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## **Concise International Chemical Assessment Document 18**

# CUMENE

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**Corrigenda published by 12 April 2005 have been incorporated in this file**

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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## FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170<sup>1</sup> for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

## Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

The CICAD Final Review Board has several important functions:

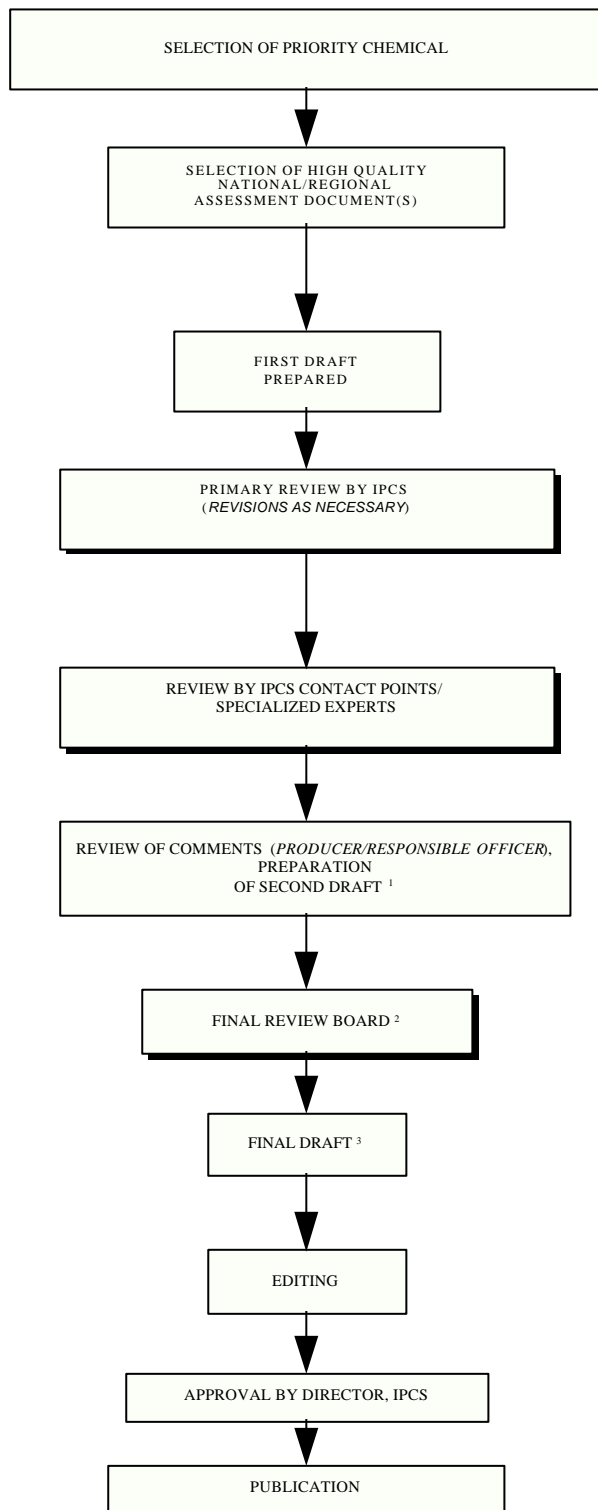
- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their

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<sup>1</sup> International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170).

### CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.  
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.  
3 Includes any revisions requested by the Final Review Board.

experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

## 1. EXECUTIVE SUMMARY

This CICAD on cumene was prepared by the US Environmental Protection Agency (EPA) and is based on the US EPA's *Health and environmental effects document for cumene* (US EPA, 1987), the US EPA's Integrated Risk Information System (IRIS) file on cumene (US EPA, 1997), and the United Kingdom's *Environmental hazard assessment (EHA): Cumene* (UK DOE, 1994), supplemented by a literature search on the ecology-based AQUIRE (Aquatic Toxicity Information Retrieval) database. The literature search for the IRIS file was through November 1996 and for the AQUIRE database through April 1998. Information on the nature of the peer review and the availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Washington, DC, USA, on 8–11 December 1998. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0170) for cumene, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Cumene (CAS no. 98-82-8) is a water-insoluble petrochemical used in the manufacture of several chemicals, including phenol and acetone. It readily volatilizes into the atmosphere from water and dry soil. Cumene is expected to adsorb moderately to strongly to soil/sediments and to undergo biodegradation in water and soil.

Cumene is metabolized primarily to the secondary alcohol, 2-phenyl-2-propanol, in both humans and animals. This alcohol and its conjugates are readily excreted by both rodents and humans.

Increases in organ weights, primarily kidney weights, are the most prominent effects observed in rodents repeatedly exposed to cumene by either the oral or inhalation route. No adverse effects were observed in rat or rabbit fetuses whose mothers had been exposed to cumene during fetal development. Although no multi-generational reproductive studies have been performed using cumene, its rapid metabolism and excretion, coupled with lack of effects on sperm morphology in a subchronic study, suggest that it has a low potential for reproductive toxicity. A guidance value for oral exposure of 0.1 mg/kg body weight per day has been derived, based on the no-observed-adverse-effect level (NOAEL) of 154 mg/kg body weight per day for increased kidney weight in female rats in a 6- to 7-month oral study; the NOAEL was adjusted for the dosing schedule, and a total uncertainty factor of 1000 was applied. Guidance values for the general population of 0.4 mg/m<sup>3</sup> and 0.09 mg/m<sup>3</sup> were derived for inhalation exposure, based

on alternative NOAELs derived from the same sub-chronic inhalation study; again, the NOAELs were adjusted to a continuous exposure, and a total uncertainty factor of 1000 was applied.

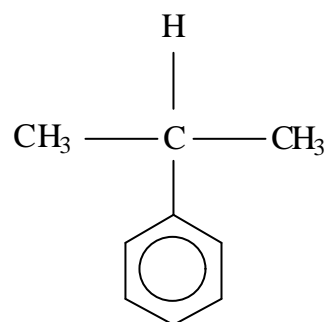
No data are available with which to quantify human exposure to cumene.

It is not possible to assess cumene's potential for carcinogenicity in humans, because long-term carcinogenicity studies with cumene have not been performed. Most genotoxicity test data with cumene are negative.

Inadequate data, especially measured exposure information, exist to allow a quantitative evaluation of the risk to populations of aquatic or terrestrial organisms from exposure to cumene. Based on existing data, however, cumene is anticipated to be of relatively low risk. Values indicate a slight potential for bioconcentration of cumene in fish. There are no data on bioaccumulation through food chains (biomagnification).

## 2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Cumene (CAS no. 98-82-8; C<sub>9</sub>H<sub>12</sub>; 2-phenylpropane, isopropylbenzene, (1-methylethyl)-benzene) is a volatile, colourless liquid at room temperature with a characteristic sharp, penetrating, aromatic odour (Ward, 1979). It is nearly insoluble in water but is soluble in alcohol and many other organic solvents (Windholz, 1983). Structurally, cumene is a member of the alkyl aromatic family of hydrocarbons, which also includes toluene (methylbenzene) and ethylbenzene. Its structural diagram is given below.



Some relevant physical and chemical properties of cumene are listed in Table 1. Additional physical/chemical properties are presented in the International Chemical Safety Card (ICSC 0170) reproduced in this document.



Table 1: Physical/chemical properties of cumene.

Property	Value	Reference
Molecular weight	120.2 g/mol	
Boiling point	152.39 °C	Ward, 1979
Vapour pressure, 25 °C	611 Pa	Mackay & Shiu, 1981
Water solubility, 25 °C	50 mg/litre	Mackay & Shiu, 1981
Log $K_{ow}$	3.66	Hansch & Leo, undated
Density, 20 °C	0.8619 g/cm <sup>3</sup>	Ward, 1979
Flashpoint (tag closed-cup)	35 °C	Ward, 1965
Odour threshold limit value (TLV)	0.088 ppm (v/v) 0.43 mg/m <sup>3</sup>	Amoore & Hautala, 1983
Conversion factor, 20 °C, 101.3 kPa	1 ppm = 5.2 mg/m <sup>3</sup> 1.0 mg/m <sup>3</sup> = 0.19 ppm	
Partition coefficients		Sato & Nakajima, 1979
Oil/air	6215	
Oil/water	4316	
Water/air	1.44	
Human blood/air	37	

### 3. ANALYTICAL METHODS

For sampling and measurement of cumene in air, Method 1501 of the US National Institute for Occupational Safety and Health (NIOSH, 1994) includes use of a solid sorbent tube (coconut shell charcoal) sampler with a gas chromatography/flame ionization detector measurement technique. The detection limit of this method is 1 mg/m<sup>3</sup> (0.2 ppm).

US EPA (1996) methods for detecting cumene in media other than air include the use of gas chromatography using photoionization Method 8021B, which is applicable to nearly all types of samples, regardless of water content. The method detection limit for cumene is 0.05 : g/litre, and the applicable concentration range for this method is approximately 0.1–200 : g/litre. The standard recovery using this method is 98%, with a standard deviation of 0.9%. Another commonly used gas chromatographic assay for volatiles including cumene is Method 8260B (US EPA, 1996), with a general estimated quantitation limit of approximately 5 : g/kg wet weight for soil/sediment samples, 0.5 mg/kg wet weight for wastes, and 5 : g/litre for groundwater.

### 4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Cumene is a naturally occurring constituent of crude oil and may be released to the environment from a number of anthropogenic sources, including processed hydrocarbon fuels. Crude oils typically contain approximately 0.1 wt% of cumene, but concentrations as high as 1.0 wt% have been reported.<sup>1</sup> Measurements of various grades of petrol revealed that cumene concentrations range from 0.14 to 0.51 vol% and that the average cumene concentration was 0.3 vol%. Premium diesel fuel contains 0.86 wt% of cumene; furnace oil (no. 2) contains 0.60 wt%.<sup>1</sup>

Primary sources of release of cumene include losses in wastewater and fugitive emissions from manufacturing and use facilities and petrochemical refineries, accidental spills of finished fuel products during transport or processing, and emissions from petrol stations and motor vehicles (US EPA, 1987). Cigarette tobacco also releases cumene (Johnstone et al., 1962). Cumene release from all these sources is estimated to be 9500 tonnes annually (US EPA, 1988). Other, unquantifiable anthropogenic cumene releases include the rubber vulcanization process (Cocheo et al., 1983), building materials (Moelhave, 1979), jet engine exhaust (Katzman & Libby, 1975), outboard motor operation (Montz et al., 1982), solvent uses (Levy, 1973), pharmaceutical production, and textile plants (Gordon & Gordon, 1981). Cumene is also released to the environment from leather tanning, iron and steel manufacturing, paving and roofing, paint and ink formulation, printing and publishing, ore mining, coal mining, organics and plastics manufacturing, pesticide manufacturing, electroplating, and pulp and paper production (Shackelford et al., 1983).

