that no toxic injury resulted from daily exposures to those concentrations of vapour that could be readily tolerated.

For most persons, the vapours became painful to the eyes and upper respiratory passages in the concentration range of 300 to 400 ppm although some persons readily tolerated concentrations considerably in excess of 400 ppm (Dow Chemical Company, 1948).

4.1.2.6.3 Summary of repeated exposure studies

Recent inhalation studies which have been done to the standard of GLP, show a clear NOAEL of 100 ppm (equivalent to 0.5 mg/l); LOAEL of 500 ppm and mild toxicity at 1200 ppm in Fischer 344 rats.

These findings are consistent with previous subchronic inhalation studies in rats with cumene (Fabre et al., 1955; Jenkins et al., 1970). Signs of toxicity indicating depression of the CNS and increases in liver, kidney and adrenal gland weight has been reported.

Increased water consumption was observed in male and female rats that were exposed to 500-1200 ppm. Increased water consumption also has been reported for others alkylbenzenes, toluene (Roberts et al., 1993) and styrene (Cruzan et al., 1993) and may reflect a response to irritation due to exposure or possibly increased urinary excretion.

Proximal tubule epithelial cell hypertrophy and hyperplasia with hyaline drop formation was observed only in male rats. Although alpha 2μ-globulin has not been specifically identified in cumene-exposed rats, the finding reported here are similar to those reported for male rats exposed to other chemicals (US EPA, 1991a; 1991b). Since their response to this group of chemicals appears to be different than that of female rats or humans, male rats do not appear to be a good model for assessing human risk of this type of nephropathy.

An increased incidence of cataracts was observed at all exposure levels; in a second study, this ophthalmic findings were consistent with the historical background data, indicating that cumene exposure did not cause an increase in cataract formation.

Decreased motor activity has been observed in male rats. This finding was not replicated in the second subchronic study. There were also no exposure related changes in the functional observation battery, brain size and weight measurements, or microscopic alterations in the peripheral and central nervous system.

At exposure concentration up to 1200 ppm, cumene did not cause peripheral auditory dysfunction as indicated by the auditory brain stem, response and therefore appears to be dissimilar to other aromatic solvents such as toluene, styrene and mixed xylenes, which cause ototoxicity at high concentrations. The exposure to cumene vapour was neither neurotoxic nor ototoxic in Fischer 344 rats in these studies.

For oral toxicity there is only one (6 months) study probably not conducted with the same rigour employed today. The study done in rats, gives a NOAEL of 154 mg/kg b.w./day and shows an increased kidney weights at 462 and 769 mg/kg b.w./day.

For dermal repeated applications the cumene caused moderate skin irritation and a development of a thin layer of devitalized tissue which resulted in exfoliation and dermatitis.

On the other hand, the limited information existing on humans indicates that cumene vapour in the concentration range of 300 to 400 ppm became painful to eyes and upper respiratory passages.

4.1.2.7 Mutagenicity

4.1.2.7.1 *In vitro* studies

Several test methods for investigating the mutagenicity and genotoxicity of cumene are available in vitro. The basic data requirements and other data for mutagenicity and genotoxicity were conducted by Microbiological Associates Inc. (1987) in compliance with the Good Laboratory Practice Regulations.

In all studies the test article vehicle was F127. It was prepared as a 50% (w/w) suspension of Pluronic Polyol F127 (CAS nº 9003-11-6) in ethanol.

Bacterial study

Lawlor and Wagner (1987) tested cumene in an Ames test using Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 at concentrations 33, 67, 100, 333, 667, 1000 and 2000 g/plate. The assay was carried out in the presence and absence of Aroclor induced rat liver, S9 (10% in S9 mix). This study employed a 20 minute preincubation period at 37ºC.

For each strain and activation condition, three dose levels of the appropriate positive control article were plated both with and without the addition of a 50 µl aliquot of pluronic F127. Due to the effects of F127 on positive control response, in the study was included a single maximally water soluble dose of cumene.

To 2000 µg/plate was a decrease in revertant colony in the presence and absence of S9.

Under the conditions of the study, cumene did not cause a positive response, with or without metabolic activation, in any of the tested strains.

In addition, Florin et al. (1980) in a screening of tobacco smoke constituents for mutagenicity using the Ames' test, cumene was assayed qualitatively using strains TA98, TA100, TA1535 and TA1537 with and without S-9 from aroclor-induced rats, at 3 µmol/plate and the results were negative. Cumene was tested quantitatively using strains TA98 and TA100 with and without S9 from 3-methyl cholanthrene - induced rats. The concentrations used were 0.03, 0.3, 3 and 30 µmol/plate. Cumene not found to be mutagenic and was toxic to the bacteria at concentrations 3 µmol/plate.

Mammalian cell studies

A well-conducted Chromosome Aberrations study in Chinese Hamster Ovary (CHO) cells, was carried out by Putman (1987a). This assay was conducted both in the absence and presence of Aroclor-1254-induced rat liver metabolic activation at cumene dose levels of 200, 125, 78, 49, 31 and 19 g/ml and 225, 156, 98, 61, 38 and 24 g/ml respectively.

In the non-activation study, the cells were exposed for 8 hours (or 14 hours for the delayed harvest times) at 37ºC. In the S9 activated study, the cells were exposed for 2 hours at 37ºC. After the exposure period the cells were incubated for an additional 6 hours. At this time, colcemid was added and the cells were exposed for 2 hours. A delayed harvest was carried out in cultures treated with cumene at 200 and 125 g/ml in the non-activated study because of cell cycle delay observed in this concentration range. Toxicity was observed at the high dose (225 g/ml) tested in each treatment condition (with and without S9).

Under the conditions of the assay, cumene did not induce structural or numerical chromosome aberrations in CHO cells when tested in the absence of an exogenous metabolic activation system. A statistically significant increase in number of aberrations per cell was observed at 156 g/ml in the presence of S9 when compared to the vehicle control; however a statistically significant increase was not observed when compared to the historical control range. This increase was considered to be due to the low F127 control values and not an increase in the cumene-treated cultures. Cumene was concluded to be negative in the CHO chromosome aberrations assay.

A gene-mutation (HGPRT) study in Chinese Hamster Ovary (CHO) cells, was carried out by Yang (1987). The optimal dose levels for the mutation assay were selected following a preliminary toxicity test based on colony-forming efficiency. CHO cells were exposed to solvent ranging from 8 µg/ml to 225 g/ml for 5 hours at 37ºC in the presence of an Aroclor-induced rat liver metabolic activation, or exposed to solvent alone and to nine concentrations of cumene ranging from 8 g/ml to 175 g/ml for 5 hours and 18 hours at 37ºC in the absence of metabolic activation.

Dose levels of 100, 125, 150, 175, 200 and 225 g/ml were selected for mutagenicity assays in the absence and presence of S9.

Treatment period of 18 hours was decided for the non-activated portion of the mutation study. The assay at dose levels of 125-100 g/ml yielded relative cloning efficiencies of 29 - 110%. Dose levels of 225, 200, 175 and 150 g/ml yielded relative cloning efficiencies of <10%.

None of the mutant frequencies of cumene treated groups were increased significantly above the controls. The activity of cumene in the mutation assay after a 5 hours treatment in the presence of S9 is not increased significantly above the controls.

The positive and negative controls fulfilled the requirements for a valid test.

Cumene was tested in the Unscheduled DNA Synthesis Test using rat primary hepatocytes. The purpose of the study conducted by Curren (1987) was to evaluate the cumene, for its ability to induce unscheduled DNA synthesis in rat primary hepatocytes as measured by autoradiographic methods.

