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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

CUMENE

1. Exposure Data

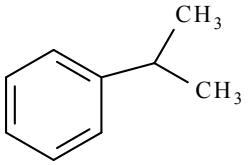
1.1 Chemical and physical data

From IPCS (1999), European Commission (2001), IPCS-CEC (2004), and HSDB (2005), unless otherwise specified

1.1.1 Nomenclature

Chem. Abstr. Services Reg. No.: 98-82-8
Chem. Abstr. Name: (1-Methylethyl) benzene;
Synonyms: Benzene, isopropyl; cumol; isopropylbenzene; isopropylbenzol; 2-phenylpropane; propane, 2-phenyl
RTECS No.: GR8575000
EINECS No.: 202-704-5
United Nations TDG: 1918

1.1.2 Structural and molecular formulae and relative molecular mass



C_9H_{12}
Relative molecular mass: 120.2

1.1.3 Chemical and physical properties of the pure substance

Description: Colourless liquid with a sharp, penetrating, aromatic odour
Boiling-point: 152 °C
Melting-point: -96 °C
Density: 0.86 g/cm^3 at 20 °C
Vapour pressure: 3.2 mm Hg at 20 °C; 4.6 mm Hg at 25 °C
Refractive index: 1.491 at 20 °C
Spectroscopy data: Infrared, ultraviolet, nuclear magnetic resonance and mass spectral data have been tabulated.
Solubility: Slightly soluble in water (50 mg/L at 25 °C); soluble in alcohol and many organic solvents
Flash-point: 31 °C; upper and lower explosive limit, 6.5% and 0.9%, respectively
Stability: Reacts violently with acids and strong oxidants, causing fire and explosions; can form explosive peroxides.
Octanol/water partition coefficient: log P_{ow}, 3.66 (Sangster Research Laboratories, 2006)
Vapour density (air = 1): 4.2
Auto-ignition temperature: 420 °C
Henry's law constant: 1.15 × 10^{-2} atm.m^3/mol at 25 °C
Oil/air partition coefficient: 6215
Water/air partition coefficient: 1.44
Human blood/air partition coefficient: 37
Conversion factor: 1 ppm = 5.2 mg/m^3; 1 mg/m^3 = 0.19 ppm (calculated from: mg/m^3 = (relative molecular

mass/24.45) × ppm, assuming a temperature of 25 °C and pressure of 101 kPa)

1.1.4 Technical products and impurities

No data were available to the Working Group.

1.1.5 Analysis

(a) Air

To measure cumene in air, Method 1501 of the US National Institute for Occupational Safety and Health (NIOSH) includes the use of a solid sorbent tube (coconut shell charcoal) sampler with gas chromatography/flame ionization detection, the detection limit of which is 0.6 µg/sample (NIOSH, 2003).

(b) Other media

Methods of the United States Environmental Protection Agency (EPA) for detecting cumene in media other than air include the use of gas chromatography with photo-ionization (Method 8021B), which is applicable to nearly all types of sample, regardless of the water content. The detection limit for cumene is 0.05 µg/L, and the applicable concentration range is approximately 0.1–200 µg/L. Another gas chromatographic assay commonly used for volatile compounds, including cumene, is EPA Method 8260B, which has a general estimated quantitation limit of approximately 5 µg/kg wet weight (wt) for soil/sediment samples, 0.5 mg/kg wet wt for wastes and 5 µg/L for groundwater (IPCS, 1999).

1.2 Production and use

1.2.1 Production

Cumene is manufactured from the distillation of coal tar and petroleum fractions, or is produced by the alkylation of benzene with propene using an acidic catalyst (European Commission, 2001).

Production volumes in the European Union (EU) ranged between 850 000 and 4 100 000 tonnes in 1992–93 (IUCLID, 2000; European Commission, 2001), and was 1 793 000 tonnes in 1985, distributed between seven countries and eight companies (IPCS, 1999; European Commission, 2001).

Production in the United States of America in 1977 was 1 200 000 tonnes, and rose to 1 800 000 tonnes in 1987 (HSDB, 2005). In 1998, 12 companies produced cumene in the USA (HSDB, 2005), and, in 2010, 50 producers were reported worldwide: eight in the People's Republic of China, 12 in East Asia, two in India, 18 in Europe, two in South and Central America and nine in the USA (Chemical Economics Handbook, 2010).

1.2.2 Use

Cumene is used primarily (95%) as an intermediate in the production of phenol and acetone. Other uses include: the manufacture of styrene, α-methylstyrene, acetophenone, detergents and di-isopropylbenzene; as a catalyst for acrylic and polyester-type resins; as a thinner for paints, enamels and lacquers; as a solvent for fat and resins; and in printing and rubber manufacture. Minor amounts are used in gasoline blending and as a component of high-octane aviation fuel.

1.3 Occurrence

1.3.1 Natural occurrence

Cumene is a natural constituent of crude oil and occurs naturally in the environment in plants, marsh grasses and foodstuff (see Section 1.3.3; HSDB, 2005). Crude oil typically contains 0.1% wt cumene but may contain up to 1% wt. Concentrations of cumene in petrol range from 0.14 to 0.51% vol, with an average of 0.3% vol. Premium diesel fuel contains 0.86% wt cumene (IPCS, 1999).

Table 1.1 Sources of exposure to cumene

Source/location	Comment	Emission rate
Releases to air		
Production	Controlled	0.08 kg/tonne cumene
	Uncontrolled	0.27 kg/tonne cumene
Use		1.03 kg cumene/tonne phenol
Production and use	Overall release[a]	1.31 kg/tonne
Gasoline engine vehicles	Catalytic converter	0.0002–0.0009 g/km
	No catalytic converter	0.002 g/km
Photocopying machines	Emission rate	140–220 µg/h
Releases to water and soil		
Production and use	Wastewater	1.5 kg/tonne cumene
	Soil	0.02 kg/tonne cumene

[a] Includes release to the air from wastewater
h, hour or hours
From European Commission (2001), HSDB (2005)

1.3.2 Environmental occurrence

(a) Release/effluents

Cumene is released into the environment during its manufacture, use and transport. Another major source of pollution is its presence in crude oil and finished fuels; cumene is released from incomplete combustion of fossil fuels from vehicles, oils spills, transportation and distribution of fossils fuels, and evaporation from gasoline stations. Minor sources of release are from its use as a solvent, during paint manufacture and vulcanization of rubber, from building materials, jet engine exhaust and outboard motor operations, during pharmaceuticals production, from textile plants and from tobacco smoke (IPCS, 1999; HSDB, 2005).