SRI International (1986) reported the 1985 Western European cumene production levels (in tonnes) for the following producer countries:

Federal Republic of Germany	438 000
Finland	70 000
France	370 000
Italy	335 000
Netherlands	240 000
Spain	120 000
United Kingdom	220 000

<sup>1</sup> Letter and attachment from W.F. O'Keefe, American Petroleum Institute, to M. Greif, Toxic Substances Control Act (TSCA) Interagency Testing Committee, US Environmental Protection Agency, Washington, DC (TS-792).

This total 1985 production of 1 793 000 tonnes may be compared with production in the USA, which was reported as 2 775 000 tonnes in 1997 (Anon., 1998).

The use pattern for cumene in the early 1970s in the USA was as follows (Anon., 1984): oxidation for phenol/acetone production, 98%; polymerization of *m*-methylstyrene, 1.8%; and exports, 0.2%. Cumene is also used captively for the production of phenol and *m*-methylstyrene (SRI International, 1986).

## 5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

In the atmosphere, cumene is expected to exist almost entirely in the vapour phase (Eisenreich et al., 1981). Cumene does not absorb ultraviolet light at wavelengths greater than 290 nm (US EPA, 1987), which suggests that cumene would not be susceptible to direct photolysis. In one study, the estimated half-life of cumene in the atmosphere from photolysis alone was approximately 1500 years (Parlar et al., 1983). Cumene is not susceptible to oxidation by ozone in the atmosphere (US EPA, 1987). Thus, reaction with ozone and direct photolysis are not expected to be important removal processes. Rather, reaction with photochemically generated hydroxyl radicals appears to be the primary degradation pathway ( $t_{1/2}$  1–2 days) (Lloyd et al., 1976; Ravishankara et al., 1978). Small amounts of cumene may be removed from the atmosphere during precipitation. Cumene has been assigned a Photochemical Ozone Creation Potential (POCP) value of 35 relative to ethylene at 100 (Derwent & Jenkin, 1990). POCP values represent the ability of a substance to form ground-level ozone as a result of its atmospheric degradation reactions.

In water, important fate and transport processes are expected to be volatilization ( $t_{1/2}$  4 h from a typical river) and aerobic biodegradation (Kappeler & Wuhrmann, 1978; Sasaki, 1978; Van der Linden, 1978). Chemical hydrolysis, oxidation, photolysis, and reaction with hydroxyl radicals are not expected to be important fate processes in water (Mill et al., 1978, 1979, 1980). Using an aerobic freshwater sediment/water test system, Williams et al. (1993) demonstrated that 10 days after addition of radiolabelled cumene (2.5 mg/litre) to the system, 46.9% was trapped as radiolabelled carbon dioxide and another 21.8% was recovered as radiolabelled organics, the overall recovery of cumene ranging from 56.8% to 88.3%. The disappearance half-life based on these results was 2.5 days. During a 20-day incubation of cumene at 10 mg/litre under aerobic conditions in either fresh water or salt water, Price et al. (1974) observed 70% degradation in fresh water but only

about 2% degradation in seawater. Cumene was, however, observed to be degraded to a significant extent by microorganisms isolated from ocean sediment samples incubated in seawater, as Walker et al. (1976) noted decreases in cumene (gas chromatographic analysis) ranging from 37% to 60% of initial amounts over a period of 21 days in three separate incubations with seawater and microorganisms isolated from Atlantic Ocean sediments. On the other hand, cumene was found to be essentially non-biodegradable under anaerobic conditions by Battersby & Wilson (1989), who noted that cumene produced only about 2% of theoretical gas production when incubated at 50 mg carbon/litre sludge for 60 days at 35 °C under anaerobic conditions; compounds at 80% of theoretical gas production under these conditions were assumed to represent complete degradation, whereas compounds at less than 30% production were considered persistent.

In soil, it appears that cumene might biodegrade fairly rapidly under aerobic conditions, because a number of microorganisms capable of degrading cumene have been isolated (Yamada et al., 1965; Jamison et al., 1970; Omori et al., 1975). Regression equations based on the limit of cumene water solubility (50 mg/litre) predicted  $K_{oc}$  (soil sorption coefficient standardized to organic carbon) values ranging from 513 to 1622. For equations based instead on log octanol/water partition coefficients ( $\log K_{ow}$ ) for cumene, predicted  $K_{oc}$  values were in a similar range, from 589 to 3890 (Lyman et al., 1982). Other estimates of  $K_{oc}$  values at 884 (Jeng et al., 1992) and 2800 (US EPA, 1987) were also in this range. These  $K_{oc}$  values indicate that cumene is expected to adsorb moderately to strongly to soil and have only slight mobility. The relatively high vapour pressure of cumene suggests that volatilization of this compound from dry soil surfaces would be significant.

Measured and estimated bioconcentration factors (BCFs) suggest a slight potential for cumene to bioconcentrate in fish species. A BCF of 36 for cumene in goldfish (*Carassius auratus*) has been measured (Ogata et al., 1984), and a BCF of 356 was estimated from the  $\log K_{ow}$  and a linear regression correlation equation ( $\log BCF = 0.76 \log K_{ow} + 0.23$ ) by the US EPA (1987). This value was concordant with the BCF of 316 calculated for fish species in general exposed to cumene (Sabljić, 1987). Cumene was detected at levels of 0.5–1.4 ng/g wet weight (detection limit 0.5 ng/g wet weight by gas chromatography/mass spectrometry) in 12 of 138 sampled fish (various species) from several locations near a potential emission source (Japan Environment Agency, 1987). Cumene has been detected in "oakmoss" (*Evernia prunastri* (L.) Ach.) (Gavin et al., 1978) and marsh grass (Mody et al., 1974a,b).

## 6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

### 6.1 Environmental levels

Cumene has been found as a contaminant in various industrial effluents and in groundwaters. Significant levels of cumene have been recorded in groundwater near chemical plants (1581 : g/litre, Botta et al., 1984; 360 : g/litre, Teply & Dressler, 1980; 11 : g/litre, Pellizzari et al., 1979), around outboard motor operations (700 : g/litre, Montz et al., 1982), near coal gasification facilities (up to 54 : g/litre, Steurmer et al., 1982), and around petroleum plants and petroleum refineries (5 : g/litre, quantification method not clear; Snider & Manning, 1982). Cumene was detected in 8 of 135 samples of surface water (detection limit 0.03 : g/litre with gas chromatography/mass spectrometry) at concentrations ranging from 0.09 to 0.44 : g/litre in several locations near a potential emission source in the 1986 monitoring of the general environment in Japan (Japan Environment Agency, 1987). Cumene levels in sediments and biota in Puget Sound, Washington, USA, ranged from 0.02 to 19 : g/g, with a mean concentration of 2.3 : g/g (Brown et al., 1979). A cumene level of 140 : g/litre was found in seawater near an offshore drilling platform in the Gulf of Mexico (Sauer, 1981). Cumene was detected in 6 of 111 sediment samples at concentrations ranging from 0.58 to 11 ng/g dry weight (detection limit 0.5 ng/g with gas chromatography/mass spectrometry) in several locations near a potential emission source (Japan Environment Agency, 1987).

Reports of air sampling in the USA indicate the mean concentration of cumene to be about 14.7 : g/m<sup>3</sup> (3 ppb) in urban settings and as high as 2.5 : g/m<sup>3</sup> (0.5 ppb) in rural settings. Samples taken in Los Angeles, California, in 1966 averaged 14.7 : g/m<sup>3</sup> (3 ppb) (Lonneman et al., 1968), and samples taken in Houston, Texas, in 1973–1974 averaged 12.15 : g/m<sup>3</sup> (2.48 ppb) (Lonneman et al., 1979). The US EPA (1987) reported a mean concentration of 16.7 : g cumene/m<sup>3</sup> (3.4 ppb) in undated samples from Los Angeles. In samples taken in the fall of 1981 in Los Angeles, Grosjean & Fung (1984) did not detect cumene, although a minimum detection level of 9.8 : g/m<sup>3</sup> (2 ppb) was reported. Although a number of sampling attempts in rural and remote areas reported no detectable levels of cumene in air (detection limit <0.05 : g/m<sup>3</sup> [ $<0.01$  ppb]), two attempts were positive: Seila (1979) reported mean levels of 2.5 : g/m<sup>3</sup> (0.5 ppb) in samples taken in a rural area near Houston, Texas, in 1978, and Arnts & Meeks (1980, 1981) reported 0.25 : g/m<sup>3</sup> (0.05 ppb) in samples taken near campfires in the Great Smokey Mountains, USA, in 1978.

Average atmospheric concentrations of cumene in Europe are reported to be somewhat less than those in the USA, although concentrations in urban areas are also consistently much higher than those in rural areas. Isodorov et al. (1983) recorded an average cumene level of 8.3 : g/m<sup>3</sup> (1.7 ppb) in the urban atmosphere of Leningrad, USSR, in 1977–1979, with a maximum of 11.8 : g/m<sup>3</sup> (2.4 ppb). Ambient air concentrations for the Netherlands in 1980 were reported to average 0.5–1.0 : g/m<sup>3</sup> (0.1–0.2 ppb), with maxima ranging up to 34.8 : g/m<sup>3</sup> (7.1 ppb) (Guicherit & Schulting, 1985). An annual average of 1.6 : g/m<sup>3</sup> (0.3 ppb) (maximum 3.9 : g/m<sup>3</sup> [0.8 ppb]) was reported from the Grenoble area in France in 1987 (Foster et al., 1991).

### 6.2 Human exposure

Humans can be exposed to cumene via industrial emissions, petrol station or motor vehicle emissions, accidental releases, food, cigarette smoke, and drinking-water (US EPA, 1987).

