NAPHTHALENE

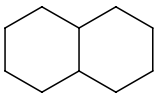
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 91-20-3
Chem. Abstr. Name: Naphthalene
IUPAC Systematic Name: Naphthalene
Synonyms: Naphthalin; naphthene; tar camphor; white tar

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{10}H_8$ Relative molecular mass: 128.17

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White monoclinic prismatic plates (Lide & Milne, 1996; O'Neil *et al.*, 2001)
(*b*) *Boiling-point*: 217.9 °C, sublimes (Lide & Milne, 1996; Verschueren, 1996)
(*c*) *Melting-point*: 80.2 °C (Lide & Milne, 1996)
(*d*) *Density*: d_4^{20} 1.162 (O'Neil *et al.*, 2001)
(*e*) *Spectroscopy data*: Infrared (prism [865]; grating [169]), ultraviolet [265], nuclear magnetic resonance (proton [62]; ^{13}C [139]) and mass spectral data have been reported[1] (Sadtler Research Laboratories, 1980; Lide & Milne, 1996)
(*f*) *Solubility*: Slightly soluble in water (31–34 mg/L at 25 °C; Verschueren, 2001); soluble in ethanol and methanol; very soluble in acetone, benzene, carbon

[1] The numbers in brackets are referenced in Sadtler Research Laboratories (1980).

disulfide, carbon tetrachloride, chloroform and diethyl ether (Lide & Milne, 1996)

(*g*) *Volatility*: Vapour pressure, 0.011 kPa at 25 °C (Lide & Milne, 1996); relative vapour density (air = 1), 4.42 (Verschueren, 1996); flash-point, 88 °C (closed-cup) (O'Neil *et al.*, 2001)

(*h*) *Stability*: Volatilizes appreciably at room temperature; sublimes appreciably at temperatures above the melting-point (O'Neil *et al.*, 2001)

(*i*) *Octanol/water partition coefficient (P)*: log P, 3.30 (Sangster, 1989)

(*j*) *Conversion factor*[1]: $mg/m^3 = 5.24 \times ppm$

1.1.4 *Technical products and impurities*

Naphthalene is usually sold commercially according to its freezing or solidification point, because there is a correlation between the freezing-point and the naphthalene content of the product; the correlation depends on the type and relative amount of impurities that are present. Because the freezing point is changed appreciably by the presence of water, values and specifications are listed as dry, wet or as-received basis, using an appropriate method, e.g., ASTM D1493 (Mason, 1995).

Typical specifications are: for crude naphthalene-CRI, solidification point, 77.5 °C min; crude naphthalene-CRII, solidification point, 78.5 °C min.; crude naphthalene-CRIII, solidification point, 79.3 °C min; [sulfur, 0.5% max.; non-volatiles, 0.25% max.; and water content, 0.5% max.]. Typical specifications for highly refined naphthalene-RFII are: solidification point, 79.9 °C min.; refined naphthalene-RFI, solidification, 79.6 °C min; naphthalene content, 99.0% min.; [sulfur, 0.1% max.; and non-volatiles, 0.005% max.] (Recochem, 1995a,b).

The naphthalene content of the technical product is at least 95%. Virtually the sole impurity found in naphthalene obtained from coal tar is benzo[*b*]thiophene (thianaphthene). Methylindenes are essentially the only impurities found in naphthalene derived from petroleum (BUA, 1989).

Trade names for naphthalene include: Albocarbon; Dezodorator (National Toxicology Program, 2000).

1.1.5 *Analysis*

Gas–liquid chromatography is used extensively to determine the naphthalene content of mixtures. Naphthalene can be separated easily from thionaphthalene, the methyl- and dimethylnaphthalenes and other aromatics. Analysis of other impurities may require the use of high-resolution capillary columns (Mason, 1995). Selected methods for the analysis of naphthalene in various media are presented in Table 1.

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[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming a temperature of 25 °C and a pressure of 101 kPa

Table 1. Selected methods for analysis of naphthalene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Air	Adsorb (charcoal or Chromosorb W); desorb (carbon disulfide)	GC/FID	1–10 µg/sample; 4 µg/sample	Eller (1994) [Method 1501]; Occupational Safety and Health Administration (1990) [Method 35]
	Adsorb (solid sorbent); desorb (organic solvent)	HPLC/UV	0.6–13 µg/sample	Eller (1994) [Method 5506]
	Adsorb (solid sorbent); desorb (organic solvent)	GC/FID	0.3–0.5 µg/sample	Eller (1994) [Method 5515]
Drinking-, ground- and surface water	Purge (inert gas); trap (Chromosorb W); desorb into capillary GC column	GC/MS	0.04 µg/L	Environmental Protection Agency (1995a) [Method 524.2]
Drinking-water and raw source water	Purge (inert gas); trap (Chromosorb W); desorb into capillary GC column	GC/PID	0.01–0.05 µg/L	Environmental Protection Agency (1995b) [Method 502.2]
Drinking-water	Extract in liquid–solid extractor; elute with dichloromethane; dry; concentrate	HPLC/UV/FD	2.20 µg/L	Environmental Protection Agency (1990a) [Method 550.1]
Wastewater, municipal and industrial	Extract with dichloromethane; dry; concentrate	HPLC/UV or GC/FID	1.8 µg/L	Environmental Protection Agency (1996a,b, 1999a) [Methods 610, 8100 & 8310]
	Extract with dichloromethane; dry; concentrate	GC/MS	1.6 µg/L	Environmental Protection Agency (1999b) [Method 625]
	Add isotope-labelled analogue; extract with dichloromethane; dry over sodium sulfate; concentrate	GC/MS	10 µg/L	Environmental Protection Agency (1999c) [Method 1625B]

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Solid waste matrices[b]	Purge (inert gas); trap (Tenax or Chromosorb W); desorb into capillary GC column	GC/PID	0.06 µg/L	Environmental Protection Agency (1996c) [Method 8021B]
	Purge (inert gas); trap (suitable sorbent); thermal desorption *or* headspace sampling *or* direct injection	GC/MS	0. 04–0.1 µg/L	Environmental Protection Agency (1996d) [Method 8260B]
Air sampling media, water samples, solid waste matrices, soil samples	Liquid–liquid extraction *or* Soxhlet extraction *or* ultrasonic extraction *or* waste dilution *or* direct injection	GC/MS	10 µg/L (aqueous); 660 µg/kg (soil/ sediment) (EQL)[c]	Environmental Protection Agency (1996e) [Method 8270C]
Soils, sludges, solid wastes	Thermal extraction; concentrate; thermal desorption	GC/MS	0.01–0.5 mg/kg	Environmental Protection Agency (1996f) [Method 8275A]
Wastewater, soil, sediment, solid waste	Liquid–liquid extraction (water); Soxhlet or ultrasonic extraction (soil/sediment/waste)	GC/FT-IR	20 µg/L	Environmental Protection Agency (1996g) [Method 8410]

[a] Abbreviations: GC, gas chromatography; FID, flame ionization detection; FT-IR, Fourier transform infrared detection; MS, mass spectrometry; PID, photoionization detection; HPLC, high-performance liquid chromatography; UV, ultraviolet detection; FD, fluorescence detection

[b] Includes: groundwater, aqueous sludges, caustic and acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments

[c] EQL, estimated quantitation limit

1.2 Production

Naphthalene is produced commercially from either coal tar or petroleum. Naphthalene has long been produced by the destructive distillation of high-temperature coal tars, called carbonization or coking (IARC, 1985). Coal tar was the traditional source of naphthalene until the late 1950s when it was in short supply, and the generation of naphthalene from petroleum by dealkylation of aromatics-rich fractions from reforming and catalytic cracking became commercially viable (IARC, 1989). In 1960, the first petroleum–naphthalene plant was brought on stream in the USA and, by the late 1960s, petroleum-derived naphthalene accounted for over 40% of total US naphthalene production. The availability of large quantities of *ortho*-xylene during the 1970s undercut the position of naphthalene as the prime raw material for phthalic anhydride. In 1971, 45% of phthalic anhydride capacity in the USA was based on naphthalene, as compared with only 29% in 1979 and 17% in 1990. The last dehydroalkylation plant for petroleum naphthalene was shut down late in 1991 (Mason, 1995).

World production of naphthalene in 1987 was around one million tonnes; about one-fourth came from western Europe (210 thousand tonnes), one-fifth each from Japan (175 thousand tonnes) and eastern Europe (180 thousand tonnes) and one-eighth from the USA (107 thousand tonnes). In 2000, over 90% of naphthalene in the USA was produced from coal tar; most naphthalene in western Europe was produced from coal tar; and all naphthalene produced in Japan was from coal tar (Lacson, 2000). Naphthalene supply and demand by major region in 2000 is presented in Table 2. Available information on production trends in Japan, the USA and western Europe is summarized in Table 3.

Table 2. Naphthalene supply and demand by major region in 2000 (thousand tonnes)[a]

Region	Capacity	Production	Consumption
Japan	221	179	172
USA	143	107	109
Western Europe	230	205	133
Total	594	491	414

[a] From Lacson (2000); data for Japan are from 1999.

Information available in 2001 indicated that crude naphthalene was manufactured by 36 companies in China, six companies in Japan, four companies each in Brazil and Russia, three companies each in Spain and the USA, two companies each in Argentina, India and Ukraine, and one company each in Australia, Bangladesh, Belgium, Bosnia, Canada, Colombia, Denmark, Egypt, France, Italy, Korea (Republic of), Mexico, the Netherlands, Turkey and the United Kingdom. Refined naphthalene was manufactured by 16 companies in China, five companies each in India and the USA, four companies

Table 3. Naphthalene production (thousand tonnes)[a]

		1965	1970	1975	1980	1985	1990	1995	2000
Japan	Crude	NR	NR	90.1	128.6	175.5	202.2	192.7	172.9[b]
	Refined	NR	NR	7.2	8.8	13.0	14.2	10.9	6.4[b]
USA	From coal tar	210.5	194.1	159.2	142.4	83.5	81.6	100.2	99.3
	From petroleum	157.4	132.0	50.0	61.7	24.9	22.7	7.3	7.3
	Total	367.9	326.1	209.1	204.1	108.4	104.3	107.5	106.6
Western Europe	Crude	NR	NR	NR	NR	212	210	160	166

[a] From Lacson (2000)
[b] Data reported for 1999
NR, not reported

each in Spain and Turkey, three companies in Japan, and one company each in Canada, the Czech Republic, Egypt, France, Italy, Korea (Republic of), the Netherlands, Ukraine and the United Kingdom. Naphthalene (grade unspecified) was manufactured by 39 companies in China, three companies in Ukraine, two companies each in Germany and Mexico, and one company each in Brazil, India, Japan, Russia, Turkey, the United Kingdom and the USA (Chemical Information Services, 2001).

1.3 Use

The main use for naphthalene worldwide is the production of phthalic anhydride by vapour-phase catalytic oxidation, particularly in Japan and the USA, where this accounted for 73% and 60% of naphthalene demand, respectively, in 1999. Phthalic anhydride is used as an intermediate for polyvinyl chloride plasticizers, such as di(2-ethylhexyl) phthalate. Naphthalene is also used in the manufacture of a wide variety of intermediates for the dye industry; in the manufacture of synthetic resins, celluloid, lampblack and smokeless powder; and in the manufacture of hydronaphthalenes (Tetralin (tetrahydronaphthalene), Decalin (decahydronaphthalene)) which are used as solvents, in lubricants and in motor fuels (Mason, 1995; Lacson, 2000; O'Neil *et al.*, 2001).

Naphthalene sulfonates represent a growing outlet for naphthalene. The products are used as wetting agents and dispersants in paints and coatings and in a variety of pesticides and cleaner formulations. Naphthalene is also a starting material for the manufacture of 1-naphthyl-*N*-methylcarbamate (carbaryl), an insecticide, and several other organic compounds and intermediates (Mason, 1995; Lacson, 2000).

The use of naphthalene as a moth-repellent and insecticide is decreasing due to the introduction of chlorinated compounds such a *para*-dichlorobenzene. In 2000, about 6500 tonnes of naphthalene were used (in Japan (1100 tonnes), the USA (450 tonnes) and Europe (5000 tonnes)), in moth-proofing and fumigation. Another new use for naphthalene is in production of polyethylene naphthalene for making plastic beer bottles. It has also been used in veterinary medicine in dusting powders, as an insecticide and internally as an intestinal antiseptic and vermicide (Sax & Lewis, 1987; Agency for Toxic Substances and Disease Registry, 1995a; Mason, 1995; Budavari, 1998; Lacson, 2000; O'Neil *et al.*, 2001).

Consumption of naphthalene by major region in selected years is presented in Table 4.

Table 4. Consumption of naphthalene by major region (thousand tonnes)[a]

End use	Japan		USA		Western Europe	
	1995	1999	1995	2000	1995	2000
Phthalic anhydride	137	124	66	66	42	45
Naphthalene sulfonates[b]	16	9	21	27	34	45
Pesticides[c]	2	1	17	14	15	22
Dyestuff intermediates	22	23	–	–	14	11
Other[d]	16	15	2	3	14	10
Total[e]	193	172	106	109	119	133

[a] From Lacson (2000)
[b] Includes alkylnaphthalene sulfonates and naphthalene sulfonate–formaldehyde condensates (NSF). NSF includes concrete additives and synthetic tanning agents.
[c] Includes carbaryl and moth repellents.
[d] Includes diisopropyl naphthalene, naphthalene dicarboxylic acid, tetrahydronaphthalene (Tetralin), decahydronaphthalene (Decalin) and chloronaphthalenes.
[e] Totals may not equal sums of the columns because of independent rounding.

1.4 Occurrence

1.4.1 *Natural occurrence*

Naphthalene, discovered in 1819 by A. Garden (BUA, 1989), is a natural constituent of coal tar and crude oil, which are major contributors to its presence in the environment. They contain up to 11% and 1.3% of the chemical, respectively (BUA, 1989; O'Neil *et al.*, 2001). Forest fires also contribute to the presence of naphthalene in the environment, as the chemical is a natural combustion product of wood (Agency for Toxic Substances and Disease Registry, 1995a).

1.4.2 *Occupational exposure*

From the National Occupational Exposure Survey conducted between 1981–83, the National Institute for Occupational Safety and Health (NIOSH) estimated that approximately 113 000 workers, about 4.6% females, in 31 major industrial groups were potentially exposed to naphthalene in the USA. The top six industries, by total workers, accounted for over 50% of the total potentially exposed workers. The petroleum and coal products and oil and gas extraction industries were among the top three industries and comprised about 21.4% of the workers potentially exposed to naphthalene. An estimated 1840 agricultural services workers were exposed to naphthalene; over 87% were females (National Institute for Occupational Safety and Health, 1990; National Toxicology Program, 1992).