Emission rates from various sources of cumene are provided in Table 1.1; releases rates of cumene in Europe and the USA are provided in Table 1.2. Reported yearly cumene emissions to the air from cumene production were 125 tonnes [417 kg per day] in 1993 and 75 tonnes [250 kg per day] in 1995. Using these values, it was estimated that, during its production and use in the EU, cumene is released into the air at a rate of 1.3 kg/tonne, resulting in a rate of 17 903 kg per day, into water at a rate of 1.5 kg/tonne, resulting in a rate of 20 500 kg per day, and into the soil at a rate of 0.02 kg/tonne resulting in rate of 33.3 kg per day. It was also estimated that 3211 kg of cumene per day are released into the air in the EU from gasoline distribution, and 20 298 kg per day are released from motor vehicles; the total estimated amount released into the air from production, process and disperse sources is 41 412 kg per day (European Commission, 2001).

It was estimated from modelling that, in Los Angeles, USA, 2 300 kg of cumene per day (for 2 days) were released into the air in 1987 (Harley & Cass, 1994).

(b) Ambient air

Levels of cumene measured in ambient air are reported in Table 1.3. The highest levels were found near industrial sites, such as an oil refinery (29.4–53.9 µg/m^3), followed by urban areas; the lowest levels were found in rural areas. In the USA, cumene was found at 14.7 µg/m^3 in urban areas and 2.5 µg/m^3 in rural areas. In general, ambient levels of cumene were lower in Europe and Asia than in the USA.

Table 1.2 Daily release rates of cumene

Geographic location	Source	Media	Emission rate (kg/day)	Reference
European Union	Total	Air	41 412	European Commission (2001)
Estimated values	Production and use	Air[a]	17 903	
		Water[b]	20 500	
		Soil[c]	273	
	Disperse sources	Air		
	Gasoline		3 211[d]	
	Motor exhaust		20 298[e]	
Reported values	Production only	Air		
	1993		[417][f]	
	1995		[250][f]	
Los Angeles, CA	All sources	Air	2 300	Harley & Cass (1994)
Measured 2 d 1987				
USA, estimated	Total	Air	[26 027][g]	US EPA (1988)

[a] Assumes maximum production of 500 000 tonnes at one site (41 000 000 tonnes/year for the entire European Union) and release factor of 1.31 kg/tonnes (see Table 1.1).
[b] Assumes maximum production of 500 000 tonnes at one site and release factor of 1.5 kg/tonne (See Table 1.1).
[c] Assumes maximum production of 500 000 tonnes at one site and release factor of 0.02 kg/tonne (See Table 1.1).
[d] Assumes 0.2% cumene from hydrocarbon loss, volatile organic compound (VOC) emission factor of 5 kg VOC/gasoline delivered and 117 205 000 tonnes/year of gasoline for the entire European Union.
[e] Assumes 0.2% of cumene in motor exhaust, emission of 617 400 tonnes VOC/year and population ratio of 6 in the entire European Union.
[f] Reported as 125 and 75 tonnes in 1993 and 1995, respectively.
[g] Reported as 9500 tonnes/year
d, day or days

Table 1.3 Environmental occurrence of cumene in ambient air

Country	Location/sample	Concentration (μg/m³)
Asia		
Nepal	Mount Everest	0.07
Taiwan, China	Urban area – heavy traffic	0.6–0.9
	Urban area – away from heavy traffic	0.5
Europe		
Belgium	Antwerp Craeybeckx tunnel (1991)	0.003–0.009 g/kg carbon-based pollutants
France	Grenoble area (1987)	1.6 (0.9–7.45)[a]
Germany	Urban area	6–9
	Hamburg – major road tunnel	3–3.8
Italy	Rome – urban area	1.1
	Milan – urban area	1.1–1.8
Netherlands	Urban area	0.3
	Rural area	0–5
	Delft	< 0.49–1.96
	Ambient air	0.49–34.79
	Rotterdam and Ede – near homes	0.3
Russian Federation	Leningrad – urban area (1977–79)	8.3 (0.98–11.76)[a]
Sweden	Near factory	4.5[a]
	Göteborg	0.6[a]
	Rural area	0.02[a]
United Kingdom	Urban air	1–20
	Gatwick airport	1.6–12
	Southampton estuary	0.6–410
Americas		
Brazil	Porte Alegre (1996–97)	900

Table 1.3 (continued)

Country	Location/sample	Concentration (μg/m³)
USA	Urban areas	14.7[a]
	Rural areas	2.5[a]
	Miami, FL – urban air	1.11–2.59
	Chicago, IL	0.59–1.1
	Boston, MA	0.1
	Lake Michigan (1976; 2 samples)	0.49
	Los Angeles, CA	
	1966, 136 samples	14.7[a], max 144
	8 samples	16.7 (2.45–36)[a]
	1981, 17 samples	ND–9.8
	Dear Park, TX – near Shell Oil Refinery	
	Downwind	29.4
	Upwind	53.9
	Houston, TX – urban and industrial areas (1973–74)	12.15 (ND–24.9)[a]
	Houston, TX (1986)	0.14–0.81
	Jones State Forest, near Houston, TX	2.5 (0.11–9.8)[a]
	Rio Blanco Country, CO	1.57
	Great Smoky Mountains, TN (9 samples)	0.25 (< 0.0–0.39)[a]

[a] Mean (range) or mean

max, maximum; ND, not detected

From IPCS (1999), European Commission (2001), HSDB (2005)

(c) Water and soil

Cumene that is released into water is predicted to adsorb to suspended solids and sediment. It is removed from water and water surfaces by volatilization (half-lives of 1.2 hours in a model river and 4.4 days in a model lake) and degradation by hydroxyl radicals (estimated half-life, 107 days) (HSDB, 2005). Cumene may also be removed by aerobic biodegradation. Results of studies on biodegradation have been mixed, with some reporting between 13 and 86% degradation after 28 days (European Commission, 2001). Studies of oil spills found that cumene disappeared within 90 minutes of the spill (HSDB, 2005). Cumene may also bioaccumulate, based on an octanol/water partition coefficient greater than 3. Estimates of its bioaccumulation factor range from 208 to 356 in fish species; a value of 36 has been measured in goldfish (IPCS, 1999; European Commission, 2001).

In soil, cumene is predicted to have low mobility based on its estimated soil absorption coefficient of 820. Similar to that from water, volatilization of cumene from moist soil (based on a Henry's Law constant of 0.0115 atm.m^3/mol) or dry soil (based on its vapour pressure of 4.5 mm Hg) may occur (HSDB, 2005).