In condensates of cigarette smoke, Johnstone et al. (1962) recorded yields of cumene ranging from 7 to 14 : g/cigarette. Holzer et al. (1976) detected cumene at 10 : g/m<sup>3</sup> (2 ppb) in air samples taken from a room immediately after a single cigarette had been smoked. No further specifics, such as indication of a median value or minimum detection level, are given.

Brugnone et al. (1989) reported cumene as measurable in all alveolar air samples collected (single breath; range 1–81 : g/m<sup>3</sup> [0.2–17 ppb], method detection limit not given) from among two groups of workers ( $n = 86$ , gender not specified) exposed to <0.1 mg cumene/m<sup>3</sup> (<0.02 ppm) through the work shift. These authors analysed for but were unable to detect any significant differences in cumene concentrations between smokers and non-smokers in either alveolar air or blood samples. In another study, gases collected from 60 min of normal continuous respiration from each of eight male volunteers (three smokers) were analysed for trace organic constituents (Conkle et al., 1975). Cumene was listed as detected in one of the three smokers (expressed as 21 : g/h) and in one of the five non-smokers (expressed as 0.13 : g/h). Krotoszynski & O'Neill (1982) also identified cumene in expired air from non-smokers.

The presence of cumene in foods can be biogenic or due to environmental contamination (US EPA, 1987). Although the detection limit of cumene in various foods was not specified, the US EPA (1987) noted that cumene has been detected but not quantified in foods as diverse as tomatoes, Concord grapes, cooked rice, fried chicken, bacon, Beaufort cheese, and dried legumes.

Only two reports of cumene quantification in drinking-water were found in the available literature. Coleman et al. (1984) detected cumene in Cincinnati, Ohio, USA, drinking-water at a level of 0.014 : g/litre (quantification method not clear). Keith et al. (1976) reported 0.01 : g cumene/litre drinking-water in Terrebonne-Parish, Louisiana, USA, but found none in the drinking-water of nine other cities across the USA. These concentrations are considerably below the 0.5 : g/litre detection limit reported by Westrick et al. (1984), who found no cumene in 945 US drinking-water systems, 479 of which were selected because of known contamination problems. Burmaster (1982) and Burnham et al. (1972) reported unquantified levels of cumene/alkylbenzenes in drinking-water obtained from groundwater. Based on the results of these studies, it may be concluded that cumene contamination above 0.5 : g/litre is uncommon in drinking-water in the USA.

One industrial hygiene survey (US EPA, 1988) reported that approximately 739 US workers were occupationally exposed to cumene. Personal exposure data in this report consisted of 1487 air samples taken over the course of 12 years (1973–1984), of which 6 were in the range of 20–150 mg/m<sup>3</sup> (4–30 ppm), 4 in the range of 15–20 mg/m<sup>3</sup> (3–4 ppm), and 25 in the range of 5–10 mg/m<sup>3</sup> (1–2 ppm), with the remaining samples below 5 mg/m<sup>3</sup> (1 ppm) (US EPA, 1988).

Based on available monitoring data, it appears that the general population would be exposed to cumene primarily by inhalation, although occupational populations may be reasonably anticipated to be exposed by the dermal route. Minor exposure may result from contact with refined petroleum products and ingestion of contaminated foods and possibly drinking-water.

## **7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS**

Cumene has been shown to be absorbed after inhalation exposure in humans and after inhalation, oral, and dermal exposure in animals (Selezuk & Litewka, 1976; Research Triangle Institute, 1989). Tests conducted in humans indicate that cumene is absorbed readily via the inhalation route, that it is metabolized efficiently to water-soluble metabolites within the body, and that these metabolites are excreted efficiently into the urine with no evidence of long-term retention within the body; these results concur with the results of animal studies.

Selezuk & Litewka (1976) exposed human volunteers (five men and five women) head only to one of three different concentrations of cumene vapours (240, 480, or 720 mg/m<sup>3</sup> [49, 98, or 147 ppm]) for 8 h every 10 days. Exhaled breath samples (10 cm<sup>3</sup>) were collected near the beginning and at the end of the exposure from a tube placed in the breathing zone. The total amount of cumene absorbed during exposure, calculated from retention, ventilation, and exposure duration, was nearly twice as high at all exposure levels in the males (466–1400 mg) as in the females (270–789 mg). The respiratory tract absorption ranged from 45% to 64% depending on the time of exposure, with the overall mean retention estimated at 50%. In rats, inhalation studies (nose only for 6 h at 510, 2420, or 5850 mg/m<sup>3</sup> [104, 494, or 1194 ppm]) indicate rapid absorption, with detectable levels of cumene appearing in the blood within 5 min of the beginning of exposure at all three exposure levels (Research Triangle Institute, 1989). Gavage studies in rats showed that cumene was absorbed readily via this route, with maximum levels in blood occurring at the earliest time point sampled (4 h) for a lower dose (33 mg/kg body weight) and at 8–16 h for a higher dose (1350 mg/kg body weight) (Research Triangle Institute, 1989). Dermal absorption of cumene was demonstrated in rats and rabbits (Monsanto Co., 1984).

The human data reported by Brugnone et al. (1989) regarding cumene distribution suggest that the cumene concentration was about 40 times higher in blood than in alveolar air, a figure concordant with the reported human blood/air partition coefficient of 37 (Sato & Nakajima, 1979; Table 1). Cumene was widely distributed in rats, and distribution, presumably determined immediately after exposure, was independent of administration route (inhalation, oral, or intraperitoneal in 10% aqueous Emulphor). Adipose, liver, and kidney were all shown to have elevated tissue/blood ratios of cumene following all doses and routes of exposure (Research Triangle Institute, 1989). Fabre et al. (1955) demonstrated that after rats inhaled cumene vapour for up to 150 days, cumene was distributed to the endocrine organs, central nervous system, bone marrow, spleen, and liver.

The patterns of cumene disappearance (as total radioactivity) from the blood in the nose-only inhalation studies were fitted with a monoexponential model, with the half-lives increasing with dose, from 3.9 h at 490 mg/m<sup>3</sup> (100 ppm) to 6.6 h at 5880 mg/m<sup>3</sup> (1200 ppm). The half-life of cumene in the blood in gavage studies with rats was calculated to be between 9 and 16 h.

Metabolism of cumene by cytochrome P-450 is extensive and takes place within hepatic and extrahepatic tissues, including lung (Sato & Nakajima, 1987), with the secondary alcohol 2-phenyl-2-propanol being a principal metabolite. Metabolites excreted in urine of rats and

rabbits include 2-phenyl-2-propanol and its glucuronide or sulfate conjugates, conjugates of 2-phenyl-1,2-propanediol, and an unknown metabolite, possibly the dicarboxylic acid that would result from complete oxidation of the 1- and 3-alkyl carbons of phenylmalonic acid (Research Triangle Institute, 1989; Ishida & Matsumoto, 1992; MAK, 1996).

Selezuk & Litewka (1976) also conducted excretion studies with human volunteers exposed to cumene vapours (240, 480, or 720 mg/m<sup>3</sup> [49, 98, or 147 ppm]) for 8 h every 10 days. These authors reported excretion of the metabolite 2-phenyl-2-propanol in the urine as biphasic, with a rapid early phase ( $t_{1/2}$  2 h) and a slower later phase ( $t_{1/2}$  10 h); excretion of this metabolite in the urine (about 35% of the calculated absorbed dose) was maximal after 6–8 h of exposure and approached zero at 40 h post-exposure. With rats, the extent of elimination across routes of administration (inhalation, oral, or intraperitoneal) and exposure concentrations was very similar, with urine being the major route of elimination, about 70% in all cases (Research Triangle Institute, 1989). Total body clearance in the rats was rapid and complete, with less than 1% of the absorbed fraction being present in the body 72 h after the highest exposure regime examined (5880 mg/m<sup>3</sup> [1200 ppm] for 6 h). Following oral administration of cumene in rabbits, 90% was recovered as metabolites in the urine within 24 h (Robinson et al., 1955).

## 8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

### 8.1 Single exposure

Cumene is not highly toxic to laboratory animals by inhalation, oral, or dermal routes of exposure. An LC<sub>50</sub> of 9800 mg cumene/m<sup>3</sup> (2000 ppm) in mice has been reported (MAK, 1996). A 4-h inhalation LC<sub>50</sub> of 39 200 mg/m<sup>3</sup> (8000 ppm) in rats was reported by several investigators (Smyth et al., 1951; Koch Refining Co., 1984; Union Carbide Corp., 1985). Acute oral LD<sub>50</sub> values for rats range from 1400 to 2900 mg/kg body weight (Smyth et al., 1951; Koch Refining Co., 1984; Monsanto Co., 1984; Ciba-Geigy Co., 1985; Union Carbide Corp., 1985). Tanii et al. (1995) reported an intraperitoneal LD<sub>50</sub> in male mice in the same range, 2000 mg/kg body weight (16.9 mmol/kg). Clinical signs of toxicity reported in rats in acute oral studies include weakness, ocular discharge, collapse, and death; pathological findings in animals that died were haemorrhagic lungs, liver discolorations, and acute gastrointestinal inflammation (Monsanto Co., 1984). The character of the dose–response for these effects is, however, unclear.

Acute dermal LD<sub>50</sub>s for cumene applied undiluted to rabbit skin range from >3160 mg/kg body weight (Monsanto Co., 1984) to >10 000 mg/kg body weight (Ciba-Geigy Co., 1985). Pathological findings in animals that died were similar to those in animals that died after a single oral exposure (Monsanto Co., 1984).

### 8.2 Irritation and sensitization

Undiluted cumene applied to the skin of New Zealand albino rabbits (0.5 ml) according to standardized guidelines caused slight defatting with skin flaking, a symptom not generally classified as relating to primary skin irritancy (Monsanto Co., 1984). A study conducted by Ciba-Geigy Co. (1985) reported a similar low level of irritation.

Cumene is an ocular irritant. Ocular irritation, including immediate discomfort followed by “erythema” (redness of the conjunctiva) and copious discharge, was observed after the instillation of undiluted cumene to rabbit, with these effects being reversible within 120 h (Monsanto Co., 1984). Ciba-Geigy Co. (1985) judged eye irritation as slight when cumene was applied to rabbit eyes. However, a study by Union Carbide Corp. (1985) reported that cumene was harmless to rabbit eyes when applied undiluted. Observations of lacrimation (Tegeris & Balster, 1994) and periocular swelling and blepharospasm (Cushman et al., 1995) also indicate that cumene may exhibit ocular irritancy at high airborne concentrations.