Naphthalene has been measured in a wide variety of workplaces for many years. On the basis of the major results summarized in Table 5, the following ranking of respiratory exposure to naphthalene in the major industries can be made: creosote impregnation > coke manufacturing > asphalt industry > other industries. Exposure to naphthalene has also been extensively measured in Germany. Samples collected between 1991 and 1995 were predominantly from wood manufacturing (50%), construction (16%) and metal-working and machine construction (12%). Ninety-five per cent of the available 183 measurements from 94 factories were below the analytical limit of detection (1.0 mg/m^3 for a 2-h sampling time). Only in the manufacture of repellents and perfumed disinfectants were concentrations above the limit of detection (Bock *et al.*, 1999).

Naphthalene is the most abundant component of creosote vapour and constitutes 10–16 wt% of creosote oils (Nylund *et al*., 1992). Dermal wipe samples were taken in a study among asphalt workers; less than 10% of the samples showed detectable concentrations ranging from 5.5 to 520 ng/cm^2 (Hicks, 1995).

Urinary naphthols have been measured as biomarkers of occupational exposure to naphthalene (Bieniek, 1997) (see Section 4.1.1(*c*)).

1.4.3 *Environmental occurrence*

The extensive use of naphthalene as an intermediate in the production of plasticizers, resins, insecticides and surface active agents, its presence as a major component of coal tar and coal-tar products such as creosote and its inclusion in a wide variety of consumer products (e.g., moth-repellents) has led to its frequent occurrence in industrial effluents and outdoor and indoor environments (Agency for Toxic Substances and Disease Registry, 1995a,b; Environmental Protection Agency, 2001).

Naphthalene has been identified in the USA by the Environmental Protection Agency (2001) and the Agency for Toxic Substances and Disease Registry (1995b) as one of the most commonly found substances at hazardous waste sites on the 'National Priorities List'. In the USA, naphthalene is listed as one of 189 hazardous air pollutants under the Clean Air Act Amendments of 1990 (Title III) of the Environmental Protection Agency which mandates reduction of its emissions (Environmental Protection Agency, 1990b; Kelly *et al*., 1994). Naphthalene features in the Canadian Priority List of hazardous substances (Fellin & Otson, 1994).

The general population is exposed to naphthalene principally by inhalation of ambient and indoor air, with naphthalene-containing moth-repellents and tobacco smoke as the main contributors. Another source is the use of kerosene heaters (Traynor *et al*., 1990). Assuming an urban/suburban average air concentration of 0.95 μg/m^3 and an inhalation rate of 20 m^3 per day, it has been estimated that the average daily intake of naphthalene from ambient air in the USA is 19 μg (Howard, 1989; Agency for Toxic Substances and Disease Registry, 1995a). Much lower exposure to naphthalene may occur from ingestion of drinking-water and/or food. Estimated exposure from drinking-

Table 5. Occupational exposure to naphthalene in various industries

Industry	Country	Year	No. of positive samples	TWA (μg/m^3)	Range (μg/m^3)	Phase	Reference
Hot mix plants	USA	–	8	2.3		Fume/vapour	Hicks (1995)
Paving	USA	–	9	6.5		Fume/vapour	Hicks (1995)
Paving, roofing, steel and silicon carbide industries	Canada	–	51	11.4		Vapour (particulate)	Lesage *et al.* (1987)
				0.1		Fume (gaseous)	
Roofing/waterproofing	USA	1985	11		0–1.9		Zey & Stephenson (1986)
Roofing manufacturing	USA	–	7	7.5		Fume/vapour	Hicks (1995)
Roofing			11	5.2		Fume/vapour	
Enhanced oil recovery	USA	1986			5.0–11.0		Daniels & Gunter (1988)
Refineries/terminals	USA	–	9	5.5		Fume/vapour	Hicks (1995)
Coke manufacturing	Belgium		16		0.7–959	Vapour	Buchet *et al.* (1992)
Coke plant	Finland	1988–90	90[b]	44–500	111–1989	Vapour	Yrjänheikki *et al.* (1995)
(modern technology)	Poland		66		0–6000	Vapour	Bieniek (1994)
Coke plant, tar distillation	Poland		69	773[a]	–	Vapour	Bieniek (1997)
Coke plant, naphthalene oil distillation	Poland		33	867[a]	–	Vapour	Bieniek (1997)
Coke plant	Poland	1997	48	170–1210	10–3280	Vapour	Bieniek (1998)
Creosote impregnation (wood)	Finland		18	2200		Vapour	Heikkilä *et al.* (1987)
Switch assembly (wood)	Finland		8	2600		Vapour	Heikkilä *et al.* (1987)
Creosote impregnation (wood)	Finland		30	1540	400–4200	Vapour	Heikkilä *et al.* (1997)
	Finland		15	1000	22–1960	Vapour	Heikkilä *et al.* (1995)
Construction	Finland		1	160		Vapour	Heikkilä *et al.* (1995)
Aluminium refinery	Canada		7	1111		Vapour	Lesage *et al.* (1987)
			7	0.5		Fume	

Table 5 (contd)

Industry	Country	Year	No. of positive samples	TWA ($\mu g/m^3$)	Range ($\mu g/m^3$)	Phase	Reference
Manufacture of graphite electrodes	Belgium		106		0.2–1212	Vapour	Buchet *et al*. (1992)
Steel industry	USA	1982	NR		< 107		Almaguer & Orris (1985)
Aluminium reduction plant	Norway				0.72–311	'Gaseous'	Bjørseth *et al.* (1978a)
Coke plant	Norway				11–1151	'Gaseous'	Bjørseth *et al.* (1978b)
Iron foundries	Denmark	1989–90	24	mean, 0.5–10.6		Vapour	Hansen *et al*. (1994)
Silicon carbide	Canada		6	75.4		Vapour	Lesage *et al*. (1987)
			6	0.0		Fume	
Refractory brick	Canada		7	16.3		Vapour	Lesage *et al*. (1987)
			7	0.0		Fume	
Printing industry	USA	1977	8		40.0–12 000		Fannick (1978)
Shoe manufacture	USA	1983	17		1–600		Gunter (1984)
	USA	1984			< 10		Albers (1984)
Forest fighting crews	USA	1991	40		< 6.1	Vapour	Kelly (1992)
Food	Finland		5[c]	[5.8] 3 h	0.2–25.6	Fume/vapour	Vainiotalo & Matveinen (1993)
Fish smokehouses	Denmark		47		2918 (max)	Vapour (gas)	Nordholm *et al*. (1986)

Abbreviations: TWA, arithmetic mean of 8-h time-weighted average personal samples; NR, not reported
Gaseous = vapour
[a] Geometric mean
[b] 2-h TWA
[c] Stationary measurements

water assuming a water concentration of 0.001–2.0 μg/L naphthalene and water consumption of 2 L per day is 0.002–4.0 μg per day (Howard, 1989).

(*a*) *Air*

Most of the naphthalene entering the environment is discharged to the air (92.2%), the largest releases (more than 50%) resulting from the combustion of wood and fossil fuels and the off-gassing of naphthalene-containing moth-repellents and deodorants. In 1989, about 12 million pounds [5.5 million kg] were released from these sources. The highest atmospheric concentrations of naphthalene have been found in the immediate vicinity of specific industrial sources and hazardous waste sites (Agency for Toxic Substances and Disease Registry, 1995a). Air emissions in the USA reported to the Environmental Protection Agency decreased from 1598 tonnes for 473 industrial facilities in 1989 to 1224 tonnes for 744 industrial facilities in 1999 (Environmental Protection Agency, 2001).

The median ambient air concentration of naphthalene determined at nine locations (84 samples) in the USA was 1.2 μg/m^3 (Kelly *et al*., 1994). In another series of data from 1970–87, the average concentration of naphthalene in ambient air at several locations in the USA was 0.991 ppb [5.19 μg/m^3] for 67 samples, 60 of which were from source-dominated locations (Shah & Heyerdahl, 1988).

In the USA, the Environmental Protection Agency (2000) reviewed studies and calculated summary statistics for concentrations of chemicals in indoor air from selected sources, including naphthalene. Studies were selected which provided the best available estimates of 'typical concentrations' in indoor environments. These sources included the Building Assessment Survey and Evaluation (BASE) study, National Association of Energy Service Companies (NAESCO) study and School Intervention Studies (SIS). The data are reported in Table 6. [The Working group noted the unusually high outdoor air concentration in the School Intervention Studies, the fact that it is based on only three positive observations and that the original data in this review are unpublished.]

Table 6. Typical concentrations of naphthalene in indoor and outdoor air according to the Building Assessment Survey and Evaluation (BASE) study and the School Intervention Studies (SIS)

	BASE (μg/m^3)		SIS (μg/m^3)	
	Indoor	Outdoor	Indoor	Outdoor
Arithmetic mean concentration	0.95	0.31	1.3	290
95th percentile upper limit	2.6	0.81	1.7	1500
No. of buildings	70	69	10	10
No. of observations	209	69	39	10
Frequency of detection	83%	58%	21%	30%

A median naphthalene concentration of 0.18 ppb [0.94 μg/m^3] has been reported in urban air in 11 cities in the USA (Howard, 1989). An average naphthalene concentration of 170 μg/m^3 in outdoor air in a residential area of Columbus, OH (Chuang *et al*., 1991) and a concentration of 3.3 μg/m^3 naphthalene in ambient air in Torrance, CA, have also been reported (Propper, 1988; Agency for Toxic Substances and Disease Registry, 1995a).

Average naphthalene concentrations in ambient air at five hazardous waste sites and one landfill in New Jersey ranged from 0.42 to 4.6 μg/m^3 (range of arithmetic means) (LaRegina *et al*., 1986). Naphthalene wasfound at concentrations of less than 0.6 ng/m^3 in the air above shale-oil wastewaters in Wyoming (Hawthorne & Sievers, 1984).

Naphthalene was found in particulate matter in the atmosphere of La Plata, Argentina, at concentrations ranging from 0.18 ± 1.05 ng/m^3 to 13.2 ± 1.30 ng/m^3 when sampled on seven occasions between September 1984 and June 1986 (Catoggio *et al*., 1989).

In a study to compare naphthalene concentrations (among 35 volatile organic compounds) in indoor and outdoor air in northern Italy in 1983–84, the mean values found in indoor and outdoor samples were 11 and 2 μg/m^3, respectively, with the median indoor/outdoor ratio being 4 for 11 samples (De Bortoli *et al*., 1986).

Average indoor air concentrations in various residential areas in the USA ranged from 0.75 to 1600 μg/m^3 (Chuang *et al*., 1991 (measurements done in 1986–87); Wilson & Chung, 1991). A more representative upper limit concentration of naphthalene in indoor air of 32 μg/m^3 was recorded in buildings in heavy traffic urban areas of Taiwan (Hung *et al*., 1992).

In a study of the effect of smoking on polycyclic aromatic hydrocarbon levels, including naphthalene, in eight homes in the USA, naphthalene was found in the living room of homes of smokers (with gas heating and electric cooking) and homes of non-smokers (electric heating and cooking) at concentrations of 2.2 μg/m^3 and 1.8 μg/m^3, respectively, and the respective outdoors concentrations of naphthalene were 0.33 and 0.11 μg/m^3 (Wilson & Chuang, 1991).

In a summary of concentrations of volatile organic compounds in 230 homes in Germany, naphthalene was found at a mean concentration of 2.3 μg/m^3 with a range of < 1.0–14 μg/m^3; the 50th and 90th percentiles were 2.1 and 3.9 μg/m^3, respectively (Gold *et al*., 1993). In a study of the relationship between climatic factors and the concentrations of 26 volatile organic compounds in Canadian homes in 1991, naphthalene concentrations in the winter, spring, summer and autumn were 3.24, 1.10, 3.82 and 8.10 μg/m^3, respectively (Fellin & Otson, 1994). In a comparison of naphthalene concentrations in the indoor air of 50 normal and 38 ‘sick’ homes (in which people complained about the odour or had symptoms) in Finland, naphthalene was found at a median concentration of 0.31 μg/m^3 in normal homes (with 6% of normal houses having 1.5–3.1 μg/m^3), while in ‘sick’ homes 2.6% had concentrations of 1.5–3.1 μg/m^3, 5.3% of 3.1–15 μg/m^3 and 5.3% of 15–62 μg/m^3 (Kostiainen, 1995).

Naphthalene has been identified in the emissions of diesel light-duty vehicles (2–6 mg naphthalene released per km ‘distance’ driven on a chassis dynamometer)

(Scheepers & Bos, 1992). The average concentration of naphthalene reported inside automobiles in commuter traffic was about 4.5 μg/m^3 (Löfgren *et al.*, 1991).

(*b*) *Water*

Naphthalene released to the atmosphere may be transported to surface water and/or soil by wet or dry deposition. About 2–3% of naphthalene emitted to air is transported to other environmental media by dry deposition (Coons *et al.*, 1982; Agency for Toxic Substances and Disease Registry, 1995a). Naphthalene is degraded in water by photolysis and biological processes. The half-life for photolysis of naphthalene in surface water is about 71 h, but in deeper water (5 m) it is estimated to be 550 days (Agency for Toxic Substances and Disease Registry, 1995a).

Surface water discharges of naphthalene from 744 industrial facilities in the USA in 1999 amounted to 17.7 tonnes, as reported to the Toxics Release Inventory. An additional 73 tonnes of naphthalene were discharged though underground injection (Environmental Protection Agency, 2001). About 5% of all naphthalene entering the environment is released to water, mostly arising from coal tar production and distillation processes (Agency for Toxic Substances and Disease Registry, 1995a).

Naphthalene was detected in 7% of 630 ambient water samples in the USA at a median concentration of less than 10 μg/L, as shown in an analysis of 1980–82 data from the Environmental Protection Agency STORET (STOrage and RETrieval) database (Staples *et al.*, 1985; Agency for Toxic Substances and Disease Registry, 1995a). Naphthalene was also detected in 11% of 86 urban run-off samples up to 1982 at concentrations ranging from 0.8 to 2.3 μg/L (Cole *et al.*, 1984).

In the USA, naphthalene was detected in 35% of samples of groundwater at an average concentration of 3.3 mg/L at five wood-treatment facilities (Rosenfeld & Plumb, 1991) and in leachate or groundwater plume from industrial and municipal landfills at concentration ranges of < 10–19 mg/L and 0.1–19 mg/L, respectively (Brown & Donnelly, 1988). Naphthalene was detected in groundwater samples from three wells at concentrations of 380, 740 and 1800 μg/L, respectively, near an underground coal gasification site in north-western Wyoming (Stuermer *et al.*, 1982). Concentrations of naphthalene ranging from < 0.2 to 63 μg/L were detected at five out of six landfill sites in southern Ontario (Barker, 1987). Naphthalene was found at concentrations of 4.3 and 8.8 μg/L in two groundwater samples collected near an Orange County landfill site in central Florida (and not in surface water) in 1989–90, but not in 1992–93; this was believed to result from the decomposition of municipal solid waste (Chen & Zoltek, 1995).

