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CUMENE

CAS-No.: 98-82-8

EINECS-No.: 202-704-5

Summary Risk Assessment Report

2001

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SUMMARY RISK ASSESSMENT REPORT

Final report, August 1999

Spain

Rapporteur for the risk assessment of Cumene is the Spanish Health Ministry.

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PREFACE

The report provides the summary 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. For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references, the reader is referred to the original risk assessment report that can be obtained from European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

[1] European Chemicals Bureau – Existing Chemicals - http://ecb.ei.jrc.it

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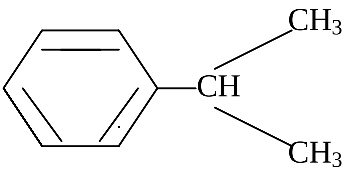
1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS-No.: 98-82-8
EINECS - No.: 202-704-5
IUPAC name: Cumene
SYNONYMS: Isopropylbenzene
1-methyl ethylbenzene
2-phenylpropane
cumol
EEC No.: 202-704-5

Molecular formula: C_9H_{12}

Structural formula:



Molecular weight: 120.19

Purity/impurities, additives

Degree of purity: 90 - 99.9%

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%.

Physico-chemical properties

Physical state: Colourless liquid.

Melting point: –96ºC at 1013 hPa.

Boiling point: 152.7ºC at 1013 hPa.

Relative density: 0.86.

Vapour pressure: 4.96 hPa at 20ºC.

Water solubility: 50 mg/l at 25ºC.
Partition coefficient
(n-octanol/water): 3.55 (log value).

Autoflammability: 424ºC at 1010 hPa.

Flammability: flammable with a lower explosive limit (LEL) of 0.9 % in vol. and an upper explosive limit (UEL) of 6.5 % in vol.

Explosive Properties: explosive under influence of a flame.

Oxidizing properties: none, according to IUCLID.

Classification and labelling

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

Symbols: Xn, N; R-phrases: 10-65-37-51/53
S-phrases: (2)-24-37-61-62

2 GENERAL INFORMATION ON EXPOSURE

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. One country imports this product from outside.

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. 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 C_9 aromatic hydrocarbon content of solvents, particularly those used in the printing industry.

3 ENVIRONMENT

3.1 EXPOSURE

Cumene may be released into the environment during its production and other life cycle steps. Emission to air is expected to be the most important entry route of cumene. General characteristics of cumene relevant for exposure assessment are: an estimated atmospheric half-life of 1-2.4 days, inherently biodegradability, a Henry's Law constant of $1.19 \cdot 10^3$ $Pa.m^3.mol^{-1}$ and a bioconcentration factor of 208 l/kg.

For the environmental exposure assessment of cumene both site-specific and generic emission scenarios are used for calculating the Predicted Environmental Concentrations (PECs) in the various compartments.

3.1.1 PECs at production/processing

Local PEC value for the sewage treatment plant is 0.0718 mg/l. Local PEC value for surface water is 7.13 µg/l and local PEC sediment is 143 µg/kg. A local PEC in agricultural soil of 0.18 mg/kg and an average concentration in air near the emission source of 0.499 $mg.m^3$ are estimated.

3.2 EFFECTS

3.2.1 Aquatic compartment

The available information includes acute toxicity data on several species of fish, aquatic invertebrates and algae, mostly in the range of 1 to 10 mg/l. Chronic toxicity tests were conducted on *Daphnia magna* and *Scenedesmus subspicatus,* while the chronic NOEC for fish was estimated by QSAR. The $PNEC_{aquatic,\ organisms}$, 22 µg/l, is derived by applying a factor of 10 to the lowest chronic toxicity value for cumene, the algae NOEC, 0.22 mg/l.

There is not enough information to derive a PNEC value for microorganisms.

Toxicity tests on sediment dwelling organisms have not been presented. Therefore, the $PNEC_{sediment}$, 388 µg/kg wwt, has been derived using the equilibrium partitioning method.

3.2.2 Atmosphere

A global warming potential or impacts on the stratospheric ozone layer and/or acidification are not expected. The POCP of cumene is 74.4 relative to ethylene, which has a POCP of 100,

No information on the effects on biota due to atmospheric exposure is available.

3.2.3 Terrestrial compartment

The data set only includes a single toxicity tests on plants (*Phaseolus aureus, Sorghum bicolor* and *Helianthus annuus*) showing no effects at 1000 mg/kg soil dw. The proposed PNEC for soil dwelling organisms, 0.347 mg/kg soil ww, has been calculated using the equilibrium partitioning method.

3.2.4 Non compartment specific effects relevant to the food chain

The $PNEC_{oral}$ for secondary poisoning has been estimated from a reported 6 months NOAEL in rats for cumene administered in olive oil by gavage of 154 mg/kg b.w.d. An assessment factor of 30 with 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

All PEC/PNEC comparisons for aquatic and sediment dwelling organisms are lower than 1, indicating that for the production of cumene 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. The information suggests that although in general a low risk for WWTP should be expected, a potential risk for episodic problems should be considered.

Table 3.1 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 Atmosphere

The available information suggests that probably cumene has not a significant impact on global warming, the stratospheric ozone layer, or acidification. However, cumene may contribute to the formation of tropospheric ozone.

The biotic effects cannot be assessed.

3.3.3 Terrestrial compartment

PEC/PNEC comparisons for soil organisms in the local, regional and continental scenarios are lower than 1, indicating that for the production of cumene 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.