Table 1.4 summarizes concentrations of cumene detected in water and soil. The highest levels in aquatic environments have been found near industrial sites and in industrial effluents, ranging up to 1581 µg/L in groundwater near underground storage tanks (Botta *et al.*, 1984). High levels were also found in contaminated soil, ranging up to 305 mg/kg for soils contaminated by garage spills. Cumene has been detected at much lower levels (usually less than 1 µg/L) in groundwater and surface waters not adjacent to industry or contaminated by fuel, in some samples of drinking-water and in snow.

1.3.3 Other occurrence

Cumene occurs in cigarette smoke and in food. Levels of cumene in condensates of cigarette smoke ranged from 7 to 14 µg/cigarette and an indoor air concentration of 2 ppb [10 µg/m^3] was reported after a single cigarette had been smoked (IPCS, 1999). The occurrence of cumene in food may result naturally or from environmental contamination. Cumene has been detected in fruits and vegetables (papaya, Sapodilla fruit, tomatoes and grapes), cooked meat (fried chicken, fried bacon and pork), cooked foods (cooked rice and baked potatoes), dairy products (cheese) and other foodstuff, including honey, dried legumes (beans, split peas and lentils), wine, southern pea seeds and plants, including curly parsley, marsh grasses and oakmoss (IPCS, 1999; HSDB, 2005).

1.4 Human exposure

Exposure to cumene may occur via the workplace, the environment, cigarette smoking and food. The major source of exposure for the general public is through inhalation of contaminated air. Little exposure occurs from consumer use of products that contain cumene.

1.4.1 Occupational exposure

Workers may be exposed to cumene during its production and use, or the use of products that contain cumene. The major route of potential occupational exposure to cumene is inhalation. Dermal exposure may occur but is predicted to be low (European Commission, 2001).

No current information was found on the number of individuals occupationally exposed to cumene. In 2001, approximately 110–200 cumene-manufacturing workers had potential exposure in the EU (European Commission, 2001); manufacturing workers exposed to cumene include shift operators, foremen, maintenance fitters, quality control personnel and

Table 1.4 Environmental levels of cumene in water and soil

Country	Industrial site	Location/sample type and size	Concentration (μg/L)
Groundwater or effluents near industrial sites			
Australia	Near dump site	Melbourne	Detected
Denmark	Contaminated with creosote and/or gasoline	Groundwater	
		Holte (3 samples)	2–22
		Fredericia (5 samples)	ND–3
Germany			0.5–5
Italy	Near underground storage tanks	Milan	Detected
Sweden		Wastewater – Göteborg	0.1–0.8
United Kingdom	Near gasoline storage tank	Groundwater – Great Ouse River basin	9.8 (0.01–30)[a]
	Contaminated Site	Solent estuary	0.01–47.3
		Groundwater	1–3
	Airfield	Groundwater	1–30
USA	Coal gasification sites	Groundwater – Hoe Creek, WV	35 (1–59)[a]
		Wyoming	19–54
	Petroleum plants and refineries		5
	Near offshore drilling platform, Gulf of Mexico	Sea water	140
	Around outboard motor operations		700
	Near chemical plants	Groundwater (3 sites)	11, 360, and1581
Groundwater – other			
USA		50 states and Puerto Rico	< 0.5
		Ames, IO	Detected
		New York State	Detected
Surface water			
Germany		River Rhine	0.028
		Lake Constance	0.006–0.028
Japan	Near potential emission sources	Surface water	0.09–0.44
Spain		River Gallego	< 0.001 ng/L

Table 1.4 (continued)

Country	Industrial site	Location/sample type and size	Concentration (µg/L)
United Kingdom		British North Sea	0.001–0.069
		River Lee (2 samples)	< 0.1, > 0.1
USA		Narraganset Bay, RI	Detected
		River Brazos, TX	0.006–0.017
Drinking-water			
Japan		Tap-water	Detected
USA		Terrebonne-Parish, LA	0.01
		9 other cities countrywide	ND
		Cincinnati, OH	0.014
		Drinking-water systems countrywide	< 0.5 mg/L[b]
		New York State	Detected
Snow			
Antarctica		1987/88	0.008
		1988/89	0.016
		1990/91	ND
Sediment			
Japan	Near potential emission source		0.6–11 µg/g
United Kingdom		Southampton	0.25–43.37 µg/g
USA		Strait of Juan de Fuka, Alaska	0.02–5.5 µg/g
		Puget Sound, Washington	2.3 (0.02–19)[a] µg/g
Soil			
Germany	Below building		24 mg/kg
Netherlands	Contaminated sites		0.012–0.02 mg/kg
	Garage oil spills		10–305 mg/kg

[a] Mean (range)
[b] Detection limit, 0.5 µg/L
ND, not detected
From IPCS (1999), European Commission (2001), HSDB (2005)

Table 1.5 Measured levels of occupational exposure to cumene

Process or work area	No. and type of samples	Concentration (ppm)
8-h TWA		
Manufacture – all job categories	7 European companies	0.1–0.65[a] (0.05–4.46)
Cumene producing plant – specific jobs: runner, filling station attendant, laboratory co-worker, chemical technology co-worker	Personal air samples	< 1
Manufacture – long-term exposure, 1991	40–50 samples	< 0.1
Offset printing works	17 person-related measurements	0.1–1.3
Printing signs using lacquering machines	2 person-related measurements	0.2
Maintenance printers – 23 different jobs	45 person-related measurements	0–0.81
Short-term (10–20 min or 20–30 min) exposure data		
Car repair work	8 person-related measurements	1.9–6.7
Rubber manufacturing process		
Shoe sole factory[b]	13	0.012–0.05
Tyre retreading[b]	6	0.0004–0.04
Tyre retreading[c]	6	0–0.002
Electrical cable insulation plant	10	ND
1 h duration of exposure – 90% value		
Production of paints	125	0.8
Surface treatment, manual (painting, paint rolling)	255	3.4
Surface treatment, manual (spraying)	300	1.01
Surface treatment, mechanical	84	0.8
Other monitoring data		
Cumene producers and processors	NR	
Distillation		0.45 (0.0001–3.35)
Oxidation		0.93 (0.0001–5.58)
Laboratory		0.39 (0.34–0.44)
Repair		1.33 (0.16–2.50)
Recovery		0.31 (0.001–1.20)
Cumene unit		0.19 (0.078–0.62)

Table 1.5 (continued)

Process or work area	No. and type of samples	Concentration (ppm)
Cumene-exposed workers, 1973–84	1457 air samples	
	6 samples	4–30
	4 samples	3–4
	25 samples	1–2
	Remainder	< 1
Exposure from solvents, United Kingdom		Up to 0.6
Gasoline delivery truck drivers		< 0.01–0.04