Based on the results of the initial UDS test and cytotoxicity test, cumene was tested at thirteen dose levels ranging from 1 to 128 g/ml and was fully evaluated at six dose levels of 1.0, 2.0, 4.0, 8.0, 16.0 and 24.0 g/ml. Doses of test article >24 g/ml proved too toxic for evaluation for UDS.

After eighteen to twenty hours of exposure, cells were evaluated for UDS. The results of the UDS assay indicate that under the test conditions, the test article did not cause a significant increase in the mean number of net nuclear grain counts (i.e., an increase of at least 5 counts over

the control), at any dose level. Therefore, the test article is considered negative in this study. The positive control, 2-acetylaminofluorene (2-AFF), induced significant increases in the mean number of rat nuclear grain counts over that in the solvent control.

Although not mutagenicity assays, a cell transformation assay, using BALB/3T3 Mouse Embryo cells in the absence of exogenous metabolic activation, was conducted by Putman (1987b).

The toxicity test was performed for the purpose of selecting dose levels for the transformation assay and was based upon colony-forming efficiency.

Cells were exposed to 50, 100, 150, 200, 250, 300, 350, 400 and 500 g/ml as well as medium, solvent and positive controls for 3 days at 36 ± 1ºC. After 7 - 10 days from initiation of treatment, the concurrent cytotoxicity dishes were fixed, stained and scored for colony formation. After 4 - 6 weeks incubation from initiation of treatment, the transformation dishes were scored for morphologically transformed Type II and Type III foci.

Treatment with cumene at concentrations of 250 - 500 g/ml was completely toxic to BALB/3T3 cells. The four lowest concentrations tested (50, 100, 150 and 200 g/ml) yielded survival levels of 102%, 87%, 19% and 4% respectively. Although survival at 200 g/ml was low (4%), the cell monolayer did reach confluence and was scored for morphologically transformed foci.

No increase in Type III foci were observed in the cumene treated cells compared to the vehicle (F127)-treated cells. Cumene was concluded to be negative in the BALB/3T3 cell transformation.

4.1.2.7.2 *In vivo* studies

There is only the summary of one unpublished study of Gulf Oil Corporation (1985b) available on genotoxicity in vivo.

Cumene was tested in micronucleus test in CDR-1 (ICR) BR Swiss mice. Cumene dissolved in 5 g - % in paraffin oil was administered by gavage for an exposure period of 2 days. Half of the animals were sacrificed on day 3 and the remaining on day 4; 1000 polychromatical erythrocytes and all mature erythrocytes were examined for each animal; 10 mice/sex/group.

In micronucleus assay, done according to GLP standards in bone marrow, cumene did not affect the ratio of polychromatic to normochromatic erythrocytes nor increase the frequency of micronucleated erythrocytes at doses of 250, 500 and 1000 mg/kg b.w.d, therefore indicating no potential for clastogenicity in vivo.

4.1.2.7.3 Studies in humans

There is no information available.

4.1.2.7.4 Summary of mutagenicity

There are several data available on the genotoxicity of cumene in vitro studies. The information in bacteria indicates that cumene is not mutagenic in Salmonella assay, as well as when the assay is carried out employing a 20 minute preincubation period at 37ºC. Cumene neither induces structural or numerical chromosome aberration in CHO cells when tested in the absence or

presence of metabolic activation. In a gene-mutation (HGPRT) study in CHO cells cumene was also considered negative in the presence and absence of an S9 activation system.

Cumene was tested also in the Unscheduled DNA synthesis test using rat primary hepatocytes and did not cause a significant increase in the mean number of net nuclear grain counts at any dose levels.

There was no evidence of increase in cell transformation frequency in an assay conducted in BALB/3T3 Mouse Embryo cells in the absence of exogenous metabolic activation.

Overall, the data available indicate that cumene is not mutagenic in studies in vitro. In mice micronucleus assay in bone marrow, cumene is not mutagenic up to doses of 1000 mg/kg b.w./day, therefore indicating no potential for clastogenicity in vivo.

4.1.2.8 Carcinogenicity

No data is available on the carcinogenicity of cumene in experimental animals.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Effects on fertility

No studies specifically investigating effects on fertility are available. However, in a study originally designed as a neurotoxicological investigation of cumene weights of testis and ovaries were examined as were testicular sperm heads and epididymal spermatozoa. Male and female Fischer 344 rats were exposed to cumene vapour at 0, 100, 500 and 1200 ppm for 6 h per day, 5 days per week, for 13 weeks. Reproductive organs from rats of the high concentration (1200 ppm) and control groups were fixed in 10% neutral buffered formalin and embedded in paraffin stained with haematoxylin and eosin and evaluated by light microscopy. No changes in reproductive organs were observed. Stages of spermatogenesis were evaluated with the right testis from male rats. The left testis of each male rat was frozen and then homogenized for spermatid counting.

There was no major effect of cumene exposure on quantitative or morphologic evaluations of spermatogenesis and no effects on testicular weights. Testicular findings were limited to atrophy in one rat at 1200 ppm. Abnormalities of the head/tail/junction regions were observed in all groups including the controls, but were attributed to individual aberrations and not exposure-related effects (Cushman et al., 1995).

Developmental studies

Two studies of developmental toxicity performed according to GLP and based on US EPA guidelines were carried out.

Studies in rats

Groups of 25 female Sprague-Dawley rats were exposed to cumene vapour for six hours/day on gestational days 6 through 15 at target concentrations of 0, 100, 500 and 1200 ppm. At scheduled sacrifice were performed on day 21.

No dams died, aborted or delivered early. Three dams at 500 ppm and two dams each at 100 and 0 ppm were not pregnant. All pregnant dams had live litters (one or more live foetuses) at scheduled sacrifice on 21 day.

A wide range of investigations of the reproductive tract was carried out at sacrifice.

All live foetuses were weighed, sexed and inspected for external malformations including cleft palate and variations. Approximately 50% of the live foetuses in each litter were examined for thoracic and abdominal visceral and craniofacial structural abnormalities. The other 50% were inspected for skeletal malformations and variations.

Maternal toxicity was observed at 500 and 1200 ppm, evidenced at 1200 ppm by significant reductions in body weight gain (about 20%), and treatment related clinical signs of toxicity (perioral wetness and perioral encrustation) following daily exposures as well as during exposures (hypoactivity and blepharospasm), decreased food consumption during the exposure period and increased relative liver weight at necropsy. Reduced food consumption and clinical observations during exposure were observed at 500 ppm too.

Gestational parameters including numbers of viable implantations per litter, sex ratio (% males) and foetal body weights per litter were unaffected by exposure. There were no significant increases in the incidences of individual malformations or of pooled external, visceral or skeletal malformations at any exposure level.

There were significantly reduced incidences of bilateral dilated ureters and distension of the urinary bladder at 1200 ppm. Eighty-one skeletal variations were recorded and none showed statistically increased incidences related to exposure. Three skeletal variations exhibited significantly reduced incidences: 1) a reduction in 11th bilobed thoracic centrum at 100 ppm, 2) reductions in poorly ossified parietal bones at 100 and 1200 (but not 500) ppm, and 3) a reduction in 5th sternebra bilobed ossification sites at 500 ppm. However there was no significant difference in the incidence of these malformations compared with controls.

For this study the NOEL for maternal toxicity was 100 ppm. The NOEL for developmental toxicity (including teratogenicity) was greater than the highest dose tested, 1200 ppm.

The authors concluded that cumene was not teratogenic in this study (Bushy Run Research Centre, 1989a).