Naphthalene has been infrequently reported in drinking-water (Agency for Toxic Substances and Disease Registry, 1995a). It was found in four samples of drinking-water extracts at concentrations ranging from 6 to 16 ng/L in Athens, GA, in 1976 (Thruston, 1978) and in another area in the USA at concentrations up to 1.4 μg/L (Coons *et al.*, 1982).

Naphthalene was measured in samples of raw river water from the Adige River, Italy, collected at 19 sampling stations in the Trento province, during two campaigns in 1989,

and detected at average concentrations of 51 ng/L (range, 3–109) and 284 ng/L (range, 3–2240), respectively (Benfenati *et al*., 1992). It was also detected in two polluted rivers, Besós and Llobregat, in Barcelona, Spain, in 1985–86 at mean concentrations of 1300 (SD, 150) ng/L and 180 (SD, 130) ng/L, respectively (Gomez-Belinchon *et al*., 1991). Naphthalene was one of the main aromatic hydrocarbons detected (at a concentration of 0.02 μg/L) in surface waters of Admiralty Bay, King George Island, Antarctica, during the summers of 1989, 1990, 1992 and 1993 (Bícego *et al*., 1996).

Naphthalene was found at concentrations of 0.5–35 ng/L (arithmetic mean, 12 ng/L) over 15 months at a coastal site near piers extending into Vineyard Sound, MA, USA. A dominant wintertime source considered was use of space-heating oil, with higher concentrations of naphthalene found in the winter and lowest concentrations found in the summer (Gschwend *et al*., 1982).

(*c*) *Soil and sediments*

Releases of naphthalene to land from 744 industrial facilities in the USA in 1999 amounted to 66 tonnes (Environmental Protection Agency, 2001).

In untreated agricultural soils, naphthalene has been found at concentrations ranging from 0 to 3 μg/kg in 1942–84 (Wild *et al*., 1990). It has been found at 6.1 (SD, 0.2) mg/kg in coal tar-contaminated soil (Yu *et al*., 1990), at 16.7 mg/kg in soil from a former tar-oil refinery (Weissenfels *et al*., 1992; Agency for Toxic Substances and Disease Registry, 1995a) and at up to 66 μg/kg in sludge-treated soils (Wild *et al*., 1990).

In the USA, naphthalene was reported to be detectable in 7% of 267 sediment samples (with the median concentration for all samples of less than 500 μg/kg) entered into the Environmental Protection Agency STORET database (1980–82) (Staples *et al*., 1985).

Naphthalene has been detected in contaminated sediments in Texas, USA, at average concentrations of 54.7 and 61.9 μg/kg at 10 m and 25 m from an oil platform and in nearby non-contaminated estuarine sediments at 2.1 μg/kg in 1982–85 (Brooks *et al*., 1990). It was found at 200 mg/kg in a tar-contaminated sediment of the River Warnow at Schwaan near Rostock, Germany, in August 1989 (Randow *et al*., 1996). Naphthalene was found in all four Canadian marine sediments analysed (representing varying concentrations and sources of polycyclic aromatic hydrocarbon contamination) at concentrations ranging from 0.1 to 115 mg/kg dry sediment (Simpson *et al*., 1995).

Naphthalene concentrations ranging from < 2 to 20.2 mg/kg dry wt were reported in three out of four sediments from lakes in the Northwest Territories in Canada (Lockhart *et al*., 1992). Primarily due to oxygen limitation, naphthalene persists in coal tar-contaminated surface sediments (Madsen *et al*., 1996). Naphthalene concentrations in soils and sewage sludges are usually less than 1 mg/kg in the United Kingdom (Wild & Jones, 1993).

(*d*) *Biodegradation*

Studies on biodegradation of polycyclic aromatic hydrocarbons in soil suggest that absorption to organic matter significantly reduces the bioavailability and thus the biodegradability of naphthalene (Heitzer *et al*., 1992; Weissenfels *et al*., 1992; Agency for Toxic Substances and Disease Registry, 1995a). Reported naphthalene half-lives in soil vary considerably. The estimated half-life of naphthalene reported for a solid waste site was 3.6 months, while in typical soils more rapid biodegradation is expected to occur (Heitkamp *et al.*, 1987; Howard, 1989).

Biodegradation of naphthalene is accomplished via the action of aerobic micro-organisms and generally declines precipitously when soil conditions become anaerobic (Klecka *et al*., 1990). Naphthalene biodegrades to carbon dioxide in aerobic soils with salicylate as an intermediate product (Heitzer *et al*., 1992; Agency for Toxic Substances and Disease Registry, 1995a).

Although polycyclic aromatic hydrocarbons are persistent in a strictly anaerobic environment, naphthalene can be degraded anaerobically under sulfate-reducing conditions: it was oxidized to carbon dioxide in petroleum-contaminated marine harbour sediments in San Diego, CA (Coates *et al.*, 1997).

(*e*) *Food*

Naphthalene was detected in only two of 13 980 samples of foods analysed in six states of the USA in 1988–89 (Minyard & Roberts, 1991). Naphthalene is not generally reported to be present in fish, but has been detected in shellfish in the USA, with concentrations ranging from 5 to 176 μg/kg in oysters, from 4 to 10 μg/kg in mussels and from < 1 to 10 μg/kg in clams (Bender & Huggett, 1989).

Naphthalene was found in 1993 in many samples of edible portions of nine types of shrimp and fish in Kuwaiti seafood at concentrations ranging from 2 to 156 μg/kg dry wt. These elevated concentrations of naphthalene were attributed to the pollution of Kuwait's territorial waters with crude oils as a result of oil spillage during the Gulf War or the chronic pollution due to oil production, transportation or natural seepage from the seabed. Naphthalene constituted the highest burden of the 14 polycyclic aromatic hydrocarbons screened (Saeed *et al*., 1995).

Mean concentrations of naphthalene of 19.5 μg/kg dry wt have been found in edible muscle of fish collected from the Red Sea coast of Yemen (DouAbul *et al*., 1997). Naphthalene has been found at maximum concentrations of 27.7 μg/kg and 137 μg/kg in muscle and liver tissue, respectively, of burbot fish from lakes in the Northwest Territories in Canada (Lockhart *et al*., 1992).

Naphthalene has also been detected in various fish species collected from the Gulf of Naples, Italy, e.g., in muscle samples of anchovy, comber and rock goby at concentrations of 63, 4 and 20 μg/kg wet wt, respectively, and in razor fish, wart venus and short-necked clams, at levels of 20, 25 and 32 μg/kg wet wt, respectively (Cocchieri *et al*., 1990).

Naphthalene was measured in 1987–88 in six species of aquatic organisms (sea mullet, bony bream, blue catfish, mud crab, pelican and the silver gull) from the Brisbane River estuarine system in Australia. The mean concentrations (µg/kg, wet wt) (in parentheses: lipid wt basis) were: bony bream, 14.1 (306; 8 samples); blue catfish, 21.3 (433; 8 samples); sea mullet, 37.3 (773; 8 samples); mud crab, 16.5 (407; 8 samples); pelican, 21.0 (276; 3 samples) and silver gull, 31.6 (395; 3 samples) (Kayal & Connell, 1995).

Naphthalene was identified in the neutral fraction of roast beef flavour isolate (Min *et al*., 1979).

Use of a mathematical model of naphthalene migration into milk from an atmosphere having a relatively high level of naphthalene suggested that naphthalene is first absorbed by the packaging material (low-density polyethylene). It was cautioned that when low-density polyethylene is used as the packaging material, the concentration of naphthalene vapour in the storage area should be kept low to minimize the transfer of naphthalene to milk (Lau *et al*., 1995).

(*f*) *Miscellaneous sources*

In the USA, naphthalene was found in mainstream cigarette smoke at a concentration of 2.8 µg per cigarette and at 46 µg per cigarette in the sidestream smoke from one commercial unfiltered cigarette, and at a concentration of 1.2 µg in the smoke from a filtered ‘little’ cigar (Schmeltz *et al*., 1976).

Naphthalene has been detected in ash from municipal refuse and hazardous waste incinerators. It was found in seven of eight municipal refuse ash samples at 6–28 000 µg/kg, with higher concentrations detected in bottom ash than in fly ash (Shane *et al*., 1990) and in five of 18 ash samples from hazardous waste incinerators at 0.17–41 (mean, 4.1) mg/kg (Carroll & Oberacker, 1989).

(*g*) *Human tissues and secretions*

Naphthalene was found in 40% of human adipose tissue samples at concentrations ranging from < 9 to 63 µg/kg in a National Human Adipose Tissue Survey (NHATS) in the USA in 1982 (Stanley, 1986). Naphthalene was also detected (concentrations not reported) in six of eight selected breast milk samples from women in four cities in the USA (Pellizzari *et al*., 1982). It was also released in expired air from three out of eight individuals at concentrations of 1.5, 2.4 and 0.12 µg/h, respectively (Conkle *et al*., 1975).

1.5 Regulations and guidelines

Occupational exposure limits and guidelines for naphthalene are presented in Table 7.

Table 7. Occupational exposure limits and guidelines for naphthalene[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Argentina	1991	50	TWA
		75	STEL (15 min)
Australia	1993	50	TWA
		75	STEL (15 min)
Belgium	1993	50	TWA
		75	STEL (15 min)
Canada	1994	50	TWA
		75	STEL (15 min)
Denmark	1993	50	TWA
Finland	2002	50[c]	TWA
		100[c]	STEL (15 min)
France	1993	50	TWA
Germany	2001	50 (CAT-2, skin)	TRK
Hungary	1993	40	TWA
		80	STEL (15 min)
Ireland	1997	50	TWA
		75	STEL (15 min)
Netherlands	1999	50	TWA
Philippines	1993	50	TWA
Poland	1993	20	TWA
Russia	1989	20	STEL (15 min)
Sweden	1991	0.2 (skin)	TWA
		0.6	STEL (15 min)
Switzerland	1993	50	TWA
United Kingdom	2000	50	TWA
		75	STEL (15 min)
USA			
ACGIH[c] (TLV)	2001	10 ppm [50] (A4, skin)	TWA
		15 ppm [75]	STEL (15 min)
NIOSH (REL)	2000	50	TWA
		75	STEL (15 min)
OSHA (PEL)	2001	50	TWA

[a] From International Labour Office (1991); American Conference of Governmental Industrial Hygienists (ACGIH) (2000, 2001); Deutsche Forschungsgemeinschaft (2001); Occupational Safety and Health Administration (OSHA) (2001); Sosiaali-ja terveysministeriö (2002); United Nations Environment Programme (2002)

[b] TWA, 8-h time-weighted average; STEL, short-term exposure limit; A4, not classifiable as a human carcinogen; CAT-2, substances that are considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk; skin, danger of cutaneous absorption; TRK, technical exposure limit; TLV, threshold limit value: REL, recommended exposure limit; PEL, permissible exposure limit

[c] Values have been rounded.

2. Studies of Cancer in Humans

Case reports

A cluster of cancer cases in a naphthalene purification plant was reported in the former East Germany (Wolf, 1976, 1978). This plant operated between 1917 and 1968 and a total of 15 employees were reported to have worked in this unit of the plant during the preceding 20–30 years. Seven employees were diagnosed with cancer, including four cases of laryngeal cancer. Diagnosis was established between 1964 and 1973 and the age at diagnosis was 60–71 years. The incidence rate for laryngeal cancer in the former East Germany in 1970 was given as 6.3 per 100 000. The four workers had been exposed for 7–31 years. The limit value for exposure to naphthalene at that time was 20 mg/m^3, with peak values of 50 mg/m^3. Concomitant exposure to various tar products was mentioned. All four cases were reported to have been smokers. [The Working Group noted that no inference on the carcinogenicity of naphthalene can be drawn from these observations.]

Ajao *et al*. (1988) reported on 23 consecutive cases of colorectal carcinoma admitted during June 1982 and May 1984 to a university college hospital in Nigeria. Eleven of these patients were 30 years or younger at diagnosis. Based on family history, proctosigmoidoscopy, barium enema and autopsy, no indication of familial polyposis among these cases was ascertained. Half of the patients mentioned a history of taking *Kafura*, a local indigenous treatment for anorectal problems, which contains naphthalene. The other half of the patients did not know whether they had been given *Kafura* during early childhood. [The Working Group noted that no inference on the carcinogenicity of naphthalene can be drawn from these observations.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: A group of 28 BD I and BD III rats [sex and number of each strain not specified], about 100 days old, was fed a diet [not specified] containing naphthalene (spectrographically pure) in oil [type unspecified] at a dose of 10–20 mg per day on six days per week, for 100 weeks. Animals were kept under observation until they died. The average life expectancy was 800 days, which was said to be similar to that of control rats [no details were provided regarding control animals]. All animals were subjected to necropsy with histopathological examination of abnormal tissues only. No tumours were found in any of the rats examined. (Schmähl, 1955). [The Working Group noted the small number of animals used and the incomplete reporting of this study.]

3.2 Inhalation exposure

3.2.1 *Mouse*

Groups of 70 male and 70 female B6C3F$_1$ mice, 10–11 weeks of age, were subjected to whole-body exposure to 0 or 10 ppm (0 or 52 mg/m^3) naphthalene (> 99% pure) and a group of 135 males and 135 females to 30 ppm naphthalene (157 mg/m^3) in inhalation chambers for 6 h per day, five days per week, for 104 weeks. During periods of non-exposure, animals were housed in groups of five. Mean body weight of exposed mice was slightly lower than that of the controls throughout the study. Survival rates at the end of the study were significantly lower in control male mice than in exposed males due to wound trauma and secondary infection related to fighting (survival: controls, 26/70 (37%); 10 ppm, 52/69 (75%); and 30 ppm, 118/133 (89%)). Survival in the exposed female mice was similar to that of controls: controls, 59/69 (86%); 10 ppm, 57/65 (88%); and 30 ppm, 102/135 (76%). There was a statistically significant increase in the incidence of bronchiolo-alveolar adenomas in high-dose females (controls, 5/69 (7%); 10 ppm, 2/65, (3%); 30 ppm, 28/135 (21%) [p = 0.01; logistic regression test]). One bronchiolo-alveolar carcinoma was noted in a high-dose female. Exposed male mice also showed an increased incidence of bronchiolo-alveolar adenomas and carcinomas but the increases were not statistically significant (adenomas: 7/70 (10%), 15/69 (22%) and 27/135 (20%); carcinomas: 0/70, 3/69 (4%) and 7/135 (5%) in controls, 10 ppm and 30 ppm dose groups, respectively). Non-neoplastic changes were seen only in the lungs and nose. A dose-related increase in bronchiolo-alveolar inflammation was seen (males: 0/70 (0%), 21/69 (30%) and 56/135 (41%); females: 3/69 (4%), 13/65 (30%) and 52/135 (39%) in the 0-, 10- and 30-ppm dose groups, respectively). Virtually all exposed animals but none of the controls had nasal chronic inflammation, respiratory epithelial hyperplasia and metaplasia of the olfactory epithelium (National Toxicology Program, 1992).