The concentration of cumene causing a 50% reduction in the respiratory rate in mice after 30 min of exposure was determined to be 10 084 mg/m<sup>3</sup> (2058 ppm) (Kristiansen et al., 1986). This concentration is quite high and in the range where repeated exposure caused death and morbidity in rats (Gulf Oil Corp., 1985; Chemical Manufacturers Association, 1989) and rabbits (Darmer et al., 1997).

No skin sensitization reactions were noted among a group of 20 female guinea-pigs treated with cumene in a Magnusson-Kligman maximization test conducted in accordance with Organisation for Economic Co-operation and Development (OECD) Guideline 406 (Hüls, 1988). No data were available on respiratory sensitization to cumene.

### 8.3 Short-term exposure

In a study by Monsanto Co. (1986), male and female Sprague-Dawley rats (10 per sex per group) were exposed whole body to cumene vapour concentrations of 0, 515, 1470, or 2935 mg/m<sup>3</sup> (0, 105, 300, or 599 ppm) for 6 h/day, 5 days/week, for approximately 4 weeks (minimum exposure, 20 days). Cage-side observations

included concentration-related increases in side-to-side head movements in both males and females in all dose groups, head tilt in all dose groups, and arched back in one female in the high-dose group. Increases in mean absolute left and right kidney weights were observed in high-dose males, as were increases in mean absolute left kidney weight in low- and mid-dose males. In high-dose females, the mean absolute weight of left kidneys was greater than in controls. This study confirms that renal weight changes occur in females and corroborates similar effects reported by Cushman et al. (1995). It should be noted that the effects associated with central nervous system perturbation (i.e., head movements) were not noted in several other longer-term studies, including that of Cushman et al. (1995), in which neurotoxicity was specifically assessed. If it is assumed that the renal changes among the males were associated with male rat-specific nephropathy (see section 8.4.1), the cage-side observations of head tilt and head movements become the critical effects for this short-term study.

Although not statistically significant, leukocytosis was noted in a group of rats ( $n = 15$ , mixed sex) exposed to cumene at  $1200 \text{ mg/m}^3$  (245 ppm) for 8 h/day, 5 days/week, for 30 exposures (Jenkins et al., 1970).

Other short-term toxicity studies are described in section 8.7.

## **8.4 Long-term exposure**

### **8.4.1 Subchronic exposure**

In an inhalation exposure study by Jenkins et al. (1970), groups of squirrel monkeys ( $n = 2$ ), beagle dogs ( $n = 2$ ), Princeton-derived guinea-pigs ( $n = 15$ ), and Sprague-Dawley and Long-Evans rats ( $n = 15$ ) were exposed whole body to cumene at concentrations of 0, 18, or  $147 \text{ mg/m}^3$  (0, 4, or 30 ppm) continuously for 90 days. Initial and terminal body weights, haematological and clinical chemistry parameters, and histopathological data were collected. No toxicologically significant effects were noted in the monkeys, dogs, or guinea-pigs. The only effect noted in the rats was a slight degree of leukocytosis at both concentrations.

Cushman et al. (1995; also reported as Bushy Run Research Center, 1989a) conducted two successive subchronic whole-body inhalation toxicity studies with cumene vapours (>99.9% pure) on Fischer-344 rats. In the first study, groups (21 per sex) were exposed to cumene vapour at 0, 490, 2430, or  $5890 \text{ mg/m}^3$  (0, 100, 496, or 1202 ppm) 6 h/day, 5 days/week, for 13 weeks. The second study was a repeat of the first, except that the group size was decreased to 15 per sex and an additional group (at  $245 \text{ mg/m}^3$  [50 ppm]) and a 4-week post-

exposure period were added. Parameters monitored included clinical signs of toxicity, auditory brain stem responses, ophthalmology, sperm count and morphology, and histopathological examination of all respiratory tract tissues (lungs and nasal turbinates) and the perfused nervous system. Evaluations of neurological function (functional observation battery and motor activity) were conducted in both studies. Light microscopic evaluation of the perfused-fixed nervous system tissues (six rats per sex per group) was conducted in the first study only.

In the first study, transient, reversible cage-side observations during exposure periods included hypoactivity, blepharospasm, and a delayed or absent startle reflex at the highest concentration. Rats exposed to  $2430 \text{ mg/m}^3$  were reported as being hypoactive during exposure, although no further specifics were given. Statistically significant ( $P < 0.05$ ) exposure-related decreases in motor activity (total) were observed in male rats exposed to the two highest concentrations of cumene, but these results were not observed in the second study in either sex. There were no exposure-related changes noted in the functional observation battery in this or the subsequent study. No effects were observed in the neurohistopathological examinations. Cataracts were reported in males at all exposure concentrations in this study. However, these results were not observed in the second study in which a more comprehensive protocol for eye examination was employed. Evaluation of the auditory brain stem responses revealed no meaningful changes in the auditory function of the exposed animals. The only gross histopathology noted was periocular swelling, which occurred in animals at the two highest concentrations (and for which neither incidence nor severity was reported). Both absolute and relative weights were increased significantly (>10%) in the kidneys, adrenal glands, and livers of both sexes at the highest concentration. These changes were also noted in the liver at the next lower concentration ( $2430 \text{ mg/m}^3$ ) for both females and males. Kidney lesions described in male rats at the two highest exposure concentrations were considered to be closely related to male rat-specific nephropathy (i.e., lesions were limited to males, and tubular proteinosis, hypertrophy, and hyperplasia as well as hyaline droplet formation were noted, although the identity of the protein in the droplets was not confirmed) and are of questionable relevance to human toxicity, principally because renal lesions characteristic of this type of nephropathy have not been observed in humans (US EPA, 1991a; Hard et al., 1993). Chronic progressive nephropathy, a common spontaneous renal disease of Fischer-344 male rats that occurs as early as 5 months of age (Montgomery & Seely, 1990), may also contribute to these renal lesions. Water consumption was significantly increased (about 40%) in male rats above control values at both 2430

and 5890 mg/m<sup>3</sup>. Several haematological and serum measures were also changed in a statistically significant dose-related manner at both 2430 and 5890 mg/m<sup>3</sup>: leukocytes (both sexes), platelets (both sexes), lymphocytes (males only), glucose (females only), and calcium/phosphorus (males only).

The results of the second study, with a 4-week post-exposure period, indicated limited reversibility of the organ weight alterations, because significant mean weight increases were still present in female liver and female adrenals of the highest exposure group. In males, only relative kidney weights (significant at 6%) and absolute liver weights remained increased significantly. Blood and serum parameters were not reported in this study. Morphological evaluation of epididymal and testicular sperm showed no cumene-related differences in count, morphology, or stages of spermatogenesis, although one high-dose rat did have diffuse testicular atrophy.

The weight alterations in the male and female adrenals and female kidney are considered potentially adverse, as the persistence noted indicates limited reversibility and engenders uncertainty about the progression and fate of these alterations under chronic exposure. The increased water consumption noted may also indicate potential for renal effects, although this effect was present at the next to highest dose level at which renal weights were not altered. Although the progression of these weight alterations from continued exposure cannot be ascertained from this subchronic study, data from the second (post-exposure) study indicate limited reversibility of effects on the adrenals, at least in females. The liver weight alterations are not viewed as adverse, because increase in liver weight without accompanying pathology is a trait of common microsomal enzyme inducing agents, although it should be noted that induction of hepatic microsomal enzymes may influence the metabolism of other substances and may either increase or decrease their toxicity (Sipes & Gandolfi, 1991). The altered haematological and serum parameters noted at the two highest concentrations may be considered as significant, although all are within normal ranges (Mitruka & Rawnsley, 1981). Based on the lowest dose at which both relative and absolute weight alterations in adrenal tissues of both sexes and in the kidneys of females are statistically ( $P < 0.05$ ) and biologically (>10%) significant, 5890 mg/m<sup>3</sup> may be considered as a lowest-observed-adverse-effect level (LOAEL), and 2430 mg/m<sup>3</sup> the corresponding NOAEL. Based on consideration of the various measures in the first study (motor effects, increased water consumption in males, haematological and serum parameters, sporadic weight increases in male adrenals and female kidneys) as significant, 2430 mg/m<sup>3</sup> may be considered as a LOAEL and 490 mg/m<sup>3</sup> as the corresponding NOAEL. It should be noted here that a LOAEL of 2391 mg/m<sup>3</sup> (488 ppm)

and a NOAEL of 485 mg/m<sup>3</sup> (99 ppm) were noted for maternal toxicity in the short-term developmental study in rats by Darmer et al. (1997), discussed in section 8.6.

#### 8.4.2 Chronic exposure and carcinogenicity

There are no long-term *in vivo* bioassays addressing the issue of cancer. No data exist to support any quantitative cancer assessment.

Wolf et al. (1956) conducted a study involving groups of 10 female Wistar rats administered cumene by gavage in olive oil at 154, 462, or 769 mg/kg body weight per day, 5 days/week, over a 194-day (6- to 7-month) period, equivalent to 110, 331, or 551 mg/kg body weight per day, adjusted for daily exposure. Rats given olive oil served as controls ( $n = 20$ ). A pronounced increase in average kidney weight, noted as a “moderate effect,” occurred at 769 mg/kg body weight per day, although no quantitative data are presented. An increase in average kidney weight was noted as a “slight effect” at 462 mg/kg body weight per day. It is stated in the report that at 154 mg/kg body weight per day, no evidence of ill effects, as determined by gross appearance, growth, periodic blood counts, analysis for blood urea nitrogen, average final body and organ weights, and bone marrow counts, was noted. The LOAEL is 462 mg/kg body weight per day, and the NOAEL is 154 mg/kg body weight per day. These results are consistent with those observed in more recent, better-reported studies described elsewhere in this document.