Studies in rabbits

In other teratogenicity study in rabbits (New Zealand White) 15 per group were exposed to cumene vapour for six hours/day on gestational days 6 through 18 at concentrations of 0, 500, 1200 and 2300 ppm.

At scheduled sacrifice on gestational day 29. At this time, a full examination of the uteri and contents was performed. All live and dead foetuses were weighed, sexed and examined for external malformations, variations and internal abnormalities (in thoracic and abdominal visceral). Skeletal malformations and variations were also evaluated. Approximately one half of live foetuses were examined for craniofacial abnormalities.

Two maternal deaths and one aborted occurred at 2300 ppm and significant reductions in weight gain and food consumption during the exposure period, clinical signs of toxicity both during and subsequent to daily exposures and a significant increase in relative liver weight. At 500 and 1200 ppm maternal effects were observed, food consumption was consistently reduced during the exposure period.

Colour changes in the lungs of four (of 12,33%) does were observed at 2300 ppm. In does which died prior to scheduled sacrifice, the most notable findings were hairball and ulceration and haemorrhagic appearance in the non-glandular portion of the stomach. Colour changes in the lung and liver were also observed in two doses (one of which was found dead and the other which aborted)

Gestational parameters exhibited no significant changes including number of corpora lutea, total, non viable, or viable implantations per litter, sex ratio, pre or postimplantation loss, and foetal body weights (total males or females) per litter.

There were no significant differences in the incidence of any individual malformation, or malformations by category (external, visceral or skeletal) or of total malformations. The only external variation noted, ecchymosis on the head, was significantly increased at 500 (but not 1200 or 2300) ppm. This external variation was also significantly increased when evaluated by category (as it was the only external variation observed).

There were no significant increases in the incidence of individual visceral, or skeletal variations. Two skeletal variations: a reduced incidence of the 13th unilateral rudimentary rib (2300 ppm) and the 3rd bilateral rudimentary rib (1200ppm) was noted.

In conclusion, exposure to cumene vapour by inhalation during organogenesis in New Zealand White rabbits resulted in consistent maternal toxicity at 2300 ppm and less severe maternal effects at 500 and 1200 ppm. No exposure related developmental toxicity was observed at any exposure concentration.

There was no NOEL established for maternal toxicity, the NOEL for developmental toxicity was at least 2300 ppm. No developmental toxicity including teratogenicity was observed at any exposure concentration employed (Bushy Run Research Centre, 1989b).

4.1.2.9.2 Studies in humans

No data is available.

4.1.2.9.3 Summary of toxicity for reproduction

In relation to fertility, there is no information available in humans and there are no animal studies specifically investigating such effects. However no changes were seen in the reproductive organs in rats exposed for 13 weeks with 0, 100, 500 and 1200 ppm to cumene.
In terms of developmental effects there is no information available in humans.

In two well-conducted studies in rats and rabbits no developmental effects were observed.

The general lack of findings in male rats and female rats exposed for 13 weeks, combined with the lack of developmental toxicity reported in studies of rats and rabbits (Bushy Run Research Center, 1989a; 1989b) exposed to cumene by inhalation indicate that cumene is not a reproductive toxicant.

4.1.2.10 Other specific studies

4.1.2.10.1 Neurotoxicity

Tham et al. (1984) studied the influence of a variety of industrial solvents on the vestibulo ocular reflex (VOR) in rats.

Female Sprague Dawley rats were used. The compounds investigated were administered by continuous intravenous infusion during 60 min. They were dissolved in an emulsion of lipids used for human parenteral nutrition (Intralipid). The concentration of the tested compound varied between 0.1 and 10%. The infusion rate of the Intralipid solution was 32 µl/min.

Threshold limit for excitatory effect of cumene on the vestibulo-oculomotor reflex in rats was 144 mg/l blood, this level was caused by an intravenous infusion at a rate of 4.8 mg cumene/kg/min during 60 min.

In the 90 day subchronic inhalation study of cumene in rats (15 rats per sex per group) including an evaluation of potential neurotoxicity and ototoxicity (Cushman et al., 1995). At exposure concentration up to 1200 ppm for 6 h per day, 5 days per week, cumene did not cause peripheral auditory dysfunction as indicated by the auditory brain stem response. Minor motor activity decreases were seen only in male rats at 500 and 1200 ppm. This result was not replicated in a second study.

Following a single, 6 h inhalation exposure to cumene at 500 or 1200 ppm some parameters of the FOB were affected at 1 and 6 h, but not at 24 h.

4.1.2.10.2 Summary of Neurotoxicity

Neurotoxicity effects are limited to unspecific CNS depression at high dose levels (500 ppm). They are readily reversible. Exposure to cumene vapour was neither neurotoxic nor ototoxic in Fischer 344 rats.

4.1.2.10.3 Immunotoxicity

Repeated administration of 0, 0.3 and 3 mg cumene/l (route and frequency unspecified) to rats caused a decrease in the number of leukocytes and changes of some of their properties after 5-6 months of treatment.

Chronic action of isopropylbenzene and -methylstyrene upon rats and rabbits results in a fall of osmotic resistance of leukocytes and in changes in the level of neutrophils, glycogen, lipids and peroxidase (Makarieva, 1972).

There is no evidence of these effects in more recent GLP studies (Cushman et al., 1995).

4.1.3 Risk characterisation

4.1.3.1 General aspects

Although there is a reasonable data base for cumene from animal studies, very little toxicological information is available from studies in humans.

In humans, cumene is associate with the human-metabolism; it is found as an organic constituent present in blood, alveolar air and urine with a significant correlation between blood and alveolar cumene concentrations. The major metabolite identified in the urinary excretion was 2-phenylpropan-2-ol. One study in humans suggests that the retention of cumene vapours in the respiratory tract ranged from 64% to 45% (mean 50% depending on the time of exposure), (Sencruk and Litewke, 1976). Brugnone et al. (1989) calculated alveolar cumene retention ranged from between 70.4% in the hospital staff to 77.8% in the workers.

There are a few studies suggesting that cumene is absorbed through the skin. Valette et al. (1954), have stated that cumene is absorbed through the skin more rapidly than toluene, xylene or benzene. Smyth et al. (1951) have reported a dermal LD50 of 10,600 mg/kg in rabbits. More recently a LD50 >3,160 mg/kg in rabbits have been reported (Monsanto, 1985).

Assessment of the available data indicates that cumene has a low acute toxicity to animals and due to the volatility of this compound, the bulk of the available acute toxicity data concerns exposure via inhalation with a LC50>17.6 mg/l (17,600 mg/m3) in rats. The principal cause of death in acutely exposed animals is due to respiratory depression, pulmonary oedema and haemorrhaging associated with further haemorrhage in the thymus, bladder and adrenals was found. Increased activity and gait abnormalities were reported in rats exposed to 500 ppm (2450 mg/m3) and 1200 ppm (5880 mg/m3) cumene for 6 hours. The effects were observed at 1 hour after exposure, but not after 6 or 24 hours. No treatment-related effects were seen at 100 ppm (490 mg/m3) cumene.

Limited information in humans indicates that cumene vapour concentrations between 300 and 400 ppm was painful to the eyes and upper respiratory passages. Experience in handling and using cumene has revealed a slight hazard of dermatitis. The information available from studies in animals indicate that cumene vapour produce irritation in the upper respiratory tract, with an RD50, reported in mice, in the range of 2058-2490 ppm. In rats, 1480 ppm caused a significant depression of respiratory frequency, severe motor impairment and narcosis.

Cumene is not a skin irritant and not eye irritant in terms of EU classification, although repeated applications of the compound could cause a more pronounced skin irritation in rabbits.

Studies conducted in guinea pig have shown that cumene do not have the potential to produce skin sensitization (Maximisation Test).