[a] Range of means
[b] Vulcanization area
[c] Extrusion area
h, hour or hours; min, minute or minutes; ND, not detected; NR, not reported; TWA, time-weighted average
From IPCS (1999), European Commission (2001), HSDB (2005)

Table 1.6 Cumene levels from non-occupational exposure

Workers	Cumene concentration (mean [range] in ng/L)		
	Environmental (8-h)	Alveolar	Blood
27 chemical workers	38.9 (1–279)	12 (1–81)	762 (43–3352)
33–40 hospital workers	9.6 (2–36)	4.7 (1–22)	176 (31–929)

h, hour or hours
From Brugnone *et al.* (1989)

others, such as delivery drivers. The National Occupational Exposure Survey, conducted in 1981–83, estimated that 14 268 workers, of whom 2760 were women, were potentially exposed to cumene in the USA. The major occupations were janitors and cleaners, maids and housemen, machine operators, including laundering, dry cleaning and unspecified, and vehicle washers and equipment cleaners (NIOSH, 1990). An industrial survey by the EPA reported that approximately 739 workers were occupationally exposed to cumene in the USA (US EPA, 1988). [The Working Group noted the large discrepancy in numbers reported by the two sources.]

Cumene is typically produced using a closed system. The European Commission (2001) reported that one manufacturing company stated that contact with cumene is limited to work activities that involve the collection of samples for analysis, loading tanks, and cleaning and maintenance. Table 1.5 lists exposure levels reported in the cumene-manufacturing industry and industries that use cumene. The mean 8-hour time-weighted average levels for seven cumene-manufacturing companies in the EU ranged from 0.1 to 0.65 ppm for all activities (range of data, 0.05–4.46 ppm). The Workplace Exposure Model predicts that inhalation exposure from the use of a closed system would be in the range of 0–0.1 ppm. It also predicts that dermal exposure for all activities would be 0–0.1 mg/cm^2 per day.

According to the European Commission (2001), the manufacture of phenol and acetone at cumene production sites is also carried out in closed systems; thus, the EU assumed that exposure levels for this industry would be similar to those observed for cumene-manufacturing. In general, exposure levels for most other uses of cumene (such as printing and rubber manufacture) were less than 1.5 ppm, although somewhat higher levels were found for short-term exposure among workers involved in car repairs (see Table 1.5). Exposure levels were less than 1 ppm in nearly all 1487 air samples evaluated in an industrial survey of cumene-exposed workers by the EPA (US EPA, 1988).

Table 1.7 Estimated human daily intake of cumene

Source	Regional intake (mg/kg bw per day)
Air	1.43×10^{-5}
Drinking-water	4.87×10^{-9}
Fish	9.8×10^{-8}
Leaf crops	7.9×10^{-8}
Root crops	3.24×10^{-8}
Meat	3.23×10^{-9}
Milk	1.91×10^{-9}
Total	1.45×10^{-5}

From European Commission (2001)

Table 1.8 Regulations and guidelines concerning occupational exposure to cumene

	TWA – 8 h		Short-term – 10 minutes		Note
	ppm	mg/m³	ppm	mg/m³	
Australia	25	125	75	375	
Austria	20	100	50	250	
Belgium	20	100	50	250	
Canada – Ontario	50				
Canada – Québec	50	246			
Denmark	20	100	40	200	
European Union[a]	20	100	50	250	
France[b]	20	100	50	250	
Germany (AGS)	20	100	50[c]	250[c]	
Germany (DFG)	50	250	200[c]	1000[c]	
Hungary		100		250	sk
Italy	20	100	50	250	sk
Netherlands	20	100	50	250	
New Zealand	25	125	75	375	
Poland		100		250	
Singapore	50	246			
Spain	20	100	50	250	
Sweden	25	120	35	170	
Switzerland	50	245	200	980	
USA – NIOSH					
TLV	50	245			
REL	50	245			
IDLH			900 (30 min)		
TWA	50				
USA – OSHA	50	245			
USA – ACGIH	50	245			
United Kingdom	25	120	75	375	

[a] Indicative occupational exposure limit values and limit values for occupational exposure
[b] Restrictive statutory limit values
[c] 15-minute average value
ACGIH, American Conference of Governmental Industrial Hygienists; AGS, Ausschuss für Gefahrstoffe; DFG, Deutsche Forschungsgemeinschaft; h, hour or hours; IDLH, immediately dangerous to life or health; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; REL, recommended exposure limit; sk, skin; TLV, threshold limit value; TWA, time-weighted average
From ACGIH (2010) and GESTIS (2011)

Table 1.9 Acute exposure guideline levels for cumene in the USA

	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	50	50	50	50	50
AEGL-2	550	380	300	190	130
AEGL-3	1300	920	730	460	300

AEGL, acute exposure guideline levels
From US EPA (2007)

1.4.2 Environmental exposure

Brugnone *et al.* (1989) measured non-occupational exposure to cumene in the breath (alveolar) and blood from workers at a benzene chemical plant (no direct exposure to cumene) and at a hospital infirmary (Table 1.6). Environmental exposure to cumene was also measured in air (8-hour work shift) at the workplace. Mean levels of exposure to cumene for all three exposure metrics was higher in 27 chemical workers than in 33–40 hospital workers, and significantly so for blood levels. Alveolar levels correlated with environmental levels at both workplaces, and blood levels correlated with environmental levels and alveolar levels in chemical workers.

1.4.3 Estimated human intake

The European Commission (2001) developed a model to predict total human intake from various sources of environmental exposure. The regional environment represents a highly industrial area (200 km × 200 km with 20 million inhabitants). Inhalation of air accounted for 97% of intake. Other sources of exposure were various food items and, to a lesser degree, drinking-water (see Table 1.7). The concentration of cumene in food was predicted from its concentration in air, water and soil and its bioaccumulation. A total daily intake of cumene of 1.45×10^{-5} mg/kg bw per day was estimated.

1.5 Regulations and guidelines

Some country-specific regulatory guidelines that are presented in Table 1.8 and Table 1.9, give more detailed guidelines for short-term exposures.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

Carcinogenicity studies of inhalation exposure of mice and rats to cumene and one of its metabolites been conducted (NTP, 2007, 2009), the results of which are summarized in Table 3.1.