In an inhalation study by Fabre et al. (1955), Wistar rats were exposed (whole body) to cumene vapour at 2500 mg/m<sup>3</sup> (510 ppm), and rabbits were exposed to 6500 mg/m<sup>3</sup> (1327 ppm), for 8 h/day, 6 days/week, for up to 180 days. Histological effects reported were “passive congestion” in the lungs, liver, spleen, kidney, and adrenals and the presence of haemorrhagic zones in the lung, haemosiderosis in the spleen, and lesions from epithelial nephritis “in some cases.” It was not clear from the study if these effects occurred in rats or rabbits, or both.

#### 8.5 Genotoxicity and related end-points

In general, negative results have been obtained in a relatively complete battery of *in vivo* and *in vitro* mutagenicity tests, including gene mutation, chromosomal aberration, and primary DNA damage (US EPA, 1997). Cumene was tested at concentrations up to 2000 : g/plate in a *Salmonella typhimurium* reverse mutation assay (modified Ames test); negative results were observed with and without metabolic activation (Lawlor & Wagner, 1987). Cumene was negative in an Ames assay at concentrations up to 3606 : g/plate with *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (Florin et al., 1980). Cumene also tested negative,

with and without metabolic activation, in a set of HGPRT assays (using Chinese hamster ovary cells) at cumene concentrations of 100–125 : g/ml, at which the relative cloning efficiencies (a measure of cytotoxicity) ranged from 29% to 110% (Gulf Life Sciences Center, 1985a; Yang, 1987). A micronucleus assay performed in mice given up to 1 g cumene/kg body weight by gavage was negative (Gulf Life Sciences Center, 1985b). Micronucleus assays done in Fischer-344 rats, however, gave values that were weakly positive, although little dose-response was seen, and deaths occurred at the highest dose (5 of 10 animals at 2.5 g/kg body weight intraperitoneally; NTP, 1996). The positive control used in the micronucleus tests, cyclophosphamide, produced strong positive responses in all assays.

Cumene failed to induce significant rates of transformation in BALB/3T3 cells (without activation) at concentrations up to 500 : g/ml (Putnam, 1987) but tested positive in an earlier cell transformation test also using BALB/3T3 cells, in which an increase in transformations was observed at 60 : g/ml (Gulf Oil Corp., 1984a). Results from an unscheduled DNA synthesis assay in rat hepatocytes conducted by Gulf Oil Corp. (1984b) indicated positive results at doses of 16 and 32 : g cumene/ml (with 128 : g/ml noted as toxic to the hepatocytes). However, apparent technical difficulties with this test (US EPA, 1988) prompted a repeat of the unscheduled DNA synthesis assay in rat hepatocytes, the results of which showed cumene to be clearly negative at doses up to 24 : g/ml, with doses above 24 : g/ml noted as being too toxic for evaluation of unscheduled DNA synthesis (Curren, 1987; US EPA, 1988).

## **8.6 Reproductive and developmental toxicity**

No multigeneration reproductive study exists for this compound by either the oral or inhalation route. There are no data concerning cumene exposure of females prior to mating, from conception to implantation, or during late gestation, parturition, or lactation.

The first subchronic inhalation study of Cushman et al. (1995), however, conducted morphological evaluation of epididymal and testicular sperm in rats exposed for 13 weeks to cumene vapours (see section 8.4.1). No cumene-related differences in count, morphology, or stages of spermatogenesis were noted, although one high-dose rat did have diffuse testicular atrophy. No alterations (weight changes, histopathology) were noted in the female reproductive organs that were examined at the termination of this same study.

In an inhalation study (Darmer et al., 1997; also reported as Bushy Run Research Center, 1989b), Sprague-Dawley rats (25 per group) were exposed whole

body to 0, 485, 2391, or 5934 mg cumene/m<sup>3</sup> (0, 99, 488, or 1211 ppm) for 6 h/day on days 6 through 15 of gestation. Perioral wetness and encrustation, a significant ( $P < 0.01$ ) decrease in body weight gain on gestation days 6 through 9 (accompanied by a significant decrease in food consumption), and a slight increase (7.7%) in relative liver weight were observed in dams at the high dose only. Hypoactivity, blepharospasm, and significantly ( $P < 0.05$ ) decreased food consumption were observed in the dams at the next highest concentration. There were no statistically significant adverse effects on reproductive parameters or fetal development. For this study, 5934 mg/m<sup>3</sup> is a developmental NOAEL, and 485 mg/m<sup>3</sup> is a maternal NOAEL.

In another inhalation study (Darmer et al., 1997; also reported as Bushy Run Research Centre, 1989c), New Zealand white rabbits (15 per group) were exposed whole body to 0, 2411, 5909, or 11 255 mg cumene/m<sup>3</sup> (0, 492, 1206, or 2297 ppm) for 6 h/day on days 6 through 18 of gestation. Two does died and one aborted at the highest exposure concentration. There were significant ( $P < 0.01$ ) reductions in body weight gain (178 g lost compared with 31 g gained in the control group) and food consumption at the highest exposure level during the treatment period. Significantly reduced food consumption was also observed in the 2411 and 5909 mg/m<sup>3</sup> exposure groups, but it was not accompanied by any decrease in weight gain. Clinical signs of toxicity observed in the does included significant ( $P < 0.01$ ) increases in perioral and perinasal wetness and blepharospasm at the highest concentration. At necropsy, there were colour changes in the lungs of 33% of the does exposed to 11 255 mg/m<sup>3</sup>. Relative liver weight was significantly ( $P < 0.01$ ) elevated (16.8% over control weight) at the highest exposure level. There were no statistically significant effects on gestation parameters; however, there were non-significant increases in non-viable implants and early resorptions and a non-significant decrease in the percentage of live fetuses concurrent with maternal toxicity at 11 255 mg/m<sup>3</sup>. Apparent increases in ecchymosis (haemorrhagic areas of the skin) of the head were shown to be within the ranges observed for the historical controls of this test facility (US EPA, 1991b). The highest exposure level resulted in maternal mortality. The next lower dose of 5909 mg/m<sup>3</sup>, at which the only effect noted was reduced food consumption without accompanying weight loss, is considered the NOAEL of the study.

## **8.7 Immunological and neurological effects**

No studies were located that examined immunotoxicity in animals after exposure to cumene by any route.



Cumene appears to be similar to many solvents, such as alcohol, that are known central nervous system depressants. The occurrence of neurological effects from inhalation exposure to cumene has been confirmed in several studies. These studies are acute exposures that show neurotoxicological effects only at quite high concentrations ( $>2450 \text{ mg/m}^3$  [ $>500 \text{ ppm}$ ]). Neurotoxicological effects were not observed in the longer-term inhalation study by Cushman et al. (1995), which included complete batteries of functional and motor activity tests and neurohistopathology and in which the highest exposure concentration was  $5890 \text{ mg/m}^3$  (1202 ppm).

Cumene was tested at 0, 9800, 19 600, or  $39\ 200 \text{ mg/m}^3$  (0, 2000, 4000, or 8000 ppm) and produced a short-lived profile of neurobehavioural effects in mice that indicated central nervous system depressant activity (Tegeris & Balster, 1994). Effects noted from brief (20-min) whole-body exposures to cumene included those on central nervous system activity (decreased arousal and rearing at  $9800 \text{ mg/m}^3$ ), muscle tone/equilibrium (changes in grip strength and mobility at  $19\ 600 \text{ mg/m}^3$ ), and sensorimotor activity (including decreased tail pinch and touch response at  $19\ 600 \text{ mg/m}^3$ ).

In an acute experiment accompanying the sub-chronic exposures (see section 8.4.1), Cushman et al. (1995) exposed Fischer-344 rats (whole body) once to 0, 490, 2430, or  $5890 \text{ mg/m}^3$  (0, 100, 496, or 1202 ppm) for 6 h and conducted functional observations 1 h post-exposure. Gait abnormalities and decreased rectal temperatures were noted for both sexes at the highest exposure level only. Decreased activity levels were noted for both sexes at the highest level and for females only at the next highest level ( $2430 \text{ mg/m}^3$ ) of exposure. Males, but not females, from the highest exposure group had decreased response to toe pinch at 6 h post-exposure.

In a 5-day inhalation study, Fischer-344 rats exposed whole body to 9800 or  $24\ 500 \text{ mg}$  cumene vapour/ $\text{m}^3$  (2000 or 5000 ppm) for 6 h/day showed toxic effects from exposure (Gulf Oil Corp., 1985). All rats in the high-exposure group died after 2 days. At the lower dose, females demonstrated central nervous system effects (hypothermia and staggering). Similar, but more severe, symptoms were observed in the high-exposure animals before they died.

Fischer-344 rats (10 per sex per group) were exposed whole body to cumene at 0, 1230, 2680, 5130, or  $6321 \text{ mg/m}^3$  (0, 251, 547, 1047, or 1290 ppm) for 6 h/day, 5 days/week, for 2 weeks (Chemical Manufacturers Association, 1989). Initial exposures to  $9800 \text{ mg/m}^3$  (2000 ppm) for 1–2 days resulted in such severe neurological and respiratory effects that the concentration levels were

reduced to those given above. During the remainder of the 2-week exposure period, clinical observations (ocular discharge, decreased motor activity or hyperactivity, and ataxia) were noted sporadically at all levels except  $1230 \text{ mg/m}^3$ . For females in the two highest dose groups, the average relative kidney weight and relative and absolute adrenal weights were increased significantly over control values. These data provide corroboration for these same effects reported in the study of Cushman et al. (1995).

## 9. EFFECTS ON HUMANS

No information was located regarding the toxicity of cumene in humans following acute, subchronic, or chronic exposure (US EPA, 1997). The minimum lethal human exposure to this agent has not been delineated. No epidemiology, case reports, or clinical controls of humans were located for this compound. There are no epidemiological or occupational studies examining the carcinogenicity of cumene in humans (US EPA, 1997).

No information was located regarding dermal irritation and sensitization in humans following exposure to cumene.