There is very little information on the health effects in humans about repeated exposure to cumene; this limited information indicates that in the use of isopropylbenzene as a solvent involving exposure over a period of 1 to 2 year, it was found that no toxic injury resulted from daily exposures to those concentrations of vapour that could be readily tolerated.

The principal signs of toxicity in animals indicating depression of the CNS and increases in liver, kidney and adrenal gland weight. These were observed following exposure of rats to 500 and 1200 ppm for 90 days. An increased incidence of cataracts was also noted at 100, 500 and 1200 ppm; in a second study, these ophthalmic findings were consistent with the historical background data (Fischer 344 rats), indicating that cumene exposure did not cause increase in cataract formations. This conclusion was supported by the lack of significance when the cataract data were analyzed statistically. At exposure concentration up to 1200 ppm, cumene did not cause peripheral auditory dysfunction as indicated by the auditory brain stem response. Thus, exposure to cumene vapour was neither neurotoxic nor ototoxic in Fischer 344 rats.

A NOAEL of 100 ppm and a LOAEL of 500 ppm were identified in rats.

Cumene's toxicokinetics does not seem qualitatively different between human and animals. No evidence for the accumulation of cumene following high doses or repeated doses was observed. The NOAEL is obtained from a quality study involving exposure to cumene vapour. In this study the observed effect at a dose above the NOAEL (500 ppm) are weak and mild toxicity response is obtained at a dose 10 times the NOAEL (1200 ppm). On the other hand, this study has been carried out in rats proved being one of the most sensitive animal species to cumene (Fabre et al., 1955). For these reasons, for risk characterisation purpose no additional safety factors has been applied.

The mutagenic potential of cumene was studied in bacteria and mammalian cells with the aid of various in vitro test systems and in vivo by means of the micronucleus test in mice. None of the test system used revealed any evidence of a genotoxic potential of cumene.

No data is available on the carcinogenicity of cumene in human populations neither in experimental animals.

There are no data available in humans or animals on fertility, however no changes were seen in the reproductive organs in rats exposed for 13 weeks with 0, 100, 500 and 1200 ppm to cumene.

There are no data available on developmental effects in humans.

Cumene caused maternal toxicity in rats at 500 and 1200 ppm but no developmental effects at the highest dose tested, 1200 ppm. A NOEL of 100 ppm for maternal toxicity and a NOEL >1200 ppm for developmental toxicity were established. For rabbits, there was no NOEL established for maternal toxicity (all doses resulted in consistent maternal toxicity at 2300 ppm; and less severe maternal effects at 500 and 1200 ppm). The NOEL for developmental toxicity was at least 2300 ppm. The conclusion of this study is that cumene was not a reproductive toxicant.

4.1.3.2 Workers

For the purpose of risk characterisation it is assumed that good personal hygiene is practised in the workplace and that no oral uptake of cumene will occur.

The risk characterisation for workers is limited to the dermal and inhalation routes of exposure.

4.1.3.2.1 Manufacture

In the cumene's manufacture, the main route of exposure is inhalation. Therefore, subchronic toxic effects and respiratory tract irritation may be caused by the cumene's inhalation.

All the available information from the workplace demonstrates that the 8 hours (TWA) exposure is below 1 ppm across all job categories. Data for all activities combined ranges from 0.05 ppm to 4.46 ppm (0.245-21.8 mg/m3, assuming a conversion factor, by volume, of 1 ppm = 4.9 mg/m3). In the worst case, the level of exposure is more than 22 times below the NOAEL (100 ppm). This MOS is considered to be sufficient regarding the toxicological considerations given above about the NOAEL and the fact that the exposure level is the worst and infrequent case found.

On the other hand, the highest exposure value is more than 11 times below the more generally used occupational exposure limit (50 ppm, 8 hours TWA).

There are a few studies suggesting that cumene is absorbed through the skin. A study indicates that cumene is absorbed at a rate similar that of toluene, xylene or benzene.

The potential dermal exposure will be low, following the TGD. In conclusion, dermal absorption of cumene will not contribute significantly to total body burden. Usually gloves are worn to avoid direct contact so dermal exposure will be extremely reduced.

Result

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

4.1.3.2.2 End uses

Cumene is used by some manufacturers in a totally closed system where there is on site phenol production. Other manufacturers transport cumene via rail or sea for further chemical conversion. In these cases we have assumed the same approach than in the manufacture scenario. Therefore, the result of risk characterisation is the same than the preceding section.

Cumene is found as a minor constituent in gasolines and some petroleum-based solvents. Measured exposures to cumene as representative of the C9 aromatic content (small and not quantified) of solvents indicated level of cumene up to 0.6 ppm (maximum level obtained) (HSE, 1994), this level of exposure is more than 166 times below the NOAEL (100 ppm) and more than 83 times below the more generally used occupational exposure limit (50 ppm, 8 hours TWA). Data from Germany reflect a worst case exposure around 3.4 ppm that is 30 times below the NOAEL.

The potential dermal exposure will be low, following the TGD. In conclusion, dermal absorption of cumene will not contribute significantly to total body burden. Furthermore, some companies have reported that gloves are worn to avoid direct contact, so, in practice dermal exposure will be considerably reduced.

Result

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

4.1.3.3 Consumers

Assuming that cumene is not present in consumer products, the **conclusion ii)** is applied.

Result

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

4.1.3.4 Man exposed indirectly via the environment

Most of the environmental exposure to cumene is predicted to be from the air contributing some 97% of the total intake.

Inhalation exposure

Repeated dose toxicity

For the risk characterisation after repeated exposure, the local atmospheric concentrations of cumene identified as reasonable worst case level is 0.499 mg/m^3. Compared with the observed NOAEL 490 mg/m3 (100 ppm) from the 90-day rat study, the margin of safety obtained is 982. When comparing the regional scale air concentration $6.65 \cdot 10^{-5}$mg/m^3 with the NOAEL 490 mg/m^3 a margin of safety of $7.36 \cdot 10^6$ is calculated. These margins of safety are considered sufficient taken into account that the observed effect at a dose above the NOAEL (500 ppm) are weak and a mild toxicity response it is obtained at a dose 10 times the NOAEL (1200 ppm).

Result

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

Reproductive toxicity

The NOAEL of 100 ppm for maternal toxicity and the NOAEL > 1200 ppm for developmental toxicity is the same or clearly above of the NOAEL of subchronic toxicity respectively. Therefore, the risk for those aspects will be covered for the risk characterisation of subchronic toxicity.

Result

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

Intake via air, drinking water and food.

Using a NOAEL of 154 mg/kg/day and dose data as reported in 4.1.1.3 we can calculate the margin of safety for indirectly exposure.

The calculated margin of safety for local scenario is: $1.39 \cdot 10^{3}$.

For the regional scale the margin of safety is: $1.06 \cdot 10^{7.}$

These margins of safety are considered sufficient indicating no concern on human safety after indirect exposure.

Result

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

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES

4.2.1 Exposure assessment

4.2.1.1 Workers

Given the fact that cumene is a flammable liquid, its use without taking controlled measures can lead to a dangerous concentration build up in air. In industry and in occupational use, the flammability risk is not of concern provided adequate safety measures are taken. On the other hand information is provided on the label and in the safety data sheet. It should be noted, that cumene is found as a minor constituent in gasolines and solvents, which are also flammable.

4.2.1.2 Consumers

Consumers are exposed to the flammability hazard in case of cumene use as a thinner for paints and enamels in do-it-yourself products. This refers not only to cumene but other solvents combined with it. The only preventive measures possible are precautions to be taken by the uses himself, in a well-ventilated place, non smoking. This information must be on the container labelled directly.