3.1 Inhalation exposure

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed by whole-body inhalation to 0, 125 (females only), 250, 500 or 1000 (males only) ppm cumene (> 99% pure) for 6 hours plus T_{90} (the time taken to reach 90% of the target concentration within the exposure chamber; 12 minutes) per day on 5 days per week for 105 weeks. Dose-related increases in the incidence of alveolar/bronchiolar adenoma and carcinoma were observed in both males and females. Treatment-related increases in the incidence of

Table 3.1 Carcinogenicity studies of inhalation exposure of experimental animals to cumene and α-methylstyrene

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Incidence (%) and/or multiplicity of tumours	Significance (poly-3 test)	Comments
Cumene				
Mouse, B6C3F$_1$ (M) 105 wk NTP (2009)	0, 250, 500 or 1 000 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Lung (alveolar/bronchiolar adenoma): 13/50 (26%), 31/50 (62%), 31/50 (62%), 29/50 (58%) Lung (alveolar/bronchiolar carcinoma): 9/50 (18%), 19/50 (38%), 32/50 (64%), 33/50 (66%)	$P < 0.001$ (all doses) $P < 0.001$ (trend) $P < 0.001$ (high dose) $P < 0.001$ (mid dose) $P = 0.014$ (low dose) $P < 0.001$ (trend)	99.9% pure Survival: 38/50, 34/50, 30/50, 23/50* Thyroid gland (follicular-cell hyperplasia): 7/50 (1.9)[j], 7/50 (2.4), 7/49 (1.7), 11/50 (1.9)
		Lung (alveolar/bronchiolar adenoma or carcinoma): 19/50 (38%), 38/50 (76%), 42/50 (84%), 43/50 (86%)	$P < 0.001$ (all doses) $P < 0.001$ (trend)	
		Spleen (haemangiosarcoma[a]): 0/50, 0/50, 0/49, 4/50 (8%)	$P = 0.045$ (high dose)	
		All organs (haemangiosarcoma[b]): 0/50, 1/50 (2%), 2/50 (4%), 4/50 (8%)	$P = 0.002$ (trend)	
		Thyroid gland (follicular-cell adenoma[c]): 0/50, 0/50, 0/49, 3/50 (6%)	$P = 0.01$ (trend)	
Mouse, B6C3F$_1$ (F) 105 wk NTP (2009)	0, 125, 250 or 500 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Lung (alveolar/bronchiolar adenoma): 1/50 (2%), 26/50 (52%), 36/50 (72%), 38/50 (76%)	$P < 0.001$ (all doses) $P < 0.001$ (trend)	99.9% pure Survival: 37/50, 36/50, 39/50, 35/50
		Lung (alveolar/bronchiolar carcinoma): 3/50 (6%), 16/50 (32%), 20/50 (40%), 34/50 (68%)	$P < 0.001$ (all doses) $P < 0.001$ (trend)	
		Lung (alveolar/bronchiolar adenoma or carcinoma): 4/50 (8%), 31/50 (62%), 42/50 (84%), 46/50 (92%)	$P < 0.001$ (all doses) $P < 0.001$ (trend)	
		Liver (hepatocellular adenoma): 18/50 (36%), 23/50 (46%), 27/50 (34%), 29/50 (58%) Liver (hepatocellular carcinoma): 10/50 (20%), 7/50 (14%), 6/50 (12%), 12/50 (24%)	$P = 0.046$ (high dose) $P = 0.04$ (trend)	
		Liver (hepatocellular adenoma or carcinoma): 25/50, 26/50, 29/50, 36/50	$P = 0.043$ (high dose) $P = 0.024$ (trend)	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Incidence (%) and/or multiplicity of tumours	Significance (poly-3 test)	Comments
Rat, F344 (M) 105 wk NTP (2009)	0, 250, 500 or 1 000 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Nose (respiratory epithelial adenoma): 0/50, 7/50 (14%), 18/49 (37%), 10/50 (20%) Kidney (renal tubule adenoma): 1/50 (2%), 4/50 (8%), 5/50 (10%), 4/50 (8%) Kidney (renal tubule carcinoma): 1/50 (2%), 1/50 (2%), 3/50 (6%), 3/50 (6%) Kidney (renal tubule adenoma or carcinoma[d]): 2/50 (4%), 5/50 (10%), 8/50 (16%), 7/50 (14%) Testis (interstitial-cell adenoma): 36/50 (72%), 38/50 (76%), 40/50 (80%), 46/50 (92%)	$P < 0.001$ (high dose) $P < 0.001$ (mid dose) $P = 0.006$ (low dose) $P = 0.004$ (trend) $P = 0.044$ (mid dose) $P = 0.007$ (high dose) $P = 0.006$ (trend)	99.9% pure Survival: 26/50, 23/50, 27/50, 24/50 Nose (olfactory epithelial basal-cell hyperplasia): 0/50, 19/50** (1.1), 27/49** (1.1), 26/50** (1.0) Nose (respiratory epithelial hyperplasia): 0/50, 15/50** (2.0), 16/49** (2.9), 23/50** (2.7) Kidney (renal tubule hyperplasia): 0/50, 3/50 (3.3), 8/50** (2.6), 6/50* (2.2) Kidney (papilla mineralization): 5/50 (1.0), 35/50** (1.7), 44/50** (2.1), 41/50** (2.1) Kidney (pelvic transitional epithelial hyperplasia): 3/50 (1.7), 5/50 (1.8), 14/50** (2.4), 15/50** (2.0) Kidney (nephropathy): 47 (2.3), 47 (2.6), 47 (2.9), 50 (2.7)
Rat, F344 (F) 105 wk NTP (2009)	0, 250, 500 or 1 000 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Nose (respiratory epithelial adenoma[e]): 0/50, 5/48 (10%), 4/50 (8%), 3/50 (6%)	$P = 0.03$ (low dose)	99.9% pure Survival: 21/50, 27/50, 31/50, 32/50 Nose (olfactory epithelial basal-cell hyperplasia): 0/50, 14/48** (1.0), 25/50** (1.0), 31/50** (1.1) Nose (respiratory epithelial hyperplasia): 0/50, 0/48, 4/50 (3.0), 6/50* (2.3)