In a screening assay based on increased multiplicity and incidence of lung tumours in a strain of mice highly susceptible to the development of this neoplasm, groups of 30 female A/J mice, 8–10 weeks of age, were exposed in inhalation chambers to 0, 10 or 30 ppm [0, 52 or 157 mg/m^3] naphthalene (purity, 98–99%) for 6 h per day, on five days per week, for six months. Survival was unaffected by treatment. At the end of the experimental period, survivors were killed and examined for pulmonary adenomas. Exposure to 10 or 30 ppm did not cause a significant increase in the incidence of lung adenomas compared with concurrent controls, but histopathological evaluation of the lungs showed an increase in numbers of alveolar adenomas per tumour-bearing mouse but not in adenomas per mouse compared with the concurrent controls (controls, 21% (0.21 ± 0.39 adenomas per mouse and 1.00 ± 0.00 adenomas per adenoma-bearing mouse); 10 ppm, 29% (0.35 ± 0.55 adenomas per mouse and 1.25 ± 0.07 adenomas per adenoma-bearing mouse); 30 ppm, 30% (0.37 ± 0.55 adenomas per mouse and 1.25 ± 0.07 adenomas per adenoma-bearing mouse) (Adkins *et al.*, 1986).

3.2.2 *Rat*

Groups of 49 male and 49 female Fischer 344/N rats, six weeks of age, were exposed in inhalation chambers to 0, 10, 30 or 60 ppm [0, 52, 157 or 314 mg/m^3] naphthalene (> 99% pure) for 6 h per day, on five days per week, for 105 weeks. Mean body weights of all exposed groups of male rats were less than that of the chamber control group throughout the study, but mean body weights of exposed groups of females were similar to that of the chamber control group. Survival rates in all exposed groups were similar to that of the chamber controls. At the end of the study, 24/49, 22/49, 23/49 and 21/49 males and 28/49, 21/49, 28/49 and 24/49 females were alive in the 0, 10, 30 and 60 ppm groups, respectively. Neuroblastomas of the nasal olfactory epithelium were observed in 0/49, 0/49, 4/48 ($p = 0.056$, Poly-3 test) and 3/48 male rats and in 0/49, 2/49, 3/49 and 12/49 ($p = 0.001$, Poly-3 test) females in the 0, 10, 30 and 60 ppm groups, respectively. In addition, adenomas of the nasal respiratory epithelium were observed in 0/49, 6/49 ($p = 0.013$, Poly-3 test), 8/48 ($p = 0.003$, Poly-3 test) and 15/48 ($p < 0.001$, Poly-3 test) males and 0/49, 0/49, 4/49 ($p = 0.053$, Poly-3 test) and 2/49 females in the 0, 10, 30 and 60 ppm groups, respectively. These olfactory neuroblastomas and respiratory epithelium adenomas had not been observed in the larger database of historical controls in National Toxicology Program two-year inhalation studies in which animals were fed National Institute of Health (NIH)-07 diet or in the smaller National Toxicology Program database [all routes] in which they were fed NTP-2000 diet. In addition to the nasal neoplasms, the incidences of a variety of non-neoplastic lesions of the nasal tract in both male and female rats were significantly increased in naphthalene-exposed animals compared with controls (see Section 4.2.2(*b*)) (National Toxicology Program, 2000).

3.3 Intraperitoneal administration

3.3.1 *Mouse*

A group of 31 male and 16 female CD-1 mice received intraperitoneal injections of a 0.05-M solution of naphthalene [purity unspecified] in dimethyl sulfoxide (DMSO) on days 1, 8 and 15 of life. The total dose received was 1.75 μmol per mouse. Groups of 21 male and 21 female mice receiving DMSO alone served as vehicle controls. [The number of mice in the above four groups are reported as the effective number of mice that survived at least six months of treatment and not the starting number.] Mice were weaned at 21 days, separated by gender and maintained until termination at 52 weeks, at which time they were necropsied and gross lesions as well as liver sections were examined histologically. There was no increase in the incidence of tumours in the naphthalene-treated mice compared with the vehicle controls (LaVoie *et al.*, 1988).

3.3.2 *Rat*

Ten BD I and BD III rats, 100 days old [sex and number of each strain not specified], received weekly intraperitoneal injections of 20 mg naphthalene (spectrographically pure) as a 2% solution in 'specially purified oil' for 40 weeks and were held under observation until they died. The average age at death was 900 days, which was reported to be similar to that of controls [no details were provided regarding control animals]. All animals were necropsied with histopathological examination of abnormal tissues only. No tumours were found in any of the rats examined (Schmähl, 1955). [The Working Group noted the small number of animals used and the limited reporting of this study.]

3.4 Subcutaneous administration

Rat: Ten BD I and BD III rats, 100 days old, [sex and number of each strain unspecified] received weekly subcutaneous injections of 20 mg naphthalene (spectrographically pure) as a 2% solution in 'specially purified oil' for 40 weeks and were kept under observation until they died. The average age at death was 700 days, which was reported to be similar to that of controls [no details were provided regarding control animals]. All animals were necropsied with histopathological examination of abnormal tissues only. No tumours were found in any of the rats examined (Schmähl, 1955). [The Working Group noted the small number of animals and the limited reporting of this study.]

Groups of 38 white inbred rats [age, strain and sex unspecified] received seven subcutaneous injections of 0 or 50 mg/kg bw naphthalene (purified by chromatography) as a 15% solution in sesame oil at intervals of around 14 days extending over 3.5 months. Survival was poor due to infectious pneumonia [agent unspecified], with 5/38 treated and 11/38 vehicle controls alive at 12 months and 0/38 treated and 4/38 vehicle controls alive at the termination of the study at 18 months. In the test group, a total of five sarcomas (one uterine and four lymphosarcomas) and a single mammary fibroadenoma developed and, in the control group, a single sarcoma and a single mammary fibroadenoma (Knake, 1956). [The Working Group noted the small number of animals, the poor survival and the limited reporting of this study.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

(*a*) *Absorption*

No studies were found that quantitatively determined the extent of absorption of naphthalene in humans following oral or inhalation exposure. Naphthalene can be absorbed through the skin. Kanikkannan *et al*. (2001a) examined the permeation of JP-8 (jet fuel) containing 0.26% (w/w) naphthalene through human skin *in vitro*. For 18 samples of human skin, the steady-state flux was 0.45 μg/cm^2 per hour and the permeability coefficient was 2.17×10^{-4} cm per hour.

(*b*) *Distribution*

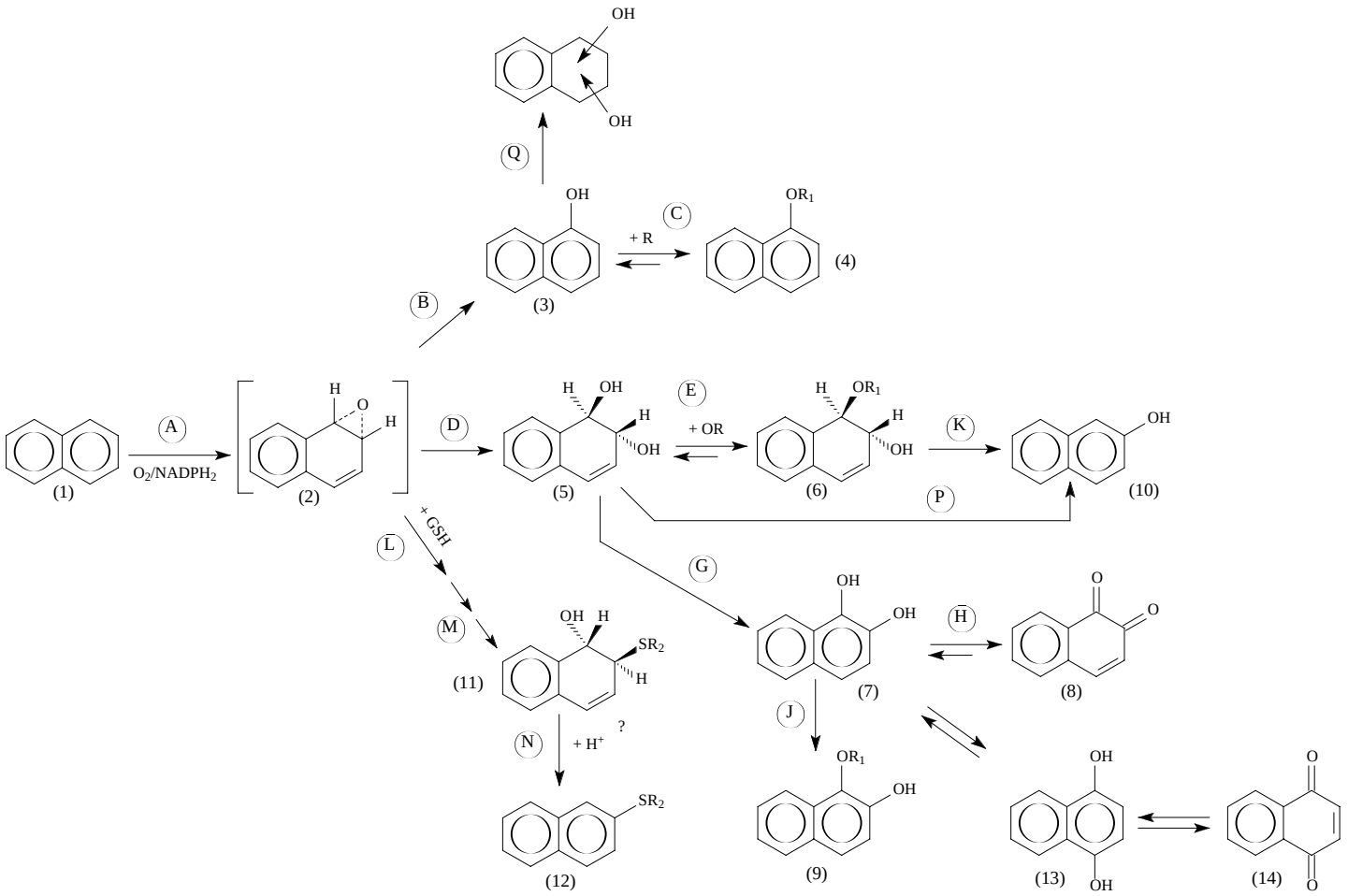
In a survey, naphthalene was detected in 40% of the human adipose tissue samples tested, with concentrations up to 63 ng/g lipid (Stanley, 1986). Naphthalene has also been identified in samples of human breast milk [incidence not clear; concentrations not reported] (Pellizzari *et al*., 1982).

(*c*) *Metabolism*

The major metabolic pathways of naphthalene are illustrated in Figure 1. Naphthalene is metabolized first to naphthalene 1,2-oxide (2, see Figure 1), which can yield 1-naphthol (3, see Figure 1) or be converted by epoxide hydrolase to *trans*-1,2-dihydro-1,2-dihydroxynaphthalene (*trans*-1,2-dihydrodiol) (5, see Figure 1). The hydroxyl group of 1-naphthol may also be sulfated or glucuronidated. The 1,2-dihydrodiol can also be converted to 2-naphthol (10, see Figure 1). The epoxide is also a substrate for glutathione *S*-transferase, yielding glutathione conjugates which are eventually eliminated as mercapturic acids. Boyland and Sims (1958) showed that trace quantities of a precursor of 1-naphthyl mercapturic acid, tentatively identified as an *N*-acetyl-L-cysteine derivative, are eliminated in human urine after oral administration of 500 mg naphthalene. Tingle *et al*. (1993) examined the metabolism of naphthalene by human and mouse liver microsomes. The ratio of the *trans*-1,2-dihydrodiol to 1-naphthol was 8.6 for human microsomes compared with 0.4 for microsomes from phenobarbital-treated mice, indicating the ready detoxification of the epoxide to the diol in humans.

Buckpitt and Bahnson (1986) measured the metabolism of naphthalene by human lung microsomes derived from two individuals and detected naphthalene dihydrodiol

Figure 1. Main metabolic pathways of naphthalene and resulting products in mammals



Based on BUA (1989) and Agency for Toxic Substances and Disease Registry (1995a)

(1) Naphthalene
(2) Naphthalene 1,2-oxide
(3) 1-Naphthol (α-naphthol)
(4) 1-Naphthyl glucuronide or sulfate
(5) *trans*-1,2-Dihydro-1,2-dihydroxynaphthalene
(6) *trans*-1,2-Dihydro-2-hydroxynaphthyl-1-glucuronide
(7) 1,2-Dihydroxynaphthalene
(8) 1,2-Naphthoquinone
(9) 2-Hydroxynaphthyl-1-sulfate or -glucuronide
(10) 2-Naphthol (β-naphthol)
(11) *N*-Acetyl-*S*-(1,2-dihydro-1-hydroxy-2-naphthyl)-L-cysteine
(12) *N*-Acetyl-*S*-(1-naphthyl)-L-cysteine (1-naphthyl mercapturic acid)
(13) 1,4-Dihydroxynaphthalene
(14) 1,4-Naphthoquinone

A,Q = O_2- and $NADPH_2$-dependent monooxygenase (e.g., cytochrome P450-NADP-cytochrome-c-reductase system, microsomal)
B = Spontaneous isomerization
C,E,J = Conjugation reaction with sulfate (sulfotransferase, cytosolic) or with glucuronic acid (UDP-glucuronyltransferase, microsomal)
D = Epoxide hydrolase, synonym: epoxide hydrase (microsomal)
F,N,P = Chemical dehydration
G = Dihydrodiol-dehydrogenase (cystosolic); 3,5-cyclohexadiene-1,2-diol-NADP-oxidoreductase
H = Chemical dehydration
K = Chemical hydrolysis + dehydration
L = Enzymatic reaction with glutathione
M = γ-Glutamyl transferase, peptidase, *N*-acetylase

GSH = Glutathione
R_1 = Sulfate or glucuronate group
R_2 = *N*-acetyl-L-cysteine residue

and three glutathione conjugates. These metabolites were also identified in animal studies, as discussed in Section 4.1.2.