## 10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The available environmental effects studies are inadequate to allow a quantitative assessment of the acute toxicity of cumene to environmental organisms owing to the variability of the data and flawed experimental designs. For example, 24-h toxicity values for water fleas ranged from an  $\text{EC}_{50}$  of 91 mg/litre (Bringmann & Kuhn, 1982) down to an  $\text{IC}_{50}$  of 0.6 mg/litre (Abernathy et al., 1986). Further, many of the reported toxicity values for aquatic invertebrates exceed the water solubility of cumene at 50 mg/litre, with Glickman et al. (1995) noting that actual measured concentrations of cumene were only about 10% of nominal concentrations. The lowest reported toxic concentration was 0.012 mg/litre, the toxicity threshold for the protozoan *Colpidium colpodia* (Rogerson et al., 1983). Concentrations of up to 50 mg/litre did not affect the growth of the larvae of the mussel *Mytilus edulis* during a 27-day exposure (Le Roux, 1977). Selected data demonstrating effect concentrations are shown in Table 2. It should be noted that the high volatility and biodegradability of cumene may further reduce the hazard to the aquatic environment, especially for chronic exposure conditions.

Table 2: Acute toxicity of cumene to organisms other than laboratory mammals.

Species	End-point (effect)	Concentration (mg/litre)	Reference
<b>Algae</b>			
Green alga ( <i>Chlorella vulgaris</i> )	3-h EC <sub>50</sub> (photosynthetic inhibition)	21	Hutchinson et al., 1980
Green alga ( <i>Chlamydomonas angulosa</i> )	3-h EC <sub>50</sub> (photosynthetic inhibition)	9	Hutchinson et al., 1980
Green alga ( <i>Selenastrum capricornutum</i> )	72-h EC <sub>50</sub> (growth inhibition)	2.6	Galassi et al., 1988
Green algae ( <i>Scenedesmus subspicatus</i> )	72-h static EC <sub>50</sub> (growth inhibition)	2.0	Hüls, 1998a
<b>Invertebrates</b>			
Water flea ( <i>Daphnia magna</i> )	24-h EC <sub>50</sub> (immobilization)	91	Bringmann & Kuhn, 1982
Water flea ( <i>Daphnia magna</i> )	24-h LC <sub>50</sub>	4.8	Glickman et al., 1995
Water flea ( <i>Daphnia magna</i> )	21-day static EC <sub>50</sub>	1.5	Hüls, 1998b
Water flea ( <i>Daphnia magna</i> )	24-h IC <sub>50</sub> <sup>a</sup>	1.4	Galassi et al., 1988
Water flea ( <i>Daphnia magna</i> )	24-h IC <sub>50</sub>	0.6	Abernathy et al., 1986
Mysid shrimp ( <i>Mysidopsis bahia</i> )	96-h flow LC <sub>50</sub>	1.3	Glickman et al., 1995
Mysid shrimp ( <i>Mysidopsis bahia</i> )	96-h flow LC <sub>50</sub>	1.2	Chemical Manufacturers Association, 1990
Ciliate protozoan ( <i>Colpidium colpoda</i> )	"toxicity threshold" (NR) <sup>b</sup>	0.012	Rogerson et al., 1983
<b>Vertebrates</b>			
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	96-h LC <sub>50</sub>	4.8	Glickman et al., 1995
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	no observed effect	1.9	Glickman et al., 1995
Sheepshead minnow ( <i>Cyprinodon variegatus</i> )	96-h flow LC <sub>50</sub>	4.7	Glickman et al., 1995
Sheepshead minnow ( <i>Cyprinodon variegatus</i> )	no observed effect	<2.9	Glickman et al., 1995

<sup>a</sup> IC<sub>50</sub> = immobilization concentration for 50% of the organisms.

<sup>b</sup> NR = not reported.

## 11. EFFECTS EVALUATION

### 11.1 Evaluation of health effects

#### 11.1.1 Hazard identification and dose–response assessment

Kinetic analysis shows that there is rapid and complete clearance of cumene and its metabolites from the body, indicating little potential for accumulation. No human toxicity data are available from exposure to cumene. Short-term exposures of animals to high concentrations (>2450 mg/m<sup>3</sup> [>500 ppm]) demonstrate that cumene, like other solvents, may be considered

harmful, inducing transient reversible central nervous system effects. However, neurotoxicity, portal-of-entry effects, developmental effects, and markedly adverse systemic toxicity were not observed after long-term repeated-dose studies conducted in animals at lower concentrations (<2450 mg/m<sup>3</sup> [<500 ppm]). Cumene has caused dermal and ocular irritation in animals in one study, but it had no such effects in others. A single study indicates that cumene does not elicit dermal sensitization in animals.

Increases in organ weights (most notably kidney) are the most prominent and consistent effects observed in rodents exposed for 6–7 months by the oral route (Wolf et al., 1956) or for 3 months by the inhalation route

(Cushman et al., 1995). No adverse effects were observed in rat or rabbit fetuses whose mothers had been exposed to airborne cumene during fetal development.

The sparsity of long-term repeated-dose toxicity data and the absence of any human toxicity data both constitute areas of scientific uncertainty. The only repeated-dose toxicity studies of any appreciable duration are the oral study of Wolf et al. (1956), at about 7 months, and the 3-month subchronic inhalation study of Cushman et al. (1995). Both of these studies are concurrent in indicating kidneys of female rats as the target organ, regardless of exposure route. Although neither of these studies is sufficient in duration to reveal the fate of the observed alterations in organ weights from lifetime chronic exposure, the subchronic study of Cushman et al. (1995) is more scientifically comprehensive in its analyses than the study of Wolf et al. (1956) and offers much more extensive data reporting on more animals (both genders). The study of Cushman et al. (1995) is therefore chosen as the pivotal study.

No multigeneration reproductive studies have been performed for cumene. The rapid metabolism and excretion of cumene, coupled with the lack of effects on sperm morphology reported by Cushman et al. (1995), indicate that cumene has low potential for reproductive toxicity. However, this lack of concern must be weighed against the fact that kinetic studies indicate extensive and wide distribution of cumene, including to reproductive organs, and the fact that the consequences of long-term repeated/continuous exposure on either organs or reproductive function have not been evaluated.

There are no data in humans or animals concerning the development of cancer following exposure to cumene. The potential hazard for carcinogenicity of cumene to humans has not been determined, although the predominant evidence suggests that this compound is not likely to produce a carcinogenic response (i.e., numerous genotoxic tests, including gene mutation, chromosomal aberration, and primary DNA damage tests, were conducted, all but one of which were negative or not reproducible). No highly reactive chemical species are known to be generated during the metabolism of cumene.

### 11.1.2 **Criteria for setting guidance values for cumene**

For oral exposures, the NOAEL for increased average kidney weight in female rats following subchronic (139/194 days) oral (gavage) exposure is 154 mg/kg body weight per day, which was adjusted, based on the dosing schedule, to 110 mg/kg body weight per day (Wolf et al., 1956). These data were not amenable to benchmark dose analysis. For purposes of quantitative assessment, the quality of the principal oral

study is marginal, because the group sizes were minimal, the groups comprised females only, and little quantitative information was presented. Full uncertainty factors of 10 each are applied for interindividual and interspecies variations. A partial uncertainty factor ( $10^{0.5}$ ) for extrapolation from subchronic to chronic duration is applied, as the study was intermediate between chronic and subchronic duration. Another partial uncertainty factor ( $10^{0.5}$ ) is also used owing to lack of a full-scale multigeneration reproductive study. The total uncertainty factor applied was 1000 ( $10 \times 10 \times 10^{0.5} \times 10^{0.5}$ ). This yields a guidance value for oral exposure of 0.1 mg/kg body weight per day. This guidance value is meant to provide information for risk managers to enable them in making decisions concerning the protection of human health.

Interpretation of the effects reported in the subchronic inhalation study of Cushman et al. (1995) allows for consideration of either the 490 mg/m<sup>3</sup> (100 ppm) (MAK, 1996) or the 2430 mg/m<sup>3</sup> (496 ppm) (US EPA, 1997) exposure level as a defensible NOAEL. Whereas the motor effects, organ weight changes, and clinical effects reported at 2430 mg/m<sup>3</sup> (496 ppm) may be regarded as non-adverse indicators of exposure (in other words, as a NOAEL), these same effects may be regarded alternatively as potentially adverse indicators of toxicologically significant effects apparent at the next highest exposure level (in other words, a LOAEL). Consideration of both these interpretations may be justified in derivation of an inhalation guidance value for cumene. The experimental exposure scenario of the NOAEL (either 490 or 2430 mg/m<sup>3</sup> [100 or 496 ppm]) is first adjusted to a continuous exposure scenario for the general population by factoring the NOAEL by the hours exposed as a fraction of the day (6/24 hours) and the number of days exposed as a fraction of the week (5/7), resulting in the figure of 436 mg/m<sup>3</sup> (89 ppm) for the 2430 mg/m<sup>3</sup> (496 ppm) experimental exposure level and 88 mg/m<sup>3</sup> (18 ppm) for the 490 mg/m<sup>3</sup> (100 ppm) experimental exposure level. Full uncertainty factors of 10 each were applied for subchronic to chronic extrapolation and for interindividual variations. A partial uncertainty factor ( $10^{0.5}$ ) is applied to account for the toxicodynamic component of the interspecies extrapolation. In long-term inhalation exposures, the blood/air partition coefficient ( $H_{b/a}$ ) is a principal factor determining the amount of compound reaching a systemic tissue (such as kidney). For a given external concentration and similar exposure conditions, the smaller the  $H_{b/a}$  values, the less compound in the blood and at the tissue. The blood/air partition coefficient has been determined with human blood (Sato & Nakajima, 1979, 1987), but not for rats. Information available on compounds structurally related to cumene (xylenes and benzene; Gargas et al., 1989) indicates that human  $H_{b/a}$  values are nearly always smaller than rat  $H_{b/a}$  values, such that, for a given external concentration, human tissues would receive less

compound than would rat tissues. Thus, use of the rat in a long-term repeated-dose study with cumene obviates the need for the toxicokinetic component of the animal to human extrapolation. An additional partial uncertainty factor ( $10^{0.5}$ ) is used for database deficiencies, owing principally to lack of a full-scale multigeneration reproductive study, as discussed above. The total uncertainty factor would be 1000 ( $10 \times 10 \times 10^{0.5} \times 10^{0.5}$ ). Application of this factor would result in guidance values of  $0.4 \text{ mg/m}^3$  (0.08 ppm) for the NOAEL of  $436 \text{ mg/m}^3$  (89 ppm), adjusted for continuous exposure from  $2430 \text{ mg/m}^3$  (496 ppm), and  $0.09 \text{ mg/m}^3$  (0.02 ppm) for the NOAEL of  $88 \text{ mg/m}^3$  (18 ppm), adjusted for continuous exposure from  $490 \text{ mg/m}^3$  (100 ppm).