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Incidence (%) and/or multiplicity of tumours	Significance (poly-3 test)	Comments
α-Methylstyrene				
Mouse, B6C3F$_1$ (M) 105 wk NTP (2007)	0, 100, 300 or 600 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Liver (hepatocellular adenoma or carcinoma): 28/50 (56%), 36/50 (72%), 33/50 (66%), 37/50 (74%) Liver (hepatocellular adenoma): 24/50 (48%), 27/50 (54%), 27/50 (54%), 25/50 (50%) Liver (hepatocellular carcinoma): 10/50 (20%), 12/50 (24%), 11/50 (22%), 17/50 (34%)		99.5% pure Survival: 35/50, 32/50, 40/50, 36/50
Mouse, B6C3F$_1$ (F) 105 wk NTP (2007)	0, 100, 300 or 600 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Liver (hepatocellular adenoma): 10/50 (20%), 20/50 (40%), 21/50 (42%), 23/50 (46%) Liver (hepatocellular carcinoma): 3/50 (6%), 9/50 (18%), 6/50 (12%), 18/50 (36%) Liver (hepatocellular adenoma or carcinoma): 13/50 (26%), 26/50 (52%), 24/50 (48%), 33/50 (66%)	$P = 0.005$ (high dose) $P = 0.007$ (mid dose) $P = 0.018$ (low dose) $P = 0.014$ (trend) $P < 0.001$ (high dose) $P < 0.001$ (trend) $P < 0.001$ (high dose) $P = 0.012$ (mid dose) $P = 0.004$ (low dose) $P < 0.001$ (trend)	99.5% pure Survival: 39/50, 38/50, 37/50, 37/50
Rat, F344 (M) 105 wk NTP (2007)	0, 100, 300 or 1 000 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	Kidney (renal tubule adenoma[f, g]): 1/50 (2%), 2/50 (4%), 2/50 (4%), 5/50 (10%) Kidney (renal tubule adenoma or carcinoma[h]): 1/50 (2%), 2/50 (4%), 3/50 (6%), 7/50 (14%) *Single sections only* Kidney (renal tubule carcinoma): 0/50, 0/50, 1/50 (2%), 2/50 (4%) Kidney (renal tubule adenoma or carcinoma): 0/50, 0/50, 2/50 (4%), 2/50 (4%) *Step section evaluation alone (3–4 sections per kidney)* No additional renal tubule carcinomas were identified Haematopoietic (mononuclear-cell leukaemia[i]): 26/50 (52%), 32/50 (64%), 29/50 (58%), 38/50 (76%)	$P = 0.026$ (high dose) $P = 0.006$ (trend) $P = 0.016$ (high dose) $P = 0.018$ (trend)	99.5% pure Survival: 27/50, 32/50, 23/50, 22/50 Kidney (papillary mineralization): 12/50 (1.1), 16/50 (1.0), 10/50 (1.0), 33/50** (1.4) Kidney (nephropathy): 41/50 (2.2), 46/50 (2.3), 46/50 (2.4), 45/50 (2.4) Kidney (renal tubule hyperplasia[k]): 1/50 (1.0), 0/50, 1/50 (1.0), 4/50 (2.3)

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Incidence (%) and/or multiplicity of tumours	Significance (poly-3 test)	Comments
Rat, F344 (F) 105 wk NTP (2007)	0, 100, 300 or 1 000 ppm 6 h plus T_{90} (12 min)/d, 5 d/wk 50 animals/group	No significant results		99.5% pure Survival: 27/50, 24/50, 36/50, 26/50

* Significantly different ($P \leq 0.05$) from the chamber control group by the poly-3 test

** $P \leq 0.01$

[a] Historical incidence in male B6C3F$_1$ mice in 2-year inhalation studies using chamber controls (mean ± standard deviation): 6/444 (1.4% ± 1.5%), range 0–4%; all routes: 24/1483 (1.7% ± 1.2%), range 0–4%

[b] Historical incidence in male B6C3F$_1$ mice in 2-year inhalation studies using chamber controls (mean ± standard deviation): 21/450 (4.7% ± 3.7%), range 0–12%; all routes: 76/1499 (5.2% ± 3.2%), range 0–12%

[c] Historical incidence in male B6C3F$_1$ mice for 2-year inhalation studies using chamber controls (mean ± standard deviation): 5/441 (1.1% ± 2.0%), range 0–6%; all routes: 21/1483 (1.4% ± 1.8%), range 0–6%

[d] Historical incidence in male F344/N rats in 2-year inhalation studies using chamber controls (mean ± standard deviation): kidney (renal tubule adenoma or carcinoma): 6/449 (1.3% ± 1.4%), range 0–4%; all routes: 10/1436 (0.7% ± 1.0%), range 0–4%; kidney (renal tubule adenoma): 4/449 (0.9% ± 1.0%), range 0–2%; all routes: 8/1436 (0.6% ± 0.8%), range 0–2%; kidney (renal tubule carcinoma): 2/449 (0.4% ± 0.9%), range 0–2%; all routes: 2/1436 (0.1% ± 0.5%), range 0–2%

[e] Historical incidence in female F344/N rats in 2-year inhalation studies using chamber controls: 0/496; all routes: 0/1343

[f] This incidence is based on the combined single section and step section evaluations. Single sections alone – renal tubule adenoma: 0/50, 0/50, 1/50, 0/50; step section evaluation alone (3–4 sections per kidney) – renal tubule adenoma: 1/50, 2/50, 1/50, 5/50 ($P = 0.033$ for trend).

[g] Historical incidence in male F344/N rats in 2-year inhalation studies using chamber controls for single section evaluations (mean ± standard deviation): kidney (renal tubule adenoma): 3/399 (0.8% ± 1.0%), range 0–2%

[h] Historical incidence in male F344/N rats in 2-year inhalation studies using chamber controls for single section evaluations (mean ± standard deviation): kidney (renal tubule carcinoma): 1/399 (0.3% ± 0.7%), range 0–2%; kidney (renal tubule adenoma or carcinoma): 4/399 (1.0% ± 1.1%), range 0–2%

[i] Historical incidence in male F344/N rats in 2-year inhalation studies with chamber control groups (mean ± standard deviation): 188/399 (47.1% ± 10.3%); range 32–66%

d, days or days; min, minute or minutes; N/A, not applicable; wk, week or weeks

[j] Numbers in parentheses indicate average grade of severity of the lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

[k] This incidence is based on the combined single and step section evaluations. In the single section evaluation, no renal tubular hyperplasia was identified (all such lesions were diagnosed in the step section evaluation).

haemangiosarcoma of the spleen in male mice and of hepatocellular adenoma of the liver in female mice also occurred (NTP, 2009).

3.1.2 Rat

Groups of 50 male and 50 female F344 rats were exposed to 0, 250, 500 or 1000 ppm cumene (> 99% pure) for 6 hours plus T_{90} (12 minutes) per day on 5 days per week for 105 weeks. Treatment-related increases were observed in the incidence of nasal tumours (respiratory epithelial adenoma) in both males and females, and kidney tumours (renal tubule adenoma or carcinoma) in males, with a dose-related increase in the incidende of nasal tumours in males, with a concurrent increase in renal tubule hyperplasia and papillary mineralization in males, which had a linear pattern. Furthermore, in a subchronic study in rats with five exposure groups (62.5, 125, 250, 500 or 1000 ppm), dose-related increases in the severity of proximal tubular hyaline droplet accumulation and regeneration occurred, together with increases in the incidence of medullary granular casts and in the levels of α2u-globulin in males. Moreover, males had a treatment-related increase in the incidence of testicular tumours (interstitial-cell adenoma) (NTP, 2009).