4.2.1.3 Man exposed indirectly via the environment

Not applicable.

4.2.2 Effects assessment

4.2.2.1 Explosivity

Explosive under influence of a flame (IUCLID data).

4.2.2.2 Flammability

Cumene is flammable liquid (flash point: 31ºC). It is a volatile liquid (vapour pressure 4.96 hPa at 20ºC).

4.2.2.3 Oxidizing potential

According to IUCLID cumene has no oxidizing properties.

4.2.3 Risk characterisation (physico-chemical properties

Regarding its physico-chemical properties, flammability is the only property of concern for cumene.

In production and in occupational use, the flammability risk is not of concern provided adequate safety measures are taken.

Concerning use by consumers, information about the flammability risk and precautionary measures must be given by a label on the containers, if others solvents combined with cumene were should to be flammable.

Conclusion

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

5 RESULTS

5.1 ENVIRONMENT

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

This conclusion applies to:

Releases of cumene to the aquatic and terrestrial compartments (including sediments) from the life cycle of cumene production and use, as well as non compartment specific effects relevant to the food chain (secondary poisoning).

5.2 HUMAN HEALTH

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

This conclusion applies to the assessment of the risk to human health through occupational and consumer exposure as well as indirect exposure to man via the environment both for toxicological and physico-chemical properties.

This risk assessment only covers the risk associated to the life cycle of cumene. The risk associated to the presence of cumene in other substances, particularly petroleum hydrocarbons, is not covered.

6 REFERENCES

Abernethy, S., Bobra, A.M., Shiu, W.Y., Wells, P.G. and Mackay, D. (1986). Acute lethal toxicity of hydrocarbons and chlorinated hydrocarbons to two planktonic crustaceans: The key role of organism-water partitioning. Aquat. Toxicol., **8**, 163-174.

Abernethy, S., Mackay, D. (1987) Partition Coefficient. QSAR Environ. Toxicolo. **II**, 1-16.

Acton, D.W., Barker, J.F. (1992). Laboratory Microcosms Biodegradation Test. J. Contam. Hydrol. **9**,325-352.

Albee, R.R., Spencer, P.J., Mattsson, J.L. and Maurissen, J.P. (1991). Evaluation of the ototoxic potential cumene inhalation in F-344 rats. Dow Chemical Company. Study ID: K-002094-005.

Aldrich. Catálogo de Química Fina. 1994-1995.

Arnts, R.R. and Meeks, S.A. (1981). Biogenic hydrocarbon contribution to the ambient air of selected areas. Atmos. Env., **15(9)**; 1643-1651.

Battersby, N.S. and Wilson, V. (1989). Survey of the anaerobic biodegradation potential of organic chemicals in digesting sludge. Appl. Environ. Microbiol **55(2)**, 433-439.

Bianchi, A.P., Varney, M.S. and Phillips, J. (1991). Analysis of volatile organic compounds in estuarine sediments using dynamic headspace and gas chromatography-mass spectrometry. J Chromatogr 542: 413-450.

Bos, R., Guicherit, R. and Hoogeveen, A. (1977). Distribution of some hydrocarbons in ambient air near Delft and the influence on the formation of secondary air pollutants. Sci. Tot. Env., **7**: 269-281.

Botta, D., Castellani Pirri, L. and Mantica, E. (1984). Ground water pollution by organic solvents and their microbial degradation products. Commision of the European Communities. Report No EUR 8518 p261-275.

Bouscaren, R., Frank, R. and Veldt, C. (1986). Hydrocarbons. Identification of air quality problems in Member States of the European Communities. Contract No 84-B-6642-11-015-11-N. EUR 10646 EN. Commision of the European Communities.

Branch, D.K. and Ribelin, W.E. (1985). Repeated inhalation toxicity study.NTIS/OTS 0513229.

Bringmann, G. and Kühn, R. (1982). Ergebnisse der Schadwirkung wassergefährden der Stoffe gegen *Daphnia magna* in einem weiterentwickelten standardisierten Testverfahren. Z., Wasser Abwasser Forsch. **15(1)**, 1-6.

Brugnone, F., Parbellini, L., Faccini, G.B., Pasini, F., Maranelli, G., Romeo, L., Gobbi, M., and Zedde, A. (1989). Breath and blood levels of benzene, toluene, cumene and styrene in non-occupational exposure. Int. Arch. Occup. Environ. Health **61**, 303-311.

Bushy Run Research Centre (1989a). Developmental toxicity study of inhaled cumene vapor in C.D. (Sprague-Dawley) rats. Project report 52-621.

Bushy Run Research Center (1989b). Developmental toxicity study of inhaled cumene vapor in New Zealand white rabbits. Project report 52-622.

Bushy Run Research Center (1989c). Cumene (isopropylbenzene) fourteen-week vapor inhalation study in rats with neurotoxicity evaluation. Project report 52-628.

Chakraborty, J. and Smith, J.N. (1967). Enzymic oxidation of some alkylbenzenes in insects and vertebrates. Biochem. J. 102, 498-503.

Church, C.: Undated unpublished analysis cited in Hansch, C., Leo, A. (1979): Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons Inc.

Cocheo, V., Bellomo, M.L. and Bombi, G.G. (1983). Rubber Manufacture: sampling and identification of volatile pollutants. Am. Ind. Hyg. Assoc. J. **44(7)**: 521-527.

CONCAWE: A survey of exposures to gasoline vapour. Environmental Protection Agency (1988).

Conkle, J.P., Camp, B.J. and Welch, B.E. (1975). Trace composition of human respiratory gas. Arch. Environ. Health **30**, 290-295.

Cruzan, G., Andrews, LA, Cushman, J.R., Miller, RR., Coombs, D. and Hardy, C.J. (1993). Subchronic (thirteen week) vapor inhalation study of styrene in rats. The SIR C Review 3:35.

Curren, R.D. (1987). Unscheduled DNA Synthesis in rat primary hepatocytes. Microbiological Associates INC. NTIS/OTS. 0522854.

Cushman, J.R., Norris, J.C., Dodd, D.E., Darmer, K.I. and Morris, C.R. (1995). Subchronic Inhalation Toxicity and Neurotoxicity Assessment of Cumene in Fischer 344 rats. J. Amer. College of Toxicol. **14(2)** 129-147.

Dabrock, B., Kebeler M., Averhoff, B. and Gottschalk, G. (1994). Identification and characterisation of a transmissible linear plasmid from *Rohodococcus erythropolis* BD2 that encodes isopropylbenzene and trichloroethene catabolism. Appl. Environ. Toxicol. **60**: 853-860.

Dannecker, W., Schröder, B. and Stechmann, H. (1990). Organic and inorganic substances in highway tunnel exhaust air. Sci. Tot. Env., 93: 293-300.

Dippell, G., Hollederer, G. and Filip, Z. (1991). Resistenz autochthoner Mikroorganismen gegen grundwassergefährdende Chemikalien. Forum Städt-Hygiene **42(4)**, 204-213.

Dow Chemical Co. (1948). Toxicology and Hygiene- Isopropylbenzene. NTIS/OTS 0206685

Dow Chem. Company (1975). The pollutional evaluation of compounds.

Dow Chemical Company (1985). Biodegradation Test. NTIS/OTS 0206726, Doc. I.D. 878214937

DPIMR (1984). Cumene. Dangerous Properties of Industrial Materials Report, **4(1)**, 59-62.

Eaton, R.W. and Timmis, K.N. (1986). Characterisation of a plasmid-specified pathway for catabolism of isopropylbenzene in *Pseudomonas putida* RE204. J. Bacteriol. **168**:123-131.