Urinary metabolites of naphthalene are useful biomarkers of exposure. Seventy-five workers exposed to naphthalene while distilling naphthalene oil excreted 7.48 mg/L (4.35 mg/g creatinine) 1-naphthol (geometric mean values) at the end of the workshift. For 24 non-occupationally exposed individuals, the mean urinary concentration of 1-naphthol was 0.13 mg/L (Bieniek, 1994). 1-Naphthol, 2-naphthol and 1,4-naphthoquinone (14, see Figure 1) were identified in the urine of 69 coke-plant workers exposed to a geometric mean air concentration of naphthalene of 0.77 mg/m^3 during tar distillation. The end-of-workshift urinary concentrations of 1-naphthol and 2-naphthol were 693 and 264 μmol/mol creatinine. The correlation coefficients between the urinary excretion of naphthols and exposure to naphthalene were 0.64–0.75 for 1-naphthol and 0.70–0.82 for 2-naphthol. There was a linear relationship between the overall concentration of naphthols in urine and the naphthalene concentration in air (Bieniek, 1997). In a further study of a coke plant, Bieniek (1998) measured the concentrations of 1-naphthol and 2-naphthol in urine from eight workers in coke batteries, 11 workers in the sorting department and 29 workers in the distillation department. The mean urinary concentrations of 1-naphthol and 2-naphthol were 294 and 89 μmol/mol creatinine for the coke-battery workers, 345 and 184 μmol/mol creatinine for the sorters and 1100 and 630 μmol/mol creatinine for the distillation workers, respectively.

Andreoli *et al.* (1999) examined 15 urine samples from workers in a naphthalene-producing plant who were exposed to 0.1–0.7 mg/m^3 naphthalene. At the end of the workshift, the median urinary concentrations of 2-naphthyl sulfate, 2-naphthyl glucuronide and 1-naphthyl glucuronide were 0.030 (range, 0.014–0.121), 0.086 (range, 0.013–0.147) and 0.084 (range, 0.021–0.448) mg/L, respectively.

Since naphthalene is the most abundant component of creosote (Heikkilä *et al*., 1987), urinary excretion of 1-naphthol was determined in three assembly workers handling creosote-impregnated wood. The average airborne concentration of naphthalene in the breathing zone was approximately 1 mg/m^3. The average end-of-shift concentration of 1-naphthol in urine changed from 254–722 (mean, 556) μmol/mol creatinine on Monday to 1820–2190 (mean, 2060) μmol/mol creatinine on Wednesday and 870–2330 (mean, 1370) μmol/mol creatinine on Friday. The same metabolite was measured in the urine of six workers exposed to creosote in a plant impregnating railroad ties (Heikkilä *et al.*, 1997). As measured by use of personal air samplers, the mean airborne concentration of naphthalene in the workers' breathing zone was 1.5 (range, 0.37–4.2) mg/m^3. The mean end-of-shift concentration of 1-naphthol was 20.5 (range, 3.5–62.1) μmol/L. There was a good correlation (r = 0.745) between concentrations of airborne naphthalene and urinary 1-naphthol. No 1-naphthol was detected (limit of detection < 0.07 μmol/L) in the urine of five non-exposed controls. Hill *et al*. (1995) measured 1-naphthol and 2-naphthol in the urine of 1000 adults without occupational exposure — a subset of the National Health and Nutrition Examination Survey III — who may have been exposed to low levels of naphthalene or pesticides that would yield

these naphthols as metabolites. The frequency of detection was 86% for 1-naphthol and 81% for 2-naphthol. The mean concentrations were 15 and 5.4 µg/g creatinine, respectively. Concentrations of 1-naphthol ranged up to 1400 µg/g creatinine.

Yang *et al.* (1999) examined the relationship between certain enzyme polymorphisms and naphthalene metabolism in 119 men who were not occupationally exposed to polycyclic aromatic hydrocarbons. A polymorphism in exon 7 of the *CYP1A1* gene was not related to urinary naphthol excretion. Smokers with the *c1/c2* or *c2/c2* genotype in *CYP2E1* excreted higher concentrations of 2-naphthol in the urine than smokers with the *c1/c1* genotype. Smokers deficient in glutathione *S*-transferase M1 (GSTM1) showed higher urinary concentrations (without correction for creatinine) of both 1-naphthol and 2-naphthol.

Nan *et al.* (2001) examined the effects of occupation, lifestyle and genetic polymorphisms of *CYP1A1*, *CYP2E1* and the glutathione *S*-transferases *GSTM1* and *GSTT1* on the concentrations of 2-naphthol in the urine of 90 coke-oven workers in comparison with 128 university students. The urinary excretion of 2-naphthol was higher in the coke-oven workers (7.69 µmol/mol creatinine) than in the students (2.09 µmol/mol creatinine). In the control group, the excretion was higher in smokers (3.94 µmol/mol creatinine) than in nonsmokers (1.55 µmol/mol creatinine). Urinary 2-naphthol concentrations were higher in coke-oven workers with the *c1/c2* or *c2/c2* genotypes than in those with the more common *c1/c1* genotype of *CYP2E1*. Urinary 2-naphthol concentrations were also higher in the urine of *GSTM1*-null workers than in *GSTM1*-positive workers.

4.1.2 *Experimental systems*

(*a*) *Absorption, distribution and excretion*

Early studies indicated that in rats naphthalene is well absorbed from the gastrointestinal tract (Chang, 1943). When naphthalene was fed to white male rats (weight, about 300 g) [strain unspecified] at a concentration of 1% (w/w) in the diet, none was detected in the faeces. Similarly, when it was administered as a single dose by stomach tube (0.1 g), it was not measurable in the faeces.

Eisele (1985) examined the distribution of [^{14}C]naphthalene in laying pullets, swine and dairy cattle following oral administration. In pullets given a dose of 0.44 mg, the major site of deposition was the kidney followed by fat, lung and liver. Following acute administration of 2.46 mg in swine, the major site of deposition was fat, where the level was up to 10 times higher than that in liver. After chronic administration (0.112 mg per day for 31 days), the lung, liver and heart were major sites of accumulation. In cows, chronic exposure (5.115 mg per day for 31 days) led to deposition primarily in the liver.

When [^{14}C]naphthalene was applied dermally (3.3 µg/cm^2; total dose, 43 µg) to male Sprague-Dawley rats, the plasma half-life for absorption was 2.1 h and that for elimination was 12.8 h. The highest concentration of radioactivity 48 h after dosing was found in the skin followed by ileum, duodenum and kidney. Seventy per cent of the radioactivity was found in the urine in the first 48 h, with 3.7% appearing in the faeces

and 13.6% in the expired air. The primary urinary metabolites identified were 2,7-dihydroxynaphthalene (31.1% of the total radioactivity in the first 12 h), 1,2-dihydroxynaphthalene (7, see Figure 1) (17.2%), 1,2-naphthoquinone (8, see Figure 1) (11.4%), 2-naphthol (4.3%) and 1-naphthol (3.4%). The parent compound naphthalene accounted for 0.3% of the radioactivity (Turkall *et al.*, 1994). [The Working Group noted that 2,7-dihydroxynaphthalene has not been identified as a major metabolite in other studies.]

Kilanowicz *et al.* (1999) studied the distribution, metabolism and excretion of tritiated naphthalene given intraperitoneally at a dose of 20 mg/kg bw to male IMP:Wist rats. Approximately 88% of the radioactivity was excreted in urine (68%) and faeces (20%) in the first 72 h, with maximum blood concentrations observed 2 h after dosing. The elimination of radioactivity from the blood was biphasic with half-lives of 0.8 and 99 h. [The Working Group noted that the 99-h half-life component may have been due to tritium exchange.] The highest initial tissue concentrations were found in fat, liver and kidneys. Urinary metabolites were identified as primarily the parent naphthalene, 1-naphthol and 2-naphthol with smaller amounts of 1,2-dihydro-1,2-dihydroxynaphthalene (1,2-dihydrodiol) and methylthionaphthalenes.

Sartorelli *et al*. (1999) investigated the percutaneous penetration of naphthalene from lubricating oil *in vitro* using full-thickness monkey skin. The flux for naphthalene was 0.274 nmol/cm^2 per hour, which was higher than that for acenaphthene, fluorene, anthracene, phenanthrene, pyrene and chrysene. Kanikkannan *et al*. (2001b) examined the percutaneous permeation of naphthalene in JP-8 + 100 jet fuel, which contained 0.26% (w/w) naphthalene and was spiked with [^{14}C]naphthalene, using a pig ear skin model. The steady-state flux was 0.42 µg/cm^2 per hour, similar to that of nonane but less than for tridecane.

(*b*) *Metabolism — species comparison*

Corner and Young (1954) compared the urinary metabolites of naphthalene in rats, rabbits, mice and guinea-pigs [strains unspecified] following administration of a single dose of naphthalene (500 mg/kg bw) either orally or by intraperitoneal injection. 1-Naphthol and its glucuronide and sulfate were identified in the urine of all four species (with the exception of the glucuronide in guinea-pigs). 2-Naphthol was detected in all four species but no conjugates of this metabolite were found. Although 1,2-dihydro-1,2-dihydroxynaphthalene (1,2-dihydrodiol) was found in the urine of all four species, 1,2-dihydroxynaphthalene was present only in urine of guinea-pigs. Rabbits and rats excreted more 2-naphthol than 1-naphthol, guinea-pigs excreted 1- and 2-naphthol in equal amounts and mice excreted more 1-naphthol than 2-naphthol. As in humans, a precursor of 1-naphthyl mercapturic acid has been detected as a urinary metabolite in all rodent species tested (Boyland & Sims, 1958); the amounts of this metabolite present in the urine of mice, rats and hamsters were greater than those observed in guinea-pigs, which were greater than those in humans. However, these data did not take into consideration the widely different doses given: mice, rats, hamsters, guinea-pigs and humans received total doses of 20, 100, 100, 400 and 500 mg per animal, respectively. Chen and Dorough

(1979) investigated the formation of glutathione conjugates using [^{14}C]naphthalene given to female Spague-Dawley rats. After intraperitoneal injection of 100 mg/kg bw [^{14}C]naphthalene, 65% of the water-soluble fraction of the radioactivity in urine was identified as glutathione-derived conjugate (premercapturic acid) over a 72-h period. Total recovery of radioactivity was 74% after 72 h, with 60% present in the urine and 14% in the faeces. 1,2-Dihydro-1,2-dihydroxynaphthalene (28%) and 1-naphthol (60%) were the major metabolites in the ether-extractable fraction, which accounted for 6% of the administered dose. Summer *et al.* (1979) found a dose-dependent increase in the urinary excretion of mercapturic acid conjugates in male Wistar rats given 30, 75 or 200 mg/kg bw naphthalene by stomach tube but did not find any such increase in chimpanzees (*Pan troglodytes* S.). A similar lack of a significant role for glutathione conjugation in primates was observed in rhesus monkeys (*Macaca mulatta*) (Rozman *et al.*, 1982). [The Working Group noted that standards of naphthalene mercapturates were not available in these studies and the analytical method employed may have underestimated the amounts of mercapturates present in the urine samples.]

Horning *et al.* (1980) gave naphthalene (100 mg/kg bw) intraperitoneally to male Sprague-Dawley rats and identified 21 oxygenated metabolites in the urine, all but one being generated via epoxidation. Along with those identified in other studies, the total number of known naphthalene metabolites was 31, excluding mercapturic acids, conjugates and related compounds. Bakke *et al.* (1985) gave [^{14}C]naphthalene orally to male Sprague-Dawley rats and found 4.6% of the ^{14}C dose as naphthols or their glucuronides in the urine by 24 h. In addition, they found 1,2-dihydro-1-hydroxy-2*S*-(*N*-acetyl)-cysteinylnaphthalene (11, see Figure 1) (38.1%), 1,2-dihydroxynaphthalene (7, see Figure 1) (4.9%), 1,2-dihydro-1,2-dihydroxynaphthalene glucuronide (23.9%), 1,2-dihydro-1-hydroxy-2-methylthionaphthalene glucuronide (4.6%) and uncharacterized metabolites (2.4%). Buonarati *et al.* (1990) showed that a consistent percentage of a dose of either *trans*-1*S*-hydroxy-2*S*-glutathionyl-1,2-dihydronaphthalene or *trans*-1*R*-hydroxy-2*R*-glutathionyl-1,2-dihydronaphthalene administered intravenously to male Swiss Webster mice was eliminated as the corresponding diastereomeric mercapturic acid in the urine. In contrast, a significant percentage of a dose of *trans*-1*R*-glutathionyl-2*R*-hydroxy-1,2-dihydroxynaphthalene (14–25%, depending on the dose) was metabolized to (2-hydroxy-1,2-dihydronaphthalenylthio)pyruvic acid. These observations indicate that mercapturic acids generated by conjugation at the C2 position of the napththalene nucleus can be used to assess the stereochemistry of naphthalene metabolism *in vivo*.

Pakenham *et al.* (2002) showed that 24–35% of an intraperitoneal dose of [^{14}C]-naphthalene was eliminated as mercapturates by both mice and rats at 24 h after dosing. For both species, this percentage was the same over a wide dose range (3.12–200 mg/kg bw). In contrast, after inhalation exposure, the amounts of mercapturic acid in mouse urine were approximately twice those in rat urine at the same level of exposure. Over a 24-h period, approximately 100–500 μmol/kg bw mercapturates were eliminated in urine of mice given intraperitoneal injections of 50–200 mg/kg bw naphthalene. In mice exposed by inhalation to 1–100 ppm (5.24–524 mg/m^3) naphthalene for 4 h,

1–240 μmol/kg bw total mercapturic acids were eliminated, while rats exposed to the same concentrations eliminated 0.6–67 μmol/kg bw.

Jerina *et al*. (1970) used rat [strain unspecified] liver microsomes to examine naphthalene metabolism *in vitro* and identified naphthalene 1,2-oxide (2, see Figure 1) as an intermediate in the formation of all major metabolites including glutathione conjugates. Bock *et al*. (1976) used hepatocytes from male Sprague-Dawley rats to show that 1,2-dihydro-1,2-dihydroxynaphthalene glucuronide was a major metabolite of naphthalene.