[Tumours of the nasal cavity and kidney and splenic haemangiosarcomas are rare spontaneous neoplasms in experimental animals.]

3.2 Carcinogenicity of metabolites

3.2.1 α-Methylstyrene

α-Methylstyrene, a major metabolite of cumene, has been identified, together with its derivatives, in the exhaled air and urine of rats and mice exposed to cumene (Chen *et al.*, 2011).

(a) Mouse

Groups of 50 male and 50 female $B6C3F_1$ mice, 6 weeks of age, were exposed by whole-body inhalation to 0, 100, 300 or 600 ppm α-methylstyrene (99.5% pure) for 6 hours plus T_{90} (12 minutes) per day on 5 days per week for 105 weeks. Treatment-related increases in the incidence of hepatocellular adenoma or carcinoma (combined) in both males and females and of hepatocellular adenomas and carcinomas (separately) in females were observed (NTP, 2007).

(b) Rat

Groups of 50 male and 50 female F344/N rats, 6 weeks of age, were exposed by whole-body inhalation to 0, 100, 300 or 1000 ppm α-methylstyrene (99.5% pure) for 6 hours plus T_{90} (12 minutes) per day on 5 days per week for 105 weeks. Dose-related increases in the incidence of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) were observed in males (NTP, 2007).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

Following oral or intravenous administration of radiolabelled cumene ([^{14}C]isopropylbenzene) to rats and mice, 16 metabolites were identified in the expired air, urine, bile and microsomes; 2-phenyl-2-propanol glucuronide was the major urinary metabolite (Chen *et al.*, 2011). The volatile organic compounds in the expired air comprised mainly cumene and up to 4% α-methylstyrene. There were some marked parallels between the

sex, species and organs in which maximum levels of radiolabel were observed (Chen *et al.*, 2011) and those in which carcinogenic effects were observed (NTP, 2009). For example, the highest levels of radiolabel in rats were found in the adipose tissue, liver and kidney; and male, but not female, rats developed kidney tubule adenomas. In mice, the highest concentrations of radiolabel were found in the liver, kidney and lung 24 hours after a single administration; after repeated dosing, radiolabel was found in the same tissues as well as in the blood, brain, heart, muscle and spleen. Cumene-treated mice had an increased incidence of tumours in the lung, spleen and liver.

A proposed metabolic pathway of cumene (Chen *et al.*, 2011) is the formation of α-methylstyrene (Morgan *et al.*, 1999) and its conversion by cytochrome P450 (CYP) to α-methylstyrene oxide, which can then be either conjugated to glutathione by glutathione *S*-transferase or converted to a glycol by epoxide hydrolase. Cumene was converted to α-methylstyrene more efficiently by mouse than by rat lung microsomes *in vitro*, which may account for the excess of radiolabelled compound found in mouse lung following multiple doses of cumene (Chen *et al.*, 2011). Also, Morgan *et al.* (1999) showed that α-methylstyrene was more lethal to female mice than to male mice or male and female rats; however, no enzymatic studies were performed (Morgan *et al.*, 1999) to clarify the metabolic pathways. Collectively, these data suggest that cumene is metabolized differentially in mice and rats, resulting in potentially higher levels of α-methylstyrene, and possibly α-methylstyrene oxide, in the lungs of mice than in those of rats.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

(a) Mutations

Cumene itself was generally not mutagenic; however, some mutagenic metabolites were identified, including α-methylstyrene oxide (Chen *et al.*, 2011), which is mutagenic in *Salmonella* (Rosman *et al.*, 1986).

Cumene was not mutagenic in the *Salmonella* mutagenicity assay in a variety of strains in the presence or absence of metabolic activation (Florin *et al.*, 1980; NTP, 2009). A summary of several unpublished reports noted that cumene was not mutagenic in *Salmonella*, yeast or Chinese hamster ovary cells (hypoxanthine (guanosine) phosphoribosyltransferase assay) in the presence or absence of metabolic activation, and gave negative or equivocal results for the induction of unscheduled DNA synthesis in rat primary hepatocytes or cell transformation in BALB/3T3 cells (US EPA, 1997).

(b) Chromosomal effects

Intraperitoneal injection (up to 1 g/kg body weight) of cumene induced small, but significant, increases in micronuclei in the bone marrow of male F344 rats in two independent trials; however, cumene did not induce micronuclei in erythrocytes in the peripheral blood of male or female B6C3F$_1$ mice exposed by inhalation to up to 1000 ppm for 6 hours per day on 5 days per week for 3 months (NTP, 2009).

(c) Alterations in oncogenes and suppressor genes in tumours

Analysis of mutations in the cumene-induced lung tumours in mice from the NTP (2009) study found that 87% had K-*ras* mutations, predominantly G to T transversions in exon 1 codon 12 and A to G transitions in exon 2 codon 61. Mutations in *Tp53* were found in 52% of the cumene-induced tumours, and were predominantly G to A transitions in exon 5 codon 155 and C to T transitions in exon 5 codon 133; 56%

of the cumene-induced tumours overexpressed p53 protein. Loss of heterozygosity was found on chromosome 4 near the *p16* gene in 13%, and on chromosome 6 near the K-*ras* gene in 12%. In contrast, among spontaneous tumours, none had *Tp53* mutations, only 14% had K-*ras* mutations and none had loss of heterozygosity (Hong *et al.*, 2008). Based on previous studies (reviewed in Hoenerhoff *et al.*, 2009), the authors suggested that this pattern of mutations indicated that DNA damage and genomic instability probably contribute to cumene-induced lung cancer in mice (Hong *et al.*, 2008). No additional mutational analyses were performed.

Analysis of changes in global gene expression showed that the lung tumours could be separated into groups with regard to K-*ras* mutations (with or without), but not based on *Tp53* mutations (Wakamatsu *et al.*, 2008). Expression of genes associated with the extracellular signal-regulated kinase-mitogen activated protein kinase signalling pathway was altered in tumours with K-*ras* mutations compared with those with no such mutations or normal lung tissue. Also, cumene-induced tumours with K-*ras* mutations had greater malignant potential than those without. The authors concluded that most cumene-induced mouse lung tumours contained K-*ras* mutations that probably resulted in increased extracellular signal-regulated kinase-mitogen activated protein kinase signalling and modification of histones (Wakamatsu *et al.*, 2008). No additional gene expression analyses were performed.