Table 3.2 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

3.3.4 Non compartment specific effects relevant to the food chain

The association of calculated PEC_{water} with the BCF, estimated from the Pow, 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.

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 Exposure

4.1.1 Occupational exposure

Workers could be exposed to cumene during its manufacture and use as raw material for the production of phenol and associated products. Both processes involve the use of closed systems. Therefore, inhalation and dermal exposure are possible during activities that involve breaching the closed system.

Range of measured data from seven European Companies goes from 0.05 ppm to 4.46 ppm (8 hour-TWA). The figure of 4.46 ppm represents a worst case exposure situation and has been considered for purposes of Risk Characterisation.

EASE model predicts that dermal exposure would be in the range of 0-0.1 mg/cm^2/day. Since on most days contact does not occur, exposure will be towards the bottom of this range. Therefore, dermal exposure will be low.

Cumene is found as an isomer in the general C_9 aromatic hydrocarbon content of many solvents, particularly those used in the printing industry. Data collected considering cumene as representative of the C_9 aromatic content of solvents (small and not quantified) shows levels of cumene up to 0.6 ppm. Data stem from different sectors ranges from 0.8-3.4 ppm.

Dermal exposure is assessed as not relevant considering cumene is a small part of the total C_9 aromatic content of solvents.

4.1.2 Consumer exposure

Current information indicates that there is no use of cumene in any consumer's product

4.1.3 Man exposed indirectly via the environment

The EUSES model has been used. 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 $1.45x10^{-5}$ mg/Kg/day for the local and regional exposure levels respectively will be used.

4.2 EFFECTS

Although there is a reasonable data base for cumene from animal studies, very little toxicological information is available from studies in humans. In studies in animals, cumene is rapidly absorbed following inhalation exposure and is also absorbed from gastrointestinal tract. In humans, cumene is associated 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 concentration. The major metabolite identified in the urinary excretion was 2-phenylpropan-2-ol both animals and man. 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).

The acute toxicity studies were performed without GLP information. Based on the available data, 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 LC_{50}> 17.6 mg/l (17600mg/m^3) in rats. The principal cause of death in acutely exposed animals is due to respiratory depression, pulmonary oedema and haemorrhaging. A dermal LD_{50}> 3160 mg/Kg in rabbits has been reported. A proposal of classification as Harmful: may cause lung damage if swallowed (R65) has been established attending the cumene's low viscosity as well as the postmorten examination after acute oral toxicity.

Cumene is not a skin irritant and not eye irritant in terms of EU classification. Studies in animals indicate that cumene vapour produce irritation in the upper respiratory tract. Limited information in humans indicates that cumene vapour concentrations between 300 and 400 ppm was painful to the eyes and upper respiratory passages.

Classification as sensitizing agent is not indicated.

With respect to repeated dose toxicity a NOAEL of 100 ppm (490 mg/m^3) is obtained from a subchronic inhalation study performed according to current guidelines. In this study, the principal signs of toxicity indicating depression of the CNS and increases in liver, kidney and dermal gland weight. These were observed following exposure of rats to 500 ppm (2450 mg/m^3) and 1200 ppm (5880 mg/m^3) for 90 days.

Cumene is considered to be not mutagenic. Data on carcinogenicity are not available.

In inhalation developmental toxicity no teratogenic effect were observed in rats, at the highest dose tested 1200 ppm. A NOAEL of 100 ppm for maternal toxicity was established. For rabbits, there was no NOAEL established for maternal toxicity. The NOAEL for developmental toxicity was at least 2300 ppm. As conclusion, cumene is not a reproductive toxicant.

4.3 RISK CHARACTERISATION

4.3.1 Workplace

The most relevant effects produced by cumene are respiratory irritation and those arising from repeated exposures.

Cumene's toxicokinetics does not seems 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 characterization purpose no additional safety factors has been applied.

Measured data for all activities combined range from 0.05 ppm to 4.46 ppm. The worst case exposure level (4.46 ppm) is more than 22 times below the NOAEL (100 ppm). This MOS is considered sufficient regarding the toxicological considerations given above about the NOAEL and the fact that the exposure level is the worst and infrequent case found. The potential dermal exposure will be low. In conclusion dermal absorption of cumene will not contribute significantly to the total body burden. (**Conclusion ii**).

4.3.2 Consumers

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

4.3.3 Man indirectly exposed via the environment

a. Inhalation

Repeated dose toxicity
For the risk characterisation for humans indirectly exposed by inhalation the concentration estimates in air are compared with the observed NOAEL of 100 ppm (490 mg/m^3) from the 90-day rat study. The margins of safety are ranging from $982\text{-}7.36 \cdot 10^6$ indicating no concern for human safety. (**Conclusion ii**).

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. Therefore, the risk for those aspects will be covered for the risk characterisation of subchronic toxicity. (**Conclusion ii**).

b. Intake via air, drinking water and food

Using a NOAEL of 154 mg/Kg from the 6 months rat study. The calculated margins of safety are ranging from: $1.39 \cdot 10^3 – 1.06 \cdot 10^7$ indicating no concern on human safety after indirect exposure. (**Conclusion ii**).

5 OVERALL RESULTS OF THE RISK ASSESSMENT

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 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 cumene. The risk associated to the presence of cumene in other substances, particularly petroleum hydrocarbons, is not covered.