The carcinogenic potential of cumene cannot be determined because no adequate data, such as well-conducted long-term animal studies or reliable human epidemiological studies, are available with which to perform an assessment.

#### **11.1.3 Sample risk characterization**

The scenario chosen as an example is continuous lifetime exposure for the general population.

No human data are available with which to characterize the toxicity of cumene directly. The reported ambient cumene concentration of  $0.0147 \text{ mg/m}^3$  (0.003 ppm) is appreciably below either of the guidance values of  $0.4 \text{ mg/m}^3$  (0.08 ppm) (27-fold) or  $0.09 \text{ mg/m}^3$  (0.02 ppm) (6-fold). The upper limit of ambient cumene concentrations reported in rural air,  $2.5 \text{ g/m}^3$  (0.5 ppb), is even further below the guidance values (36- to 160-fold). Other data presented in this report, such as estimates from cigarette smoke, suggest that humans would primarily be exposed through inhalation, although ingestion through food may occur. Exposure via drinking-water is probably unlikely.

The critical effect in the principal study for the oral assessment is increased kidney weight in female rats and, although poorly reported, is corroborated by inhalation studies with cumene. Increased organ weights have been found in other toxicity studies with cumene and have been observed across routes of exposure. Insufficient data on oral exposure exist to apply the guidance value of  $0.1 \text{ mg/kg}$  body weight per day derived above.

Following inhalation exposure, the effects observed included increased kidney and adrenal weights and central nervous system, haematological, and clinical biochemical alterations, which were observed in rats. The critical effect was observed across species and was observed in several studies. These results partially corroborate and reinforce the significance of similar results seen in the long-term oral study of cumene.

The potential hazard for carcinogenicity of cumene in humans cannot be determined. Studies have indicated that cumene has low, if any, genotoxicity.

Neither chronic nor multigeneration reproductive studies are available for this substance.

Data are not available to determine whether young or aged animals are more susceptible than adult animals (e.g., 2-year-old rats) to the effects of cumene, and there is no evidence to suggest that this would be so in young or aged humans. There is also no convincing evidence to suggest that gender differences in susceptibility to cumene toxicity would exist in humans.

## **11.2 Evaluation of environmental effects**

Cumene is a volatile liquid and exists mainly in the vapour phase in the atmosphere. It degrades in the atmosphere via reaction with hydroxyl radicals. Although small amounts of cumene may be removed from the atmosphere by precipitation, cumene is not expected to react with ozone or directly with light. In water, cumene can be volatilized, undergo biodegradation, or adsorb to sediments. In soil, it is expected to biodegrade rapidly under aerobic conditions; as in water, it can readily adsorb to soil or volatilize.

BCFs suggest a slight potential for cumene to bioconcentrate in fish species. No data were available on the bioconcentration of cumene in terrestrial organisms. Although the existing toxicological database and limited exposure data do not permit a quantitative risk assessment, the available information suggests that cumene will not adversely affect populations or communities of terrestrial or aquatic organisms based on its low availability (volatility, rapid degradation).

## **12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES**

No previous evaluations by international bodies were identified.

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

## 13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventive and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0170) reproduced in this document.

### 13.1 Human health hazards

Cumene is flammable. Exposure could cause central nervous system effects and at high concentrations could result in unconsciousness.

### 13.2 Advice to physicians

In the event of poisoning, treatment is supportive.

### 13.3 Health surveillance advice

For workers exposed to cumene, a health surveillance programme should include surveillance of kidney function.

### 13.4 Spillage

In the event of spillage, measures should be taken to prevent cumene from reaching drains and water-courses, owing to the potential for hazardous effects on aquatic organisms.

### 13.5 Storage

Cumene should be stored away from acids and strong oxidants. Long-term storage could result in the formation of explosive peroxides. Proper safety and handling procedures must be used.

## 14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards may be obtained from UNEP Chemicals (IRPTC), Geneva.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

**CUMENE**0170  
April 2000

**CAS No: 98-82-8**  
RTECS No: GR8575000  
UN No: 1918  
EC No: 601-024-00-X

(1-Methylethyl)benzene  
2-Phenylpropane  
Isopropylbenzene  
 $C_9H_{12}$  /  $C_6H_5CH(CH_3)_2$   
Molecular mass: 120.2

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
<b>FIRE</b>	Flammable.	NO open flames, NO sparks, and NO smoking.	Powder, AFFF, foam, carbon dioxide.
<b>EXPLOSION</b>	Above 31°C explosive vapour/air mixtures may be formed.	Above 31°C use a closed system, ventilation, and explosion-proof electrical equipment. Prevent build-up of electrostatic charges (e.g., by grounding).	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE		PREVENT GENERATION OF MISTS!	
<b>Inhalation</b>	Dizziness. Ataxia. Drowsiness. Headache. Unconsciousness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
<b>Skin</b>	Dry skin.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
<b>Eyes</b>	Redness. Pain.	Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
<b>Ingestion</b>	(See Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. (Extra personal protection: filter respirator for organic gases and vapours.)	Xn Symbol N Symbol R: 10-37-50/53-65 S: (2-)24-37-61-62 Note: C UN Hazard Class: 3 UN Pack Group: III Marine pollutant.

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-30G35 NFPA Code: H2; F3; R1	Fireproof. Separated from strong oxidants, acids. Cool. Keep in the dark. Store only if stabilized.



### IMPORTANT DATA

**Physical State; Appearance**

COLOURLESS LIQUID, WITH CHARACTERISTIC ODOUR.

**Physical dangers**

As a result of flow, agitation, etc., electrostatic charges can be generated.

**Chemical dangers**

Reacts violently with acids and strong oxidants causing fire and explosion hazard. The substance can form explosive peroxides.

**Occupational exposure limits**

TLV: 50 ppm; (ACGIH 1999).  
MAK: 50 ppm; 250 mg/m<sup>3</sup>; (skin) (1999)

**Routes of exposure**

The substance can be absorbed into the body by inhalation and through the skin.

**Inhalation risk**

A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

**Effects of short-term exposure**

The substance irritates the eyes and the skin. Swallowing the liquid may cause aspiration into the lungs with the risk of chemical pneumonitis. The substance may cause effects on the central nervous system. Exposure far above the OEL may result in unconsciousness.

**Effects of long-term or repeated exposure**

Repeated or prolonged contact with skin may cause dermatitis.

### PHYSICAL PROPERTIES

Boiling point: 152°C  
Melting point: -96°C  
Relative density (water = 1): 0.90  
Solubility in water: none  
Vapour pressure, Pa at 20°C: 427  
Relative vapour density (air = 1): 4.2

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.01  
Flash point: 31°C c.c.  
Auto-ignition temperature: 420°C  
Explosive limits, vol% in air: 0.9-6.5  
Octanol/water partition coefficient as log Pow: 3.66

### ENVIRONMENTAL DATA

The substance is toxic to aquatic organisms.

### NOTES

Check for peroxides prior to distillation; eliminate if found.

### ADDITIONAL INFORMATION

**LEGAL NOTICE**

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

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## APPENDIX 1 — SOURCE DOCUMENTS

**US EPA (1997): *Integrated Risk Information System (IRIS) online at <http://www.epa.gov/iris> (including the Toxicological review of cumene in support of summary IRIS information, National Center for Environmental Assessment, Cincinnati, OH), US Environmental Protection Agency, Washington, DC***

The peer review process that this and other recent (post-1996) IRIS assessments undergo includes internal (i.e., US Environmental Protection Agency) and external review rounds. Comments of and responses to the external reviewers are a matter of record in the *Toxicological review*. Other aspects of the IRIS review process are explained in Mills & Foureman (1998).

**US EPA (1987): *Health and environmental effects document for cumene, August 1987, National Center for Environmental Assessment, Office of Health and Environmental Assessment, US Environmental Protection Agency***

The US EPA (1987) report is used as an expanded reference source for the IRIS document.

**UK DOE (1994): *Environmental hazard assessment (EHA): Cumene, Toxic Substances Division, Directorate for Air, Climate, and Toxic Substances, United Kingdom Department of the Environment, Garston***

The *Environmental hazard assessment (EHA): Cumene* document was drafted by the Building Research Establishment (United Kingdom Department of the Environment) and the Institute of Terrestrial Ecology (United Kingdom Natural Environment Research Council), with I.R. Nielsen, J. Diment, and S. Dobson as the authors. The draft document was peer reviewed both within the United Kingdom and internationally. Comments and additional material were received from A.L. Barton (US Environmental Protection Agency), C.B. Buckley (South Western Water Services, United Kingdom), J.H. Duffus (Heriot-Watt University, Edinburgh, United Kingdom), D. Keating (Health & Safety Executive, United Kingdom), S. Killeen (National Rivers Authority, United Kingdom), J.S. Lawson (ICI Chemicals, United Kingdom), P. Matthiessen (Ministry of Agriculture, Fisheries and Food, United Kingdom), H.A. Painter (Freshfield Analysis Ltd.), N. Passant (Department of Trade and Industry, United Kingdom), T. Sheils (Department of the Environment, United Kingdom), and G. Thom (US Environmental Protection Agency) and were incorporated into the final document. The document was published in 1994 and covers published and unpublished material up to 1993.

## APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on cumene was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

Commission of the European Communities, Directorate-General, Luxembourg

Federal Institute for Health Protection of Consumers & Veterinary Medicine (BgVV), Berlin, Germany

GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberscheissheim, Germany

Health & Safety Executive, Merseyside, United Kingdom

Institut de Recherches en Santé et Sécurité du Travail du Québec, Montreal, Canada

Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Ministry of Health, Beijing, People's Republic of China

Institute of Terrestrial Ecology, Cambridgeshire, United Kingdom

Joint Food Safety and Standards Group, London, United Kingdom

National Chemicals Inspectorate, Solna, Sweden

National Industrial Chemicals Notification and Assessment Scheme, Sydney, Australia

National Institute of Health Sciences, Tokyo, Japan

National Institute of Occupational Health, Budapest, Hungary

National Institute of Public Health, Czech Republic

United States Department of Health and Human Services (National Institute of Environmental Health Sciences)

United States Environmental Protection Agency (National Center for Environmental Assessment; Region VIII)

## **APPENDIX 3 — CICAD FINAL REVIEW BOARD**

**Washington, DC, USA, 8–11 December 1998**

### **Members**

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden (*Vice-Chairperson*)

Mr R. Cary, Toxicology Unit, Health Directorate, Health and Safety Executive, Bootle, Merseyside, United Kingdom (*Rapporteur*)

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr O. Faroon, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA, USA

Dr G. Foureman, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA (*Chairperson*)

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Dr I. Mangelsdorf, Documentation and Assessment of Chemicals, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Dr A. Nishikawa, Division of Pathology, National Institute of Health Sciences, Tokyo, Japan

Dr E.V. Ohanian, Office of Water/Office of Science and Technology, Health and Ecological Criteria Division, US Environmental Protection Agency, Washington, DC, USA

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Professor P. Yao, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Ministry of Health, Beijing, People's Republic of China

### **Observers**

Dr K. Austin, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr I. Daly (ICCA representative), Regulatory and Technical Associates, Lebanon, NJ, USA

Ms K.L. Lang (CEFIC, European Chemical Industry Council, representative), Shell International, London, United Kingdom

Ms K. Roberts (ICCA representative), Chemical Self-funded Technical Advocacy and Research (CHEMSTAR), Chemical Manufacturers Association, Arlington, VA, USA

Dr W. Snellings (ICCA representative), Union Carbide Corporation, Danbury, CN, USA

Dr M. Sweeney, Document Development Branch, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberschleissheim, Germany

### **Secretariat**

Dr M. Baril, Institut de Recherches en Santé et Sécurité du Travail du Québec (IRSST), Montreal, Quebec, Canada

Dr H. Galal-Gorchev, Chevy Chase, MD, USA

Ms M. Godden, Health and Safety Executive, Bootle, Merseyside, United Kingdom

Dr R.G. Liteplo, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Ms L. Regis, Programme for the Promotion of Chemical Safety, World Health Organization, Geneva, Switzerland

Mr A. Strawson, Health and Safety Executive, London, United Kingdom

Dr P. Toft, Programme for the Promotion of Chemical Safety, World Health Organization, Geneva, Switzerland

## RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au cumène a été préparé par l'Environmental Protection Agency (EPA) des Etats-Unis sur la base d'une de ses publications intitulée *Health and environmental effects document for cumene* (US EPA, 1987), du dossier cumène provenant de son système intégré d'information sur les risques (IRIS) (US EPA, 1997) et d'un document du Royaume Uni paru sous le titre de *Environmental hazard assessment (EHA): Cumene* (UK DOE, 1994), complétés par une étude bibliographique à partir de la base de données écologiques AQUIRE (Aquatic Toxicity Information Retrieval). Les recherches bibliographiques effectuées pour l'établissement du dossier IRIS vont jusqu'à novembre 1996 et celles qui ont été effectuées à partir de la base de données AQUIRE, jusqu'à avril 1998. On trouvera à l'appendice 1 des indications sur le mode d'examen par des pairs ainsi que sur les sources documentaires utilisées. Les renseignements concernant l'examen du CICAD par les pairs font l'objet de l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Washington du 8 au 11 décembre 1998. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information internationale sur la sécurité chimique (ICSC 0170) relative au cumène, établie par le Programme internationale sur la sécurité chimique (IPCS, 1993) est également reproduite dans ce document.

Le cumène (CAS No 98-82-8) est un produit pétrochimique insoluble dans l'eau utilisé dans la préparation d'un certain nombre d'autres substances chimiques, notamment le phénol et l'acétone. Il se volatilise facilement dans l'atmosphère à partir de l'eau et des sols secs. Il devrait en principe n'être que modérément adsorbé aux particules du sol et aux sédiments et subir une décomposition dans l'eau et le sol.

Le métabolisme du cumène donne principalement naissance, chez l'Homme comme chez l'animal, à un alcool secondaire le 2-phényl-2-propanol. Cet alcool et ses conjugués sont rapidement excrétés chez les rongeurs comme chez l'Homme.

Les effets les plus marqués observés chez des rongeurs exposés de façon répétée au cumène par la voie orale ou respiratoire, consistent en une augmentation du poids de certains organes, mais plus particulièrement du rein. Aucun effet indésirable n'a été relevé chez des foetus de rats et de lapins dont la mère avait été exposée à ce produit au cours du développement foetal. Il n'y a pas eu d'étude de reproduction portant sur plusieurs générations, mais la métabolisation et l'excrétion rapides du composé et le fait qu'une étude subchronique n'ait

pas mis en évidence d'effets sur les spermatozoïdes, semblent indiquer que le cumène est dépourvu de toxicité génésique. On a établi une valeur-guide de 0,1 mg/kg par jour en se basant sur la dose sans effet nocif observable (NOAEL) de 154 mg/kg p.c. obtenue après avoir fait ingérer du cumène à des rats pendant 6 à 7 mois, le critère retenu étant l'hypertrophie rénale chez les femelles. Cette valeur de la dose a été corrigée pour tenir compte du programme d'administration et on a appliqué un facteur d'incertitude de 1000. D'autres valeurs de la NOAEL tirées d'une même étude d'inhalation en mode subchronique ont abouti à des valeurs-guides respectivement égales à 0,4 mg/m<sup>3</sup> et 0,09 mg/m<sup>3</sup> pour la population générale; dans ce cas également, on a corrigé la valeur de la NOAEL pour tenir compte d'une exposition en mode continu et on a appliqué un facteur global d'incertitude égal à 1000.

On ne possède pas de données qui permettent d'évaluer quantitativement l'exposition humaine au cumène.

Il n'est pas possible d'évaluer le pouvoir cancérogène du cumène chez l'Homme en raison de l'absence d'études de cancérogénicité à long terme. La plupart des études de génotoxicité ont donné des résultats négatifs.

Les données qui permettraient une évaluation du risque encouru par les organismes aquatiques et terrestres sont insuffisantes, notamment en ce qui concerne la mesure de l'exposition à ce composé. Toutefois, si l'on se base sur les données existantes, on peut penser que ce risque est relativement faible. Les valeurs disponibles indiquent une légère tendance à la bioconcentration chez les poissons. On dispose d'aucune donnée sur la bioaccumulation du cumène le long des diverses chaînes alimentaires (bioamplification).

## RESUMEN DE ORIENTACIÓN

Este CICAD sobre el cumeno, preparado por la Agencia para la Protección del Medio Ambiente de los Estados Unidos (EPA), se basa en un documento de la EPA sobre los efectos sanitarios y medioambientales del cumeno (US EPA, 1987), en un archivo sobre el cumeno del sistema integrado de información sobre riesgos (IRIS) de la EPA de los Estados Unidos (US EPA, 1997) y en un documento del Reino Unido sobre la evaluación de los riesgos medioambientales del cumeno (UK DOE, 1994), con el complemento de una búsqueda bibliográfica en la base de datos AQUIRE (Aquatic Toxicity Information Retrieval), especializada en ecología. La búsqueda bibliográfica en el archivo del IRIS se realizó hasta noviembre de 1996 y en la base de datos AQUIRE hasta abril de 1998. La información relativa al carácter del examen colegiado y a la disponibilidad de los documentos originales figura en el apéndice 1. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Washington, DC, Estados Unidos, los días 8-11 de diciembre de 1998. La lista de participantes en esta reunión figura en el apéndice 3. La ficha internacional de seguridad química (ICSC 0170) para el cumeno, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El cumeno (CAS No 98-82-8) es un producto petroquímico insoluble en agua que se utiliza en la fabricación de varias sustancias químicas, entre ellas el fenol y la acetona. Se volatiliza fácilmente a la atmósfera a partir del agua y del suelo seco. Se supone que se adsorbe al suelo/sedimentos con una intensidad entre moderada y fuerte y que se biodegrada en el agua y en el suelo.

El cumeno se metaboliza fundamentalmente al alcohol secundario 2-fenil-2-propanol, tanto en el ser humano como en los animales. Los roedores y las personas excretan con facilidad este alcohol y sus conjugados.

Los efectos más notables observados en los roedores expuestos a dosis repetidas de cumeno por vía oral o por inhalación son un aumento del peso de los órganos, en particular de los riñones. No se detectaron efectos adversos en los fetos de rata o de conejo cuyas madres habían estado expuestas al cumeno durante el desarrollo fetal. Si bien no se han realizado estudios de reproducción multigeneracional con exposición al cumeno, la rapidez de su metabolismo y su excreción, junto con la falta de efectos en la morfología del esperma en un estudio subcrónico, parecen indicar un potencial

bajo de toxicidad reproductiva. Se ha obtenido un valor guía para la exposición oral de 0,1 mg/kg de peso corporal al día, basado en una concentración sin efectos adversos observados (NOAEL) de 154 mg/kg de peso corporal al día para el aumento del peso del riñón en ratas hembras en un estudio de administración oral de 6 a 7 meses de duración; la NOAEL se ajustó para un calendario de dosificación y se aplicó un factor de incertidumbre de 1 000. Con respecto a la exposición por inhalación, se obtuvieron valores guía para la población general de 0,4 mg/m<sup>3</sup> y 0,09 mg/m<sup>3</sup>, basados en otras NOAEL derivadas del mismo estudio de inhalación subcrónica; en este caso también se ajustaron las NOAEL para una exposición continua y se aplicó un factor de incertidumbre total de 1 000.

No hay datos disponibles para cuantificar la exposición humana al cumeno.

No es posible evaluar el potencial de carcinogenicidad del cumeno en el ser humano, debido a que no se han realizado estudios de larga duración con esta sustancia. La mayor parte de los datos obtenidos en pruebas genotóxicas son negativos.

Son insuficientes los datos, especialmente de información de la exposición medida, para poder realizar una evaluación cuantitativa del riesgo de la exposición al cumeno para las poblaciones de organismos acuáticos o terrestres. Sin embargo, teniendo en cuenta los datos existentes, se prevé para el cumeno un riesgo relativamente bajo. Los valores indican un ligero potencial de bioconcentración del cumeno en los peces. No hay datos acerca de la bioacumulación a través de la cadena alimentaria (bioamplificación).