4.3 Mechanistic data

4.3.1 Effect on cell physiology

Cumene induced renal tubule adenomas, which might involve an α2u-globulin mechanism, in male rats. However, one of the mutagenic metabolites of cumene, α-methylstyrene oxide, could play a role in the initiation of such tumours. In a subchronic study in rats, dose-related increases in proximal tubular hyaline droplet accumulation and the levels of α2u-globulin were observed in males (NTP 2009). Exposure to α-methylstyrene also resulted in increased accumulation of hyaline droplets in the renal tubules of male rats (Morgan *et al.*, 1999). Hyaline droplets, which contain α2u-globulin, can lead to granular casts and single-cell necrosis, increased cell division and tubule hyperplasia, and finally renal tubule adenoma and carcinoma (Rodgers & Baetcke, 1993).

The development of kidney tumours in male rats in association with chemically induced α2u-globulin nephropathy is one mechanism that is not considered to be a predictor of carcinogenic risk to humans by the IARC or the EPA (US EPA, 1991; Swenberg & Lehman-McKeeman, 1999). The lack of relevance of the α-2u-globulin mechanism for the evaluation of carcinogenic risk is based on the absence of the production of an analogous protein in humans. Strict scientific criteria have been outlined to establish the role of α2u-globulin-associated nephropathy in male rat renal carcinogenesis (Swenberg & Lehman-McKeeman, 1999; see also Section 4.4 of the *Monograph* on Methyl isobutyl ketone in this Volume). Because these criteria are not met, the data do not support a mechanism that involves α2u-globulin-associated nephropathy in the development of these kidney tumours.

4.3.2 Structure–activity relationships

The two main tumour types induced by cumene are nasal adenomas in rats and lung tumours in mice. The genes that are mutated and have altered expression in cumene-induced mouse lung tumours are similar to those that are mutated and have altered expression in tumours induced in rodents by other related compounds, as well as to those found in human lung tumours (Hong *et al.*, 2008; Wakamatsu *et al.*, 2008; Hoenerhoff *et al.*, 2009).

Cruzan *et al.* (2009) compared the metabolism of cumene and some structurally related compounds (coumarin, naphthalene, styrene and ethylbenzene) that produce a similar tumour profile, i.e. bronchiolar/alveolar lung tumours in mice and nasal tumours in rats. They concluded that metabolism of the compounds in the Clara cells of mouse lung by CYP2F2 and in the nasal tissues of rats by CYP2F4 results in the production of cytotoxic metabolites that produce the respective tumours. Rat lung, human lung and human nasal turbinates also have the orthologous isozymes (CYP2F4 in rats and CYP2F1 in humans) that allow them to produce the necessary cytotoxic and mutagenic metabolites. These enzymes are polymorphic in humans. A detailed modelling of CYP2F substrates among various species was performed (Lewis *et al.*, 2009) that showed that the CYP2F subfamily of enzymes exists in a variety of species; however, differences exist between humans and rodents in the activities of this enzyme subfamily. Although Cruzan *et al.* (2009) argue for a cytotoxicity-driven model, consistent with the lack of mutagenicity of cumene itself, a mutagenic metabolite of cumene, α-methylstyrene oxide, could provide the basis for a genotoxicity-driven model both in rodents and humans — especially because the necessary enzymes are present in humans.

4.4 Mechanisms of carcinogenesis

At least one mutagenic metabolite of cumene, α-methylstyrene oxide, has been found in rats and mice. Moreover, mouse lung tumours had an elevated frequency of mutations in K-*ras* and *Tp53*, and exhibited a variety of changes in gene expression that involve pathways that are well known in both murine and human carcinogenesis. Comparisons among a group of compounds that are related structurally to cumene showed that the enzymes that probably produce mutagenic/carcinogenic metabolites in rodent lung and nose are also present in humans. Thus, a mutational mechanism is possibly the means by which cumene could produce lung or nasal tumours in both rodents and humans. The data do not support a mechanism that involves α2u-globulin in the development of tumours of the kidney.

5. Summary of Data Reported

5.1 Exposure data

Cumene is produced from the distillation of coal tar and petroleum fractions or by the alkylation of benzene with propene using an acidic catalyst. It is used almost exclusively to produce phenol and acetone. Cumene occurs naturally in crude oil, and is found in the environment in plants and foodstuff.

Cumene is primarily released into the environment during its production and use, and from emissions from gasoline engines. It can also be released during the transportation and distribution of fossil fuels or accidental spills of fuel. Cumene has also been detected in cigarette smoke. The major source of exposure of the general public is through inhalation of contaminated air. Occupational exposure, primarily via inhalation, occurs during its production and use, or the use of products that contain cumene. Cumene is typically produced under closed conditions and most reported levels of occupational exposure are low.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Exposure of male and female mice and rats to cumene by whole-body inhalation increased the incidence of tumours of the respiratory tract in

rats (nasal adenoma in males and females) and mice (alveolar/bronchiolar adenoma and carcinoma in males and females), of the kidney (renal tubule adenoma and carcinoma) in male rats, of the spleen (haemangiosarcoma) in male mice and of the liver (hepatocellular adenoma) in female mice. Exposure by inhalation to α-methylstyrene, a probable major metabolite of cumene, resulted in an increased incidence of hepatocellular adenoma or carcinoma (combined) in male mice, hepatocellular adenoma, carcinoma and adenoma or carcinoma (combined) in female mice and renal tubule adenoma or carcinoma (combined) in male rats.

5.4 Other relevant data

No data on the toxicokinetics of cumene in humans were available. In rats and mice exposed to radiolabelled cumene, more than a dozen metabolites are formed; 2-phenyl-2-propanol glucuronide is the major urinary metabolite.

Cumene itself is generally not mutagenic, but its metabolite, α-methylstyrene oxide, is mutagenic in bacteria. Intraperitoneal injection of cumene induced micronuclei in the bone marrow of male rats, but no micronuclei were observed in erythrocytes in the peripheral blood of mice exposed by inhalation.

At least one mutagenic metabolite of cumene, α-methylstyrene oxide, has been found in rats and mice. The mouse lung tumours induced by cumene had an elevated frequency of mutations in K-*ras* and *p53*, and showed a variety of changes in the expression of genes that are involved in the pathways of carcinogenesis in mice and humans. The enzymes that produce α-methylstyrene oxide in rodents are also present in humans. Thus, there is moderate evidence that a mutational mechanism underlies the development of cumene-induced lung or nasal tumours in rodents and possibly in humans.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of cumene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of α-methylstyrene.

6.3 Overall evaluation

Cumene is *possibly carcinogenic to humans (Group 2B)*.

α-Methylstyrene is *possibly carcinogenic to humans (Group 2B)*.

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