Usanov *et al*. (1982) compared the metabolism of naphthalene by microsomal preparations from rat liver and rabbit lung [strains and sex not specified] by measuring the formation of 1-naphthol. The metabolic efficiency, i.e. the rate of hydroxylation per nmol of cytochrome P450, was 7.35 times higher in rabbit lung than in rat liver microsomes.

d'Arcy Doherty *et al*. (1985) examined the metabolism of 1-naphthol by a reconstituted cytochrome P450 system from male Wistar rats and identified the products as 1,2- and 1,4-naphthoquinones (8 and 14, see Figure 1). Smithgall *et al*. (1988) examined the metabolism of *trans*-1,2-dihydro-1,2-dihydroxynaphthalene (*trans*-1,2-dihydrodiol) to the *ortho*-quinone by cytosolic dihydrodiol dehydrogenase from rat liver, and investigated the reactivity of the *ortho*-quinone with the cellular nucleophiles, cysteine and glutathione. The results showed that *ortho*-quinones formed by enzymatic oxidation of dihydrodiols may be effectively scavenged and detoxified by nucleophiles. Buckpitt and coworkers (Buckpitt & Warren, 1983; Buckpitt *et al*., 1984, 1985) examined the relationships among the initial steps in the oxidative metabolism of naphthalene, conjugation with glutathione and the ability of reactive metabolites of naphthalene to covalently bind to protein in tissues of male Swiss Webster mice given intraperitoneal doses of [^{14}C]naphthalene. Binding of naphthalene in lung, liver and kidney was similar *in vivo*, but the rate of microsomal metabolic activation of naphthalene was much lower in the kidney than in liver or lung. Phenobarbital pretreatment increased the binding in all three tissues but only at the highest dose (400 mg/kg bw). 1-Naphthol was shown not to be an obligate intermediate in the binding process. The metabolism of naphthalene by mouse, rat and hamster pulmonary, hepatic and renal microsomal preparations was compared by Buckpitt *et al*. (1987). In all cases, glutathione adducts derived from naphthalene 1,2-oxide were formed and overall activity was particularly high in mouse lung, with a particular preference in this tissue for the formation of the naphthalene 1*R*,2*S*-oxide isomer (10:1 ratio with the 1*S*,2*R*-isomer).

Lanza *et al*. (1999) examined the ability of microsomal fractions from human lymphoblastoid cells expressing recombinant human CYP2F1 enzyme to metabolize naphthalene to glutathione adducts. The predominant conjugates formed were derived from naphthalene 1*S*,2*R*-oxide (see Table 8), in contrast to the findings in mice (Buckpitt *et al*., 1992) (see Figure 2).

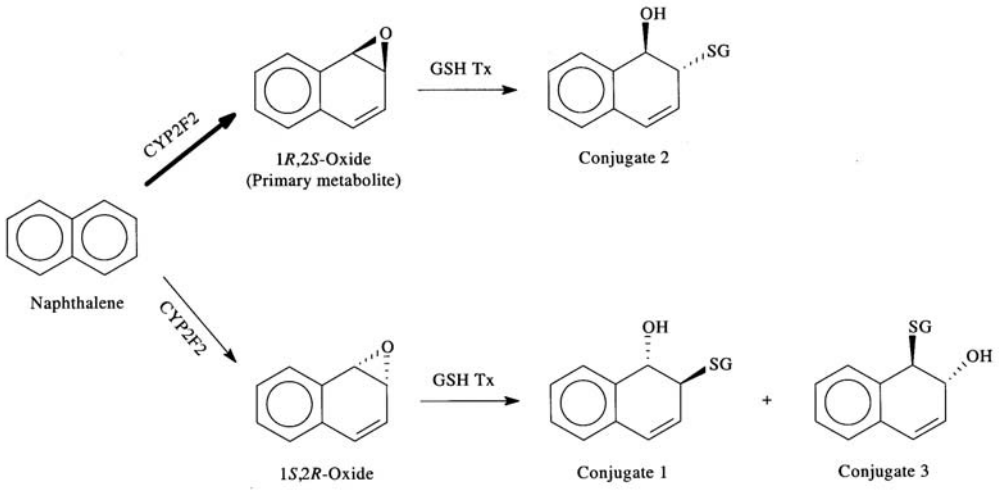
In view of the mouse lung as a target tissue, a number of investigators have examined species, tissue and cytochrome P450 (CYP) isozyme specificities in naphthalene metabolism. Nagata *et al*. (1990) identified the principal pulmonary enzyme in the mouse as

Table 8. Species comparison in the rates of conversion of naphthalene to naphthalene 1,2-oxides by recombinant enzymes

Recombinant enzyme	Species	Rate of metabolism[a]	Stereoselectivity[b]	Reference
CYP2F1	Human	35.5[c]	0.13:1	Lanza *et al*. (1999)
CYP2F2	Mouse[d]	104 000[e]	66:1	Shultz *et al*. (1999)

Modified from Buckpitt *et al*. (2002)
[a] Expressed in pmol/min/nmol enzyme
[b] Expressed as ratio of epoxide stereoisomers (1*R*,2*S*):(1*S*,2*R*)
[c] Total amount of glutathione conjugates (1 + 2 + 3) (see Figure 2)
[d] Sequence homology with human enzyme, 82%
[e] Amount of glutathione conjugate 2 (see Figure 2)

Figure 2. Metabolism of naphthalene by murine CYP2F2 to reactive epoxides and their subsequent trapping as glutathione conjugates



From Shultz *et al.* (1999)
Conjugates are numbered in the order of their elution after separation by reversed-phase HPLC.
GSH Tx, glutathione transferases

P450m50b [CYP2F2], which formed predominantly naphthalene 1*R*,2*S*-oxide (see Table 8 and Figure 2). Ritter *et al*. (1991) confirmed that the primary isoform responsible for naphthalene metabolism in the mouse lung was in the 2F subfamily. It was not inducible by phenobarbital, pyrazole, pregnenolone 16α-carbonitrile or 3-methylcholanthrene. Kanekal *et al*. (1991) examined the relationship between cytotoxicity and metabolism of naphthalene oxide using the isolated perfused lung of male CFW mice.

Perfusion of the lung with naphthalene 1,2-oxide reduced glutathione levels to 40–60% of control. 1,4-Naphthoquinone and naphthyl-glucuronide were the major polar metabolites, along with smaller amounts of the dihydrodiol and thioether conjugates. When lungs were perfused with naphthalene, the thioethers and the dihydrodiol predominated as metabolites. Chichester *et al.* (1991, 1994) demonstrated that Clara cells isolated from male Swiss Webster mice metabolized naphthalene to the dihydrodiol and glutathione conjugates. Microsomal preparations from Clara cells (supplemented with glutathione and glutathione *S*-transferases) metabolized naphthalene to the dihydrodiol as a minor product and formed a single glutathione adduct, derived from the 1*R*,2*S*-isomer of naphthalene oxide, as the major product, whereas the dihydrodiol predominated in intact cells. Buckpitt *et al.* (1992) determined the rates of formation and the stereochemistry of metabolites of naphthalene in postmitochondrial supernatant (S9) preparations from nasal mucosa and in microsomes from lung and liver of mice (Swiss Webster), rats (Sprague-Dawley), hamsters (Syrian golden) and rhesus monkeys (*Macaca mulatta*) (see Table 9 for details). Metabolism by mouse lung was considerably greater than that by the lungs of the rat, hamster and monkey. Using total diol and conjugates for comparison, the activity of mouse lung was two orders of magnitude higher than that of the monkey lung. In mouse lung there was preferential formation of the naphthalene 1*R*,2*S*-oxide, as judged from the stereochemistry of the glutathione conjugates. In microdissected airways, the extent of metabolism of naphthalene to the dihydrodiol and the glutathione conjugates was much higher in the airways of Swiss Webster mice compared with Sprague-Dawley rats or Syrian golden hamsters. In all three species, the rate of metabolism was higher in the distal airways than in the trachea (Buckpitt *et al*., 1995). In mice, there was a high degree of stereoselectivity, the only glutathione conjugate being

Table 9. Species comparison in the rates of conversion of naphthalene to naphthalene oxides: pulmonary and nasal tissue

Microsome source	Species	Rate of metabolism (nmol/min/mg protein)[a]	Stereoselectivity ratio (1*R*,2*S*):(1*S*,2*R*)[b]	Dihydrodiol as % of total metabolites
Pulmonary microsomes	Mouse	13.8	11.1	7.6
	Rat	1.69	0.48	4.6
	Hamster	5.12	0.61	24.6
	Rhesus macaque	0.15	0.12	20.6
Post-mitochondrial supernatant (olfactory)	Mouse	87.1	12.7	7.4
	Rat	43.5	~ 36	4.1
	Hamster	3.9	?	7.8

Modified from Buckpitt *et al.* (2002)

[a] Total amount of dihydrodiol plus conjugates 1, 2, 3 formed (see Figure 2)

[b] The stereoselectivity varies with the concentration of substrate; the values given here are derived from incubations containing 0.5 mM naphthalene.

that derived from the 1*R*,2*S*-oxide of naphthalene. Airways of mice formed the dihydrodiol and naphthalene 1*R*,2*S*-oxide at rates substantially higher than those of rats. Immunolocalization of CYP2F2 correlated well with the sites of metabolism, in agreement with the findings of Nagata *et al.* (1990) and Ritter *et al.* (1991) as to the importance of this isoenzyme. This was confirmed in later studies (Shultz *et al.*, 1999), in which CYP2F2, expressed in *Spodoptera frugiperda* and *Trichoplusia ni* cells by use of a baculovirus expression vector system, metabolized naphthalene with a high degree of stereoselectivity to naphthalene 1*R*,2*S*-oxide (66:1 enantiomeric ratio). Substituted naphthalenes such as 1-nitronaphthalene and 2-methylnaphthalene are also substrates for purified CYP2F2 (Shultz *et al.*, 2001).

Willems *et al.* (2001) developed a physiologically based pharmacokinetic model for naphthalene administered by inhalation or by intravenous injection to Fischer 344 rats and $B6C3F_1$ mice. Model simulations for exposure by inhalation indicated that approximately 88–96% of the absorbed naphthalene was metabolized by rats and 96–98% by mice. The overall percentage of naphthalene metabolized by mice exposed to 30 ppm [157 mg/m^3] was higher than for rats exposed to 60 ppm [314 mg/m^3] because of the higher ventilation and metabolic rates in mice. The steady-state concentrations in the lungs of the mice and rats were similar at the same level of naphthalene exposure. Cumulative metabolism of naphthalene by the lung was markedly higher in the mouse than in the rat. The rates of metabolism did not increase proportionally with concentration, suggesting saturation of metabolism in this organ. The model indicated that the metabolism of naphthalene by the liver was similar in the two species.

4.2 Toxic effects

4.2.1 *Humans*

The major toxicological responses reported in humans from acute exposure to naphthalene have been haemolytic anaemia and cataracts (Zuelzer & Apt, 1949; Ghetti & Mariani, 1956; Dawson *et al.*, 1958; Zinkham & Childs, 1958). Poisoning from naphthalene has been accidental or suicidal and occurs as a result of either inhalation of fumes containing naphthalene or by ingestion of mothballs (Ojwang *et al.*, 1985; Todisco *et al.*, 1991). Accidental ingestion of household products containing naphthalene, such as mothballs or deodorant blocks, frequently occurs in children. Twelve cases of haemolytic anaemia in children secondary to the ingestion of naphthalene were reported between 1949 and 1959 (Anziulewicz *et al.*, 1959). Each child had either sucked or swallowed mothballs. Haemolytic anaemia was also observed in babies exposed to naphthalene from mothball-treated diapers, blankets or clothes (Anziulewicz *et al.*, 1959; Valaes *et al.*, 1963). In 1990, 2400 cases of accidental naphthalene ingestion were reported to 72 poison control centres in the USA. Nearly 90% of these cases occurred in children under six years of age (Woolf *et al.*, 1993). Haemolytic anaemia has also been associated with ingestion of naphthalene-containing anointing oil (Ostlere *et al.*, 1988).

Siegel and Wason (1986) reviewed a number of case studies to examine the haematological properties of naphthalene; one day after exposure, Heinz-body haemolytic anaemia leads to a sharp fall in haemoglobin, haematocrit and red blood cell counts and, in some cases, to concurrent leukocytosis. Reticulocytosis then follows with a gradual restoration of normal blood levels, except in cases of severe poisoning.

Individuals with decreased glucose-6-phosphate dehydrogenase activity in their erythrocytes are sensitive to haemolytic anaemia following exposure to naphthalene, although toxic reactions have also been observed in individuals without red cell defects. Four black patients (three male and one female) who had been exposed to naphthalene were found to have haemolytic anaemia. One of the patients was a newborn whose mother had ingested mothballs. All four patients had red blood cell glucose-6-phosphate dehydrogenase deficiency (Zinkham & Childs, 1958).

[The Working Group noted that in all of these cases the amount of naphthalene ingested was not reported.]

Additional data on the effects of exposure to naphthalene in infants and children are presented in Section 4.3.1.

4.2.2 *Experimental systems*

(*a*) *In-vivo studies with single doses*

The oral LD_{50} of naphthalene in CD-1 mice was 533 mg/kg bw for males and 710 mg/kg bw for females (Shopp *et al*., 1984).

Naphthalene causes cataracts in rats (Rathbun *et al*., 1990; Tao *et al*., 1991), rabbits (van Heyningen, 1979) and mice (Wells *et al*., 1989). Haemolytic anaemia has not been reported in experimental animals.

The biochemical pathways that modulate the cataractogenicity of naphthalene were investigated using biochemical probes and naphthalene bioactivation and detoxification in C57BL/6 and DBA/2 mice (Wells *et al*., 1989). These mouse strains differ in susceptibility to the induction of CYP enzymes and the development of naphthalene-induced cataracts. Intraperitoneal injection of 500–2000 mg/kg bw naphthalene caused cataracts in C57BL/6 mice in a dose-dependent fashion. 1-Naphthol (56–62 mg/kg bw), 1,2-naphthoquinone and 1,4-naphthoquinone (5–250 mg/kg bw), metabolites of naphthalene, administered intraperitoneally to these mice were also found to cause cataracts. Pretreatment of the mice with SKF525A or metyrapone (CYP inhibitors), several types of antioxidants, the glutathione precursor *N*-acetylcysteine or the free radical-trapping agent, α-phenyl-*N*-*tert*-butylnitrone, decreased the incidence of cataracts. Cataracts were enhanced by pretreatment with phenobarbital and the glutathione depletor diethyl maleate. DBA/2 mice treated intraperitoneally with naphthalene (2000 mg/kg bw), 1,2- or 1,4-naphthoquinone or diethyl maleate followed by naphthalene did not develop cataracts. These results support the hypothesis that the cataractogenesis by naphthalene in C57BL/6 mice requires CYP-catalysed bioactivation to a reactive intermediate and that detoxification is dependent upon glutathione. The lack of cataract

induction in DBA/2 mice after treatment with naphthalene or its metabolites 1,2- or 1,4-naphthoquinone suggests that these mice may be unable to convert the latter into free radical intermediates.