Eggleston, H.S. (1987). The calculation of emissions from UK petrol engined motor vehicles. Report No LR 612(AP)M. Warren Spring Laboratory, Department of Trade and Industry, United Kingdom.

Envirosystems study number 9019-CMA (1990). Acute flow through toxicity of cumene to *Mysidopsis bahia*. NTIS/OTS 0532653.

Erben, R. (1978). Acute toxicity of cumene to aquatic invertebrates. Verh. Internat. Verein Limnol, 20, 1988-1991.

Erben, R. and Beader, B. (1983a). The effect of cumene, acetone and acrylonitrile on crabs *Asellus aquaticus L* and *Gammarus fossarum Koch* (Isopoda: Amphipoda). Poljopr. Sumar., **29 (2)**, 105-114.

Erben, R. and Beader, B. (1983b). Influence of some petrochemical products on the survival of the snails *Lymnea stagnalis* L. and *Radix peregra* Mull. (Pulmonata). Poljopr. Sumar., **29(1)**, 29-36.

Fabre, R., Truhaut, R., Bermuchon, J., and Loisillier, F. (1955). Toxicological studies on solvents replacing benzene. III Study of isopropylbenzene or cumene. Arch. Malad. Prof. **16**, 285-299.

Florin, I., . Rutberg, L., Curvall, M. and Enzell, C.R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames's test. Toxicological, 18, 219-232.

Foster, P., Laffond, M., Baussand, P., Jacob, V. and Denis, I. (1991). VOC measurements in the Grenoble area and study of the benzaldehyde behaviour in a simulation chamber. Poll. Atmos., 175-191.

Galassi, S., Mingazzini, M. and Viganó, L. (1987). Circolazione ed effetti degli idrocarburi aromatici negli ambienti acquatici, Acqua-Aria **5**,561-567.

Galassi, S., Mingazzini, M., Vigano, L., Cesareo, D. and Tosato, M.L. (1988). Approaches to modelling toxic responses of aquatic organisms to aromatic hydrocarbons. Ecotox. Environ. Safety **16(2)** 158-169.

Gerarde, H., and Linden, N.J. (1959). Toxicological studies on hydrocarbons. A.M.A. Arch. Ind. Health **19**, 403-418.

Gerarde, H.W. (1960). Toxicology and biochemistry of some aromatic hydrocarbons. Elsevier Publishing Company, Amsterdam.

Guicherit, R. and Schulting, F.L. (1985). The occurence of organic chemicals in the atmosphere of The Netherlands. Sci .Tot. Env., **43**: 193-219.

Gulf Oil Corporation (1985a). Five-day repeated dose inhalation toxicity study in rats of cumene. NTIS/OTS 0206783.

Gulf Oil Corporation (1985b). Micronucleus test *in vivo*. NT1S/0TS. 0206782.

Hawley's. Condensed Chemical Dictionary, 12th Edition. 1993.

Holmberg, B. and Malmfors, T. (1974). The cytotoxicity of some Organic solvents. Environmental Research 7, 183-192 .

HSE (Health & Safety Executive). Cumene Criteria document for an occupational Exposure limit by Gardner, R., Delic, J. and White, J. HSE Books.

Huels (1984) (unpublished). Biodegradation reports: Nº. GF-176 (Closed bottle test, Nº. BO-89/25 (Bodis Test).

Huels-Produktdatenblatt "Cumol". Melting Point study Artikel-Nr. 001124, Marl 1985.

Huels (1988a) (unpublished). Acute toxicity to *Daphnia magna*.Methodology DIN 38412. Report Nº D377

Huels (1988b) (unpublished). Skin sensitisation study. Maximisation test. OECD Guideline 406. Report Nº 1219.

Huels (1989) (unpublished). Report on log P_{ow} Determination

Huels AG- Sicherheitsdatenblatt vom 08.12.93. Melting Point study.

Huels Infracor. (1998a). Chronic toxicity of cumene on *Daphnia magna*. Final report DL-172.

Huels Infracor (1998b). Toxicity of cumene on the green algae *Scenedesmus subspicatus*. Final report AW-469

Hung, I.F. and Liao, M.H. (1991). Aromatic hydrocarbons in indoor air. J. Environ. Sci. Health. **A 26(4)**: 487-492.

Huntingdon Research Center (1979). Skin irritation. Report No. 325a (unpublished).

Hurford, N., Law, R.J., Payne, A.P. and Fileman, T.W. (1989). Concentrations of chemicals in the North Sea arising from discharges from chemical tankers. Oil Chem. Poll. **5(6)**: 391-410.

Hurford, N. Law, R.J., Fileman, T.W., Payne, A.P. and Colcomb-Heiliger, K. (1990). Concentrations of chemicals in the North Sea due to operational discharges from chemical tankers - Results from the second survey. Oil Chem. Poll. **7(4)**: 251-270.

Hutchinson, T.C., Hellebust, J.A., Tam, D., Mackay, D., Mascarenhas, R.A. and Shin, W.Y. (1980). The correlation of the toxicity to algae of hydrocarbons and halogenated hydrocarbons with their physico-chemical properties. Environ. Sci. Res., **16**, 577-586.

Imperial Chemical Industries Ltd. (1954). Toxicological report. Ref. B 104.

Isidorov, V.A., Zenkevich, I.G. and Ioffe, B.V. (1983). Methods and results of gas chromatographic-mass spectrometric determination of volatile organic substances in an urban atmosphere. Atmos. Environ. **17(7)**; 1347-1353.

IUCLID's version 23 August 1995. Data sheet for Cumene.

Izmerov, N.F., Sanotsky, I.V. and Sidorov, K.K. (1982). Toxicometric parameters of industrial chemicals under single exposure. United Nations Environment Programme. P. 78.

Jenkins, L.J., Jones, R.A., and Siegel, J. (1970). Long-term inhalation screening studies of benzene, toluene, p-xylene and cumene on experimental animals. Toxicol. Appl. Pharmacol. **16**, 818-823.

Juhnke, I., Lüedemann, D. (1978). Ergebnisse der Untersuchung von 200 chemischen verbindungen auf acute Fischtoxizität mit dem Goldorfentest. Z. Wasser Abwasser Forsch. **11(5)** 161-164.

Jüttner, F. (1988). Motor-boat derived volatile organic compounds (VOC) in lakewater. Z Wasser Abwasser Forsch **21(2)**: 36-39.

Kliest, J., Fast, T., Boley, J.S.M., Van de Wiel, H. and Bloemen, H. (1989) The relationship between soil contaminated with volatile organic compounds and indoor air pollution. Environment International **15**: 419-425.

Kristiansen, U., Hansen, L., Nielsen, G. D. and Holst, E. (1986). Sensory irritation and pulmonary irritation of cumene and n-propanol: mechanims of receptor activation and desensitization. Act. Pharmacol. Toxicol. **59**, 60-72.

Krotoszynski, B., Gabriel, G. and O'Neill, H. (1977). Characterisation of Human Expired Air: A Promising Investigative and Diagnostic Technique. J. Chrom. Sci. **15**, 239-244.

Lawlor, T. E. and Wagner, V.O. (1987). Salmonella/Mammalian-microsome preincubation mutagenicity assay (Ames Test) NTIS/OTS. 0522851 (Microbiological Associates inc.).

Lebret, E., Van De Wiel, H.J., Bos, H.P., Noij, D. and Boleij, J.S.M. (1986). Volatile organic compounds in Dutch homes. Environment International,**12**; 323-332.