Spiro-(2,7-difluorofluorene-9,4′-imidazoline)-2′,5′-dione (ALØ1576) is an aldose reductase inhibitor that can prevent the development of naphthalene-induced cataracts in rats. This action is believed to involve inhibition of the reduction of naphthalene dihydrodiol to 1,2-dihydroxynaphthalene (Xu *et al*., 1992; Lou *et al*., 1996). Male rats of five strains (4–5 weeks of age), including two pigmented (Long-Evans and Brown Norway) and three albino (Sprague-Dawley, Wistar and Lewis) strains, were given naphthalene by gavage at 500 mg/kg bw per day for three days, then 1000 mg/kg bw per day for up to six weeks. Each experiment included groups treated with vehicle alone (control), naphthalene, naphthalene plus ALØ1576 or ALØ1576 alone. The aldose reductase inhibitor was given at 10 mg/kg bw per day by gavage one hour before the naphthalene feeding. Naphthalene induced cataracts in all five strains. During administration of naphthalene, whole-lens glutathione levels were 20–30% lower than those of controls. After four weeks of administration, an almost 20-fold increase in the content of protein–glutathione mixed disulfides was observed in the lenses. ALØ1576 completely prevented all morphological and chemical changes in the lenses of naphthalene-treated rats (Xu *et al*., 1992). To determine whether pigmentation is required for naphthalene-induced cataract formation, Murano *et al*. (1993) studied the progression of cataracts in Brown Norway and Sprague-Dawley rats that had received an oral dose of naphthalene (1000 mg/kg bw) every other day for six weeks. The changes in the lens were qualitatively similar in the two strains, but the cataract progressed more uniformly and more rapidly in the Brown Norway rats.

An intraperitoneal injection of 0.05–2.0 mmol/kg bw naphthalene in corn oil in C57BL/6J mice (weighing 15–20 g) caused a specific bronchiolar lesion characterized by a dilation of Clara cells with loss of apical projections. The Clara cells later became exfoliated from large areas of the bronchioles. After loss of the Clara cells, abnormalities appeared on the surface of the ciliated cells and, within 48 h after administration of naphthalene, there was rapid division of the remaining cells. The repopulated Clara cells were distributed randomly in the bronchioles, with gradual re-establishment of the classic canal-like pattern (Mahvi *et al*., 1977).

Intraperitoneal injection of 200–375 mg/kg bw naphthalene in male Swiss Webster mice produced highly selective necrosis of the bronchiolar epithelial cells but no necrosis in the kidney or liver. This pulmonary damage was more severe when the mice were pretreated with diethyl maleate (which depletes glutathione) and less severe after pretreatment with piperonyl butoxide (which inhibits CYP enzymes). In contrast, treatment with SKF 525A (another CYP inhibitor) before treatment with naphthalene had no effect on naphthalene-induced pulmonary damage. Intraperitoneal injection of 25–600 mg/kg bw [^{14}C]naphthalene resulted in covalent binding of naphthalene-derived radioactivity to tissue macromolecules, with the highest levels of binding in lung, liver and kidney. The level of binding corresponded with rapid depletion of glutathione in both the lung and

liver. Pretreatment with diethyl maleate increased the binding of radiolabelled material, while piperonyl butoxide and SKF 525A decreased the binding by 75% and 50%, respectively (Warren *et al*., 1982).

O'Brien *et al*. (1985) studied the species-dependent pulmonary toxicity of naphthalene. Male Swiss T.O. mice (weighing 20–25 g) and male Wistar-derived rats (weighing 200–225 g) were given intraperitoneal doses of naphthalene at 200–600 and 400–1600 mg/kg bw, respectively. The lungs, livers, kidneys and spleen were removed 24 h after the injection and prepared for light microscopy. In mice, there was selective damage to the non-ciliated bronchiolar epithelial (Clara) cells at low doses of naphthalene. At high doses of naphthalene, vascular and hydropic degeneration of cells in the proximal convoluted tubule was observed together with protein casts in the collecting ducts. Tissue damage was not observed in the lung, liver or kidney of rats that received up to 600 mg/kg bw naphthalene. Non-protein sulfhydryl was depleted in a time-dependent manner in the lungs, liver, spleen and kidneys of naphthalene-treated mice, but only in the lung and liver of treated rats. Administration of 1-naphthol (200 mg/kg bw to mice and 200–250 mg/kg bw to rats) did not lead to depletion of non-protein sulfhydryl levels or tissue damage in the liver, lung or kidney of either species. Covalent binding and metabolism of naphthalene were approximately 10-fold greater in mouse lung microsomes than in rat lung microsomes. The authors attributed the differences in naphthalene-induced toxicity in mice and rats to differences in metabolism between the two species.

Intraperitoneal injection of 1.6–4.7 mmol/kg bw (200–600 mg/kg bw) naphthalene in male ddY mice resulted in a dose-dependent increase in lung damage mainly in the bronchiolar region, with no damage following a dose of 0.78 mmol/kg (100 mg/kg bw). The response was enhanced by diethyl maleate treatment. Increasing the dose of naphthalene from 1 to 3 mmol/kg bw resulted in a decrease in pulmonary glutathione levels. Naphthalene did not affect lipid peroxidation or phospholipid content in the lungs. In lung slice preparations, the covalent binding of naphthalene was increased or decreased when the mice had been pretreated with inducers or inhibitors of CYP enzymes, respectively (Honda *et al*., 1990).

A single intraperitoneal injection of 2 mmol/kg bw naphthalene in ddY mice resulted in a 50% reduction of carbonyl reductase activity and microsomal mixed-function oxidase activities in the Clara cells (Matsuura *et al*., 1990).

Naphthalene was given by intraperitoneal injection to Swiss Webster mice (0–400 mg/kg bw), Syrian golden hamsters (0–800 mg/kg bw) and Sprague-Dawley rats (0–1600 mg/kg bw). The animals were killed 24 h later for identification of the specific sites of the respiratory tract affected by the treatment (nasal cavity and tracheobronchial airway tree). In mice, the injury to the tracheobronchial epithelium was dose-dependent and Clara cell-specific. At 50 mg/kg bw, naphthalene produced swelling and vacuolation of Clara cells in terminal bronchioles. The number of terminal bronchioles with vacuolated Clara cells and the number of Clara cells within the terminal bronchioles that showed vacuolation increased after 100 mg/kg bw naphthalene. Following 200 and 300 mg/kg bw, almost all of the non-ciliated cells lining the terminal bronchioles in mice

were exfoliated and necrotic. In contrast, no effect was observed on Clara cells or ciliated cells of terminal bronchioles in rats treated with up to 1600 mg/kg bw naphthalene. Only minor changes in Clara cells at some terminal bronchioles were observed in hamsters dosed with 800 mg/kg bw naphthalene. The nasal cavity showed specific injury in the olfactory epithelium in a dose- and species-dependent manner, with rats being the most sensitive species (Plopper *et al*., 1992a). A morphometric comparison of changes in the epithelial population of the terminal bronchioles and lobar bronchi showed that Clara cells and ciliated cells in mice were affected by treatment with naphthalene, while the bronchiolar epithelium of rats and hamsters was insensitive to this treatment (Plopper *et al*., 1992b). In a companion study, Buckpitt *et al*. (1992) demonstrated that the stereochemistry of the epoxidation of naphthalene may be important in the target tissue (lung) and species selectivity (mouse) of naphthalene toxicity (see Section 4.1.2(*b*)).

Female FVB/n mice (2–4 months of age) were given an intraperitoneal injection of 0, 50, 100 or 200 mg/kg bw naphthalene in corn oil and killed at various time points to investigate the phenotypic changes in airway epithelial cells after acute Clara cell injury. Clara cell cytotoxicity from naphthalene resulted in the exfoliation of epithelial cells containing CC10 protein, a Clara cell secretory protein. This exfoliation occurred at the same time (24 h after treatment) as a reduction in the levels of mRNA for CC10 and CYP2F monooxygenase. The mRNA for cyclin-dependent kinase 1 (CDK1), a marker of cell cycling, was detected in a large number of cells in and around the bronchioles and terminal bronchioles 48 h after treatment with naphthalene. The airways were re-populated with immature epithelial cells lacking normal levels of CC10 mRNA and over-expressing the mRNA for surfactant protein B. At 72 h after injection of naphthalene, a reduction in the number of CDK1 mRNA-positive cells was observed, except at the airway bifurcations, where increased expression of mRNA CDK1 was observed relative to the 48-h time point. The results suggest that the repair of acute airway epithelial cell injury induced by naphthalene occurs in overlapping stages, beginning with clearance of dead cells followed by the proliferative re-population of injured areas and maturation of newly re-populated regions (Stripp *et al*., 1995).

Naphthalene (300 mg/kg bw) was administered intraperitoneally to male FVB/n mice (7–9 weeks of age) 36–72 h before intraperitoneal administration of [^{3}H]thymidine (20 Ci/mmol) at a dose of 2.5 μCi/kg bw. Lungs were removed five days after treatment. Naphthalene toxicity resulted in pulmonary neuroendocrine-cell hyperplasia, which was characterized by increased numbers of neuroepithelial bodies without significant changes in the number of isolated pulmonary neuroendocrine cells and with increased [^{3}H]thymidine labelling of cells that produce calcitonin gene-related peptide, a marker of neuroendocrine cells. These results suggest a key role of neuroendocrine cells in the reparative process of airway epithelial cell renewal after naphthalene-induced injury in mice (Stevens *et al*., 1997). Five days after an intraperitoneal injection of naphthalene (300 mg/kg bw) to male FVB/n mice (12–14 weeks of age), an abundance of pulmonary neuroendocrine cells and neuroepithelial bodies was observed along the main axial pathway of the right middle lobe of the lung. Calcitonin gene-related peptide was used

to identify the location, size and number of these cells in the airways. Neuroepithelial bodies were significantly increased in number and pulmonary neuroendocrine cells were significantly enlarged in naphthalene-treated lungs compared with controls (Peake *et al*., 2000).

Immature Clara cells of neonatal mice are more susceptible to the toxicity of naphthalene than are mature Clara cells of adult mice. Vacuolation and exfoliation associated with cytotoxicity of Clara cells were dose-dependent when 7-day-old, 14-day-old or adult Swiss Webster mice were given a single intraperitoneal injection of 0, 25, 50 or 100 mg/kg bw naphthalene in corn oil and killed 24 h later. The range of doses at which Clara cell injury occurred varied with age, with the youngest animals being the most susceptible. The 7- and 14-day-old mice were more sensitive to the toxicity of naphthalene despite the fact that, at these ages, the airways have lower ability to activate naphthalene to its reactive intermediates compared with adult mice (Fanucchi *et al*., 1997).

To define the repair pattern of Clara cells after massive injury, male Swiss Webster mice (2–3 months of age) were given an intraperitoneal injection of naphthalene (200 mg/kg bw) in corn oil and the lungs were evaluated at various times up to 14 days after treatment. Clara cells of terminal bronchioles were vacuolated and swollen on day 1 after the naphthalene injection, exfoliated on day 2 and resembled those of the controls on day 14. Cell proliferation was increased within the epithelium and interstitium at day 1, reached a maximum at day 2 and was close to the control level at all other time points. Markers of Clara cell differentiation were barely detectable in the terminal bronchiolar epithelium at days 1 and 2, clearly detectable at day 4 and returned to control levels between days 5 and 14. The results showed that repair of the bronchiolar epithelium after naphthalene treatment involved distinct phases of cell proliferation and differentiation, including proliferation of cells other than Clara cells, and interaction of multiple cell types including non-target cells (Van Winkle *et al*., 1995).

Swiss-Webster mice (8–10 weeks of age) were given an intraperitoneal injection of 0 or 200 mg/kg bw naphthalene and the temporal pattern of intracellular changes was evaluated up to 6 h following treatment. Whole-lung preparations from these mice were stained with cell-permeant and -impermeant nuclear binding fluorochromes and examined by means of high-resolution light, electron and confocal fluorescence microscopy. These methods allowed the assessment of Clara cell necrosis and cell permeability on the same samples. After acute exposure to naphthalene *in vivo*, early stages of injury to bronchiolar Clara cells included swelling of the smooth endoplasmic reticulum and bleb formation, followed by increases in cell membrane permeability (Van Winkle *et al*., 1999).

In a study in which mice were treated similarly, intracellular glutathione content was measured and compared with the degree of cytotoxicity up to 3 h after treatment. Loss of intracellular glutathione is an early event that precedes initial signs of cellular damage. Once glutathione concentration dropped below 25% of the control, injury was irreversible (Plopper *et al*., 2001).

Male Swiss Webster mice and male Sprague-Dawley rats were exposed to naphthalene (0–110 ppm) [0–580 mg/m^3] for 4 h via whole-body inhalation (West *et al*., 2001). Other groups of mice were given an intraperitoneal injection of 0, 50, 100, 200 or 400 mg/kg bw naphthalene. Inhalation exposure of rats to naphthalene did not result in any detectable changes in the airway epithelial cells. In mice, exposure to naphthalene at concentrations above 2 ppm [10.5 mg/m^3] resulted in a concentration-dependent increase in Clara cell injury. At low concentrations, naphthalene caused injury in the proximal airways, while at high concentrations, there was injury both in proximal airways and in the more distal conducting airways. Parenteral exposure of mice to naphthalene caused injury that was limited to the distal airways at low dose (≤ 200 mg/kg bw), while at higher doses (> 300 mg/kg bw), the injury also included the proximal conducting airways. The higher sensitivity of the distal airways was initially attributed to higher rates of naphthalene metabolism (Buckpitt *et al*., 1995), but the results of West *et al*. (2001) suggest that cells throughout the airways are equally sensitive and that sensitivity differences between proximal and distal airways to naphthalene treatment may be due to differences in the distribution of the compound, although there are no data to support this suggestion. In conclusion, the pattern of injury after exposure to naphthalene is species-specific and highly dependent on route of exposure.

The ability of naphthalene to cause oxidative stress was assessed in female Sprague-Dawley rats (weighing 160–180 g) given vitamin E succinate for three days and then administered 1100 mg/kg bw naphthalene as a single oral dose on day 4. Another group of rats received naphthalene alone. Naphthalene induced oxidative stress as measured by increased lipid peroxidation in mitochondria in liver and brain and reduction of glutathione concentrations in these organs. The treatment also increased DNA single-strand breaks in liver tissue, and induced an increase in membrane fluidity in liver and brain microsomes, together with increases in the urinary elimination of malonaldehyde, formaldehyde, acetaldehyde and acetone. These indices of oxidative stress were less strong in the rats that had been pretreated with vitamin E succinate (Vuchetich *et al*., 1996). [The Working Group noted the high dose used in this study.]

(*b*) *In-vivo studies with multiple doses*

Yamauchi *et al*. (1986) reported that daily administration of oral doses [number of days not given] of 1 g/kg bw naphthalene to male Wistar rats (weighing 150–170 g) resulted in increases in levels of serum and liver lipid peroxides, suggesting enhanced lipid peroxidation. Oral administration of naphthalene in dose increments up to 750 mg/kg bw over nine weeks also enhanced lipid peroxidation and decreased the activity of selenium-dependent glutathione peroxidase in the liver of male Blue-Spruce rats (Germansky & Jamall, 1988).

Male albino rats (weighing 100–125 g) were administered 1 g/kg bw naphthalene orally in refined groundnut oil daily for 10 days. Biochemical alterations in the liver, kidney and eye were evaluated. Significant changes were observed only in the liver, including increased liver weight, lipid peroxidation and aniline hydroxylase activity.

Alkaline phosphatase activity was slightly increased in the liver and eye. No significant changes were observed in the kidney (Rao & Pandya, 1981). [The Working Group noted the high dose used in this study.]

Male and female CD-1 mice were administered daily doses of 0, 27, 53 or 267 mg/kg bw naphthalene orally for 14 consecutive days or a suspension of 0, 5.3, 53 or 133 mg/kg bw naphthalene in corn oil daily for 90 consecutive days. Surviving animals were killed 24 h after the final dose. In the 14-day study, naphthalene caused a decrease in body weight and thymus weight in male mice and decreases in body and spleen weights and increases in lung weights in female mice, at the high dose only. In the 90-day study, the spleen weights were also reduced in the female mice at the high dose only. Immunotoxicity end-points (e.g., humoral immune response, response to mitogens, delayed hypersensitivity response, popliteal lymph node response, bone-marrow stem cell number and bone-marrow function) did not show any significant change from controls after either 14 days or 90 days of naphthalene administration. Although there was a slight alteration in haematological parameters, no haemolytic anaemia was observed. Serum enzymes, electrolyte levels and hexobarbital sleep times did not show consistent or dose-dependent changes after 14 or 90 days of naphthalene treatment. There was no treatment-related effect on the hepatic mixed-function oxidase system or glutathione levels after 90 days of exposure. A dose-related inhibition of hepatic aryl hydrocarbon hydroxylase activity was observed in both males and females (Shopp *et al*., 1984).

Bronchiolar airways from male Swiss Webster mice treated intraperitoneally with naphthalene daily for seven days (50, 100 or 200 mg/kg bw) differed only slightly from those of untreated control mice, with no evidence of necrotic or exfoliated cells. In contrast, a single intraperitoneal dose of naphthalene (50, 100 or 200 mg/kg bw) caused a dose-dependent increase in the incidence and severity of bronchiolar epithelial cell necrosis. Also, when mice were treated with intraperitoneal doses of 200 mg/kg bw daily for seven days and then challenged on day 8 with a dose of 300 mg/kg bw naphthalene, the bronchiolar injury was less severe than in mice treated with a single dose of 300 mg/kg bw naphthalene. To evaluate the mechanism of this tolerance to naphthalene, the rate of formation of naphthalene 1*R*,2*S*-oxide was measured in microsomes from treated (7 × 200 mg/kg bw) and control mice. In lung microsomes from naphthalene-treated mice, there was a > 60% decrease in the rate of naphthalene metabolism compared with lung microsomes from controls. This effect was not seen in liver microsomes from these mice. However, there was no difference in the rate of formation of reactive, covalently bound naphthalene metabolites *in vivo* or *in vitro* (measured in lung microsomal preparations) between tolerant and control mice (O'Brien *et al*., 1989).

The bronchiolar epithelium of male Swiss Webster mice treated orally daily for seven days with 200 mg/kg bw naphthalene resembled that of control mice with respect to the ciliated and non-ciliated cells and nuclear and cytoplasmic volumes. Subsequent treatment of these mice with higher doses (300 mg/kg bw) did not cause the Clara cell injury observed previously in untreated mice after a single injection of 300 mg/kg bw naphthalene. Repeated exposure to naphthalene resulted in lower activities of CYP

monooxygenases in the bronchiolar epithelium. Covalent binding of reactive naphthalene metabolites to proteins in lungs of tolerant mice was similar to that in control mice (Lakritz *et al*., 1996).

Male Swiss Webster mice were made tolerant by seven daily injections of 200 mg/kg bw naphthalene. The concentration of glutathione in the terminal airways, measured 24 h after the last injection, was 2.7-fold higher than in vehicle control mice. A challenge dose of naphthalene (300 mg/kg bw, given on day 8) did not produce injury. However, tolerant mice that were allowed to recover for 96 h after the seventh injection were again susceptible to injury induced by a challenge dose, and the concentration of glutathione in the terminal airways had declined to control values. Tolerant mice treated on day 8 simultaneously with the challenge dose of naphthalene and buthionine sulfoximine, an inhibitor of γ-glutamylcysteine synthetase, appeared as susceptible to injury as naphthalene-challenged controls. These results showed that increased rates of glutathione synthesis were critical for resistance to naphthalene toxicity in male Swiss-Webster mice (West *et al*., 2000).

A 10% solution (w/v) of naphthalene in corn oil was administered by gavage to Brown Norway rats at a dose of 0.7 g/kg bw per day for 102 days; control rats received corn oil only. Two of the naphthalene-treated groups were given normal diet containing one of two types of aldose reductase inhibitor at concentrations known to inhibit sugar cataract formation in galactose-treated rats. The remaining naphthalene-treated groups and the controls were given unmodified diet. Gradual, progressive development of zonal opacities with decreased lens glutathione peroxidase and glutathione reductase activities was observed in rats given naphthalene or naphthalene plus a carboxylic acid aldose reductase inhibitor, but not naphthalene plus a hydantoin-type aldose reductase inhibitor. These results led the authors to suggest an oxidative mechanism in naphthalene-induced cataract formation (Tao *et al*., 1991). Rathbun *et al*. (1990) also showed the progressive development of cataracts in Black-Hooded rats given a daily dose of 1 mL of a 10% (w/v) solution of naphthalene in corn oil by gavage for up to 79 days, together with a progressive loss of lens glutathione peroxidase and glutathione reductase activity, i.e., impairment of the defence system against oxidative damage. Holmén *et al*. (1999) later demonstrated that 0.5 and 1.0 g/kg bw naphthalene given by gavage twice a week for 10 weeks causes cataractous changes in Brown Norway rats.

Male and female B6C3F$_1$ mice (10–11 weeks of age) were exposed by inhalation to 0, 10 or 30 ppm [0, 52 or 157 mg/m^3] naphthalene for 6 h per day on five days per week for 104 weeks (Abdo *et al*., 1992; National Toxicology Program, 1992). Naphthalene caused increased incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium and hyperplasia of the respiratory nasal epithelium and chronic inflammation in the lungs of both male and female mice. In another chronic inhalation study, male and female Fischer 344 rats were exposed to 0, 10, 30 or 60 ppm [0, 52, 157 or 314 mg/m^3] naphthalene for 6 h per day on five days per week for 105 weeks (National Toxicology Program, 2000). Non-neoplastic lesions that were observed in exposed rats at incidences greater than those in the chamber controls included atypical

hyperplasia, atrophy, chronic inflammation and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia. The incidence and severity of these lesions increased with increasing exposure concentration.

(*c*) *In-vitro studies*

Naphthalene and its metabolite 1-naphthol (0–100 μM; 2 h, 37°C) were cytotoxic to mononuclear leukocytes after metabolic activation with human liver microsomes. Other metabolites of naphthalene, including 1,2-naphthoquinone and 1,4-naphthoquinone (0–100 μM; 2 h, 37 °C), were directly toxic to mononuclear leukocytes and depleted glutathione to 1.0% of control levels. The primary metabolite of naphthalene, the 1,2-epoxide, was not cytotoxic at concentrations up to 100 μM and did not deplete glutathione, suggesting that the quinones are responsible for the cytotoxicity of naphthalene in human mononuclear leukocytes (Wilson *et al.*, 1996).

Perfusion of the lungs of male Swiss Webster mice (4–5 weeks of age) with naphthalene (0.02–2 mM in Waymouth's medium for a one-hour period followed by 4 h in medium) resulted in swelling and vacuolation of Clara cells. This was followed by concentration-dependent losses of Clara cells from the bronchiolar epithelium. Pulmonary glutathione levels decreased over a range of 60% (at the 0.2-mM dose) to less than 10% (at the 2-mM dose) of the corresponding control level. Following perfusion with [^{14}C]naphthalene (1.67–167 μM for 30 min followed by 4.5 h in medium), reactive metabolites were covalently bound to protein in the lung and perfusate. Total binding (nanomoles bound) and specific activity (nanomoles per milligram protein) increased in lung tissue with increasing concentrations of naphthalene (Kanekal *et al*., 1990). A subsequent study with this isolated perfused mouse lung system demonstrated that the circulating epoxides of naphthalene play a significant role in naphthalene-induced lung injury. Injury to Clara cells in lungs perfused with naphthalene or secondary metabolites such as naphthoquinones, 1-naphthol and 1,2-dihydro-1,2-dihydroxynaphthalene was less dramatic than the effects observed following exposure to naphthalene 1,2-oxide (Kanekal *et al*., 1991).

The metabolism and cytotoxicity of naphthalene and its metabolites were investigated *in vitro* in Clara cells isolated from male Swiss Webster mice (4–5 weeks of age). The cells were incubated for 2 or 4 h with 0.1, 0.5 and 1 mM naphthalene, 1,4-naphthoquinone, 1,2-naphthoquinone, 1-naphthol, naphthalene 1,2-oxide and 1,2-dihydroxy-1,2-dihydronaphthalene. The only metabolites that were more toxic to the Clara cells than the parent compound were 1,4-naphthoquinone and naphthalene 1,2-oxide, the latter being the most potent. Piperonyl butoxide, a CYP monooxygenase inhibitor, blocked the toxic effect of naphthalene but not that of naphthalene 1,2-oxide, which suggested that the epoxide is a key participant in the process leading to the loss of cell viability in isolated Clara cells (Chichester *et al*., 1994).

Airways microdissected from male Swiss Webster mice by filling the trachea with 1% agarose were maintained in culture for 8 h. When these explants were incubated with 0.5 mM naphthalene, the cytotoxic response of the bronchial epithelium was identical to the vacuolation and exfoliation observed *in vivo* in bronchioles of mice 24 h after intraperitoneal administration of naphthalene (100 or 300 mg/kg bw). Pre-incubation with piperonyl butoxide prevented naphthalene-induced cytotoxicity (Plopper *et al*., 1991).

To determine whether the formation of reactive metabolites of naphthalene in defined target and non-target regions of the lung correlates with the susceptibility of these areas to naphthalene toxicity, the binding of metabolites in various cell types and in various subcompartments of the mouse lung was investigated. Binding was greater in distal bronchioles and isolated Clara cells incubated with [^{3}H]naphthalene than in explants of mouse trachea or bronchus. Binding was also greater in mouse Clara cells than in mouse hepatocytes (non-target cells) or rat trachea cells (non-susceptible species). There was a good correlation between cellular susceptibility to toxicity and the amount of reactive metabolite bound *in vitro* (Cho *et al*., 1994a,b).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Sensorineural hearing loss was reported in an infant with neonatal hyperbilirubinaemia from haemolysis due to glucose-6-phosphate dehydrogenase deficiency and naphthalene exposure. The baby had normal hearing at 13 days of age, but had developed profound bilateral hearing loss by seven months of age. On the day of admittance to hospital, the infant had been dressed in clothes and placed on a blanket that had all been stored in naphthalene mothballs for five years (Worley *et al*., 1996).

In a survey of neonatal jaundice in association with household drugs and chemicals in Nigeria, the overall incidence of jaundice did not differ significantly in neonates from households with or without a history of exposure to drugs or chemicals. Severe neonatal jaundice, as judged by the need for exchange blood transfusion or death of the infant, was, however, significantly more frequent among neonates from families with a history of naphthalene exposure than in those without (Familusi & Dawodu, 1985). [The Working Group noted that aflatoxin-contaminated food is a possible confounder in this populaton.]

Melzer-Lange and Walsh-Kelly (1989) reported naphthalene-induced haemolysis in a black female infant deficient in glucose-6-phosphate dehydrogenase. Fourteen of 24 children identified as having glucose-6-phosphatase deficiency were diagnosed with haemolysis associated with exposure to naphthalene-containing moth-repellents (Santucci & Shah, 2000).

Acute haemolysis with the presence of Heinz bodies and fragmented erythrocytes occurred following inhalation of naphthalene in 21 newborn Greek infants, 12 of whom

had deficient glucose-6-phosphate dehydrogenase activity in the erythrocytes (Valaes *et al*., 1963).

Two case reports of haemolytic anaemia in newborn infants secondary to maternal ingestion of mothballs or inhalation exposure to naphthalene have been reported. This indicates that naphthalene and/or its metabolites can pass the placenta (Anziulewicz *et al*., 1959; Athanasiou *et al.*, 1997). [The Working Group noted that the exposure concentration of naphthalene was not reported.]

4.3.2 *Experimental systems*

(*a*) *Developmental toxicity studies* in vivo

In CD-1 mice given 300 mg/kg bw naphthalene per day by gavage on gestation days 7–14, maternal lethality was increased, maternal weight gain was decreased and the average number of live offspring per litter was decreased. There was no concomitant increase in the number of dead pups, suggesting that the smaller litter size was due to early embryonic resorption (Plasterer *et al.*, 1985).

In a teratogenicity study in New Zealand white rabbits treated by gavage with up to 120 mg/kg bw on gestation days 6–19, no signs of developmental or maternal toxicity were found (Navarro *et al.*, 1992).

When Sprague-Dawley rats were given intraperitoneal injections of 395 mg/kg bw naphthalene per day on days 1–15 of gestation, no evidence of maternal toxicity or developmental toxicity was found (Hardin *et al.*, 1981).

Some indications of developmental toxicity were observed when Sprague-Dawley rats were given up to 450 mg/kg bw naphthalene per day by gavage on gestational days 6–15. Maternal weight gain was reduced in the groups that received 150 and 450 mg/kg bw per day. There was a significant trend towards decreased fetal body weight and towards an increased percentage of adversely affected implants per litter (i.e., non-live or malformed). An increased incidence of visceral malformations was reported, especially enlarged ventricles of the brain. The percentage of malformed fetuses per litter seen in the 450-mg/kg bw group was 2.5 times greater than in controls, but this difference was not significant (Navarro *et al.*, 1991).

(*b*) *Developmental toxicity studies* in vitro

Preimplantation embryos of ICR mice exposed *in