Lee, V. (1967): M.S. Thesis, San Jose State College cited in Hans, C., Leo, A. (1979). Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons Inc.

Lonneman, W.A., Seila, R.L. and Bufalini, J.J. (1978). Ambient air hydrocarbon concentrations in Florida.. Environ. Sci. Technol., **12(4)**: 459-463.

Lloyd, A.C., Darnall, K.R., Winer, A.M. and Pitts, Jr J.N. (1976) Relative rate constants for reaction of the hydroxyl radical with a series of alkanes, alkenes and aromatic hydrocarbons. J. Phys. Chem. **80(8)**: 789-794.

Makarieva, L.M. (1972). The effect of isopropylbenzene and α-methylstyrene on the leucopoiesis. Farmakol. Toxicol. **35**, 491-492.

Mc Donald, T.J., Kennicut II, M.C. and Brooks, J.M. (1988). Volatile organic compounds at a coastal Gulf of Mexico site. Chemosphere **17(1)**: 123-136.

McLean, M. and Kenneth G. Doe. (1989). The comparative toxicity of crude and Refined oils to *Daphnia Magna* and *Artemia*. Environmental Protection Directorate. River Road Environmental technology Centre Ottawa, Ontario K1AOH3.

McNamara, P.C. (1990). Cumene (Isopropyl Benzene). Acute toxicity to Dapnids (*Daphnia magna*) During a 48 hours flow-trough exposure. Springborn laboratories, In. Environmental Sciences División 790 Main Street, Vareham, M A 02571, 1-70

Merck Index, 11th Edition

Mill, T., Hendry, D.G. and Richarson, H. (1980). Free-radical oxidants in natural waters. Science, 207: 886-887.

Monsanto Company (1985). Health and Safety studies on cumene. NTIS/OTS. 0512312.

National Fire Protection Association (1984). NFPA 325M Fire Hazards Properties of Flammable Liquids, Gases and Volatile Solids. 1984. Batterymarch Park, Quincy, MA: National Fire Protection Association.

Nelson, P.F., Quigley, S.M. and Smith, M.Y. (1983). Sources of atmospheric hydrocarbons in Sydney: A quantitative determination using a source reconcilation technique. Atmos Env **17(3)**: 439- 449.

Nielsen, G.D. and 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, I.R., Diment, J. and Dobson, S. (1994). Environmental hazard assessment: cumene (TSD/20). UK Department of Environment.

Office of Health Studies (1991) Chemicals in the Environment. Report on Environmental Survey and Wildlife Monitoring of Chemicals in FY 1988 and 1989. Department of Environmental Health. Environment Agency, Japan.

Ogata M., Fujisawa K., Ogino, Y. and Mano, E. (1984). Partition coeficients as a measure of bioconcentration potential of crude oil compounds in fish and shellfish. Bull. Environ. Contam. Toxicol. **33**:561-567.

Parbellini, L., Pasini, F., Faccini, Gb., Danzi, B., Gobbi, M., Zedde, A., Cirillo, P. and Brugnone, F. (1988). Determinazione di solventi ad uso industriale nel sangue, nell'aria alveolare e nell'urina di un gruppo di donatori di sangue. Med. Lav. **79** (6) 460-467.

Pesticide and Toxic Chemical News (1990). January 31, 9-10

Pettersson, B., Curvall, M. and Enzell, C.R. (1980). Effects of tobacco somoke compounds on the noradrenaline induced oxidative metabolism is isolated brown fat cells. Toxicology, **18**, 1-15.

Petersson, G. (1982a). Ambient hydrocarbons from motor car assembly plants in Scandinavia. Environ Poll (B) **4**: 207-217.

Petterson, B., Curvall, M. and Enzell, C.R. (1982b). Effects of tobacco smoke compound on the ciliary activity of the embryo chicken trachea *in vitro*. Toxicology, **23**, 41-55.

Pilotti, A., Ancker, K., Arrhenius, E. and Enzell, C. (1975). Effects of tobacco and tobacco smoke constituents on cell multiplication in vitro. Toxicology, **5**, 49-62.

Price, K.S., Waggy, G.T., and Conway, R.A. (1974). Brine shrimp bioassay and seawater BOD of petrochemicals, J. Wat. Poll. Control Fed, **46(1)**, 63-77.

Procter and Gamble (1985). 28 Day sub-acute percutaneous toxicity with cover letter. US EPA Document No. 8785029.

Putman, D.L. (1987a).Chromosome aberrations in Chinese hamster ovary (CHO) cells. NTIS/OTS. 0522852.Microbiological Associates, Inc.

Putman, D.L. (1987b). Morphological transformation of BALB/3T3 mouse embryo cells in the absence of exogenous metabolic activation. NTIS/OTS. 0206782. Microbiological Associates, Inc.

Pyykkö, K. (1986). Inhibition of microsomal monooxygenases in vitro by aromatic Hydrocarbons. Arch. Toxicol., Suppl. **9**, 371-373.

Pyykkö, K., Paavilainen, S., Metsä-Ketelä, T. and Laustiola, K. (1987). The increasing and decreasing effects of aromatic hydrocarbon solvents on pulmonary and hepatic cytochrome P-450 in the rat. Pharmacology and Toxicology **60**, 288-293.

Research Triangle Institute (1989). Metabolism, disposition and pharmacokinetics of cumene in F-344 rats following oral, i.v. administration or nose-only inhalation exposure. RTI Study Number 3543.

Research Triangle Institute (1992). Identification of an unknown urinary metabolite of cumene RTI Study number 311C-4353.

Riddick Hohn, A. (1986). 4.th Ed, Organic Solvents.

Roberts, L.G., Vernot, E., Bevan, C., Bui, Q., Koschier, F., Panson, R., Brooker, A. and Harris, S. (1993). Developmental toxicity of toluene in the rat. Teratology **47**, 434.

Robinson, D., Smith, J.N. and Williams, R.T. (1954). Studies in Detoxication. The metabolism of alkilbenzenes, isopropylbenzene (cumene) and derivatives of hydratropic acid. Biochem. J. 59, 153-159.

Rogerson, A. et al., (1983). Acute toxicity test protozoa: *Colpidium colpoda* and *Tetrahymena alliozzi*. Aquatic Toxicol. **3**, 215-228.

Sabljic, A. 1987. The prediction of fish bioconcentration factors of organic pollutants from the molecular connectivity model. Z. Gesamte Hyg. 33 (10) 493-496. Reported by Nielsen, Diment and Dobson, Environmental hazard assessment: Cumene.

Sato, A. and Nakajima, T. (1987). Pharmacokinetics of organic solvent vapors in relation to their toxicity. Scand y Work Environ Health **13**, 81-93.

Scheffers, T.M.L. (1985). Development of effect-specific limit values (ESLVs) for solvent mixtures in painting. Ann. Occup. Hyg. Vol. 29 No. 2, 191-199.

Senczuk, W. and Litewka, B. (1976). Absorption of cumene through the respiratory tract and excretion of dimethylphenylcarbinol in urine. Brit. J. Ind. Med. **33**, 100-105.

Smyth, H.F., Carpenter, C.P. and Weil, C.S. (1951). Range-finding toxicity data: list IV. AMA Arch. Ind. Hyg. Occup. Med. **4**, 119-122.

Springborn Laboratories, Inc. (1990a). Cumene. Acute toxicity to Sheepshead Minnow (*Cyprinodon variegates)* under flow through conditions. Unpublished Report No. 90-1-3215.Prepared for the CMA Washington.

Springborn Laboratories, Inc. (1990b). Cumene. Acute toxicity to Rainbow Trout (*Oncorhynchus mykiss)*under flow through conditions. Unpublished Report No. 90-1-3200. Prepared for the CMA Washington.

Springborn Laboratories, Inc. (1990c). Cumene. Acute toxicity to Daphinids (*Daphnia magna)* during 48 hour flow-through conditions. Unpublished Report Nº 89-11-3153. Prepared for the CMA. Washington.

Stuermer, D.H., Ng, D.J. and Morris, C.J. (1982). Organic contaminants in groundwater near an underground coal gasification site in Northeastern Wyoming. Environ. Sci. Technol. **16(9)**: 582-587.

Tegeris, J.S. and Balster, R.L. (1994). A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fund. Appl. Toxicol. **22**, 240-250.

Tester, D.J. and Harker, R.J. (1981) Groundwater pollution investigations in the Great Ouse basin. Wat. Poll. Control 80(5): 614-631.

Tham, R., Bunnfors, I., Eriksson, B., Larsby, B., Lindgren, S. and Ödkvist, L.M. (1984). Vestibulo-Ocular Disturbances in Rats Exposed to Organic Solvents. Acta pharmacol et toxicol, **54**, 58-63.

Thelestam, M., Curvall, M. and Enzell, C.R. (1980). Effect of tobacco smoke compounds on the plasma membrane of cultured human lung fibroblasts. Toxicology **15**, 203-217.

Tsani-Bazaca, E., McIntyre, A., Lester, J. and Perry, R. (1982). Ambient concentrations and correlations of hydrocarbons and halocarbons in the vicinity of an airport. Chemosphere **11(1)**: 11-23.

Turner, F.C. et al., (1962). Skin irritation NTIS/OTS 0206726; Doc. I.D. 878214935.

Union Carbide Corporation (1985).Cumene toxicity studies: Acute inhalation toxicity, skin irritation NTIS/OTS 0206745; Doc. I.D. 878214980.

US EPA (1979a). Atmospheric reaction products of organic compounds. Hendry DG and Kenley RA. US EPA Report No EPA-560/12-79-001.

US EPA (1979b). Investigation of petroleum in the marine environs of the Strait of Juan de Fuca and Northern Puget Sound. Brown DW et al. US EPA Report NO EPA-600/7-79-164.

US EPA (1979c). Hydrocarbons in Houston air. Lonneman, WA., Namie, G. and Bufalini, JJ. US EPA Report No EPA-600/3-79-018.

US EPA (1980). Organic chemical manufacturing. **7**: Selected processes. Hobbs FD, Stuewe CW, Dylewski SW, Pitts DM and Peterson CA. US EPA Report No EPA-450/3-80-028b.

US EPA (1986). Report on the interim data base for state and local air toxic volatile organic chemical measurements. Hunt Jr, WF., Faoro, RB. and Freas, W. US EPA Report No EPA-450/4-86-012.

US EPA (1988). Toxic air pollutant emission factors- a compilation for selected air toxic compounds and sources. Pope AA, Cruse PA & Most CC. US EPA Report No EPA-450/2-88-006a.

US EPA (1991a).. Alpha 2µ-globulin: association with chemically induced renal toxicity and neoplasia in the male rat. EPA/625/3-91/019F.

US EPA (1991b). Report of the EPA peer review workshop on alpha 2µ-globulin: association with chemically induced renal toxicity and neoplasma in the male rat. EPA/625/3-91/021

Valette, G. and Calver, R. (1954). Percutaneus absoption and chemical composition of hydrocarbons, alcohols and esters. Arch. Inter. Pharmacodyn **97**; 232-240.

Van Doorn, R., Leijdekkers, Ch. M., Bos, R.P., Brouns, M.E. and Henderson, P. Th. (1981). Alcohol and Sulphate Intermediates in the Metabolism of Toluene and Xylenes to Mercapturic Acids. Journal of Applied Toxicology, **1(4)**, 236-242.

Verschueren, K. (Ed) (1983). Handbook of Environmental Data on Organic Chemicals. 2nd Edition. Van Nostrand Reinhold Co, New York.

Waggy, G.T. and Payne, J.R. (1974). Biodegradation study Progress Report, File No. 19751, Research and Development Department, Union Carbide Corporation. Cited in Union Carbide Corporation (1985): NTIS/OTS 0206745; Doc I.C.878 21 4981.

Werner, H.W., Dunn, R.C. and Von Oettingen, W.F. (1944). The acute effects of cumene vapors in mice. J. Ind. Hyg. Toxicol. **26**, 264-268.

Williams, R.T., Ziegenfuss, P.S. and Lee, C.M. (1993). Aerobic biodegradation of cumene: An ecocore study. Environ. Toxicol. Chem., **12 (3)**, 485-492.

Windeatt, A.J. and Trapp. J.F. (1990). Toxicity to Terrestrial Plants. ICI Brixham Laboratory Report BL/3759/A.

Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L. and Oyen, F. (1956). Toxicological Studies of certain alkylated benzenes and benzene. Experiments on Laboratory Animals. AMA Arch. Ind. Health **14**, 387-398.

Yang, L.L. (1987). CHO/HGPRT Mutation Assay. NTIS/OTS 0522853. Microbiological Associates Inc

GLOSSARY

Standard term / Abbreviation	Explanation/Remarks and Alternative Abbreviation(s)
Ann.	Annex
AF	assessment factor
BCF	bioconcentration factor
bw	body weight / *Bw*, *b.w.*
°C	degrees Celsius (centigrade)
CAS	Chemical Abstract System
CEC	Commission of the European Communities
CEN	European Committee for Normalisation
CEPE	European Council of the Paint, Printing Ink and Artists' Colours Industry
d	day(s)
d.wt	dry weight / dw
DG	Directorate General
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{50lab}	period required for 50 percent dissipation under laboratory conditions (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
$DT_{90field}$	period required for 90 percent dissipation under field conditions (define method of estimation)
EC	European Communities
EC	European Commission
EC_{50}	median effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
EU	European Union
EUSES	European Union System for the Evaluation of Substances
f_{oc}	Fraction of organic carbon
G	gram(s)

PNEC(s)	Predicted No Effect Concentration(s)
$PNEC_{water}$	Predicted No Effect Concentration in water
(Q)SAR	Quantitative Structure Activity Relationship
STP	Sewage Treatment Plant
TGD	Technical Guidance Document[5]
UV	UltraViolet region of spectrum
UVCB	Unknown or Variable composition, Complex reaction products or Biological material
v/v	volume per volume ratio
w/w	weight per weight ratio
w	gram weight
GLP	Good Laboratory Practice
h	hour(s)
ha	Hectares / *h*
HPLC	High Pressure Liquid Chromatography
IARC	International Agency for Research on Cancer (WHO)
C_{50}	median immobilisation concentration or median inhibitory concentration 1 / explained by a footnote if necessary
ISO	International Standards Organisation
IUPAC	International Union for Pure Applied Chemistry
kg	kilogram(s)
kPa	kilo Pascals
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	Solids water partition coefficient
l	litre(s)
log	logarithm to the basis 10
$L(E)C_{50}$	lethal concentration, median
m	Meter
µg	microgram(s)

[5] Commission of the European Communities, 1996. Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on risk assessment for new substances and the Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. Commission of the European Communities, Brussels, Belgium.
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mg	milligram(s)
MOS	Margins Of Safety
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal
pH	potential hydrogen -*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
Pa	Pascal unit(s)
PEC	Predicted Environmental Concentration

European Commission

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cumene, Volume 6

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

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 risk assessment for Cumene concludes that there is at present no concern for the environment or for human health. There is at present no need for further information and/or testing or for risk reduction measures beyond those, which are being applied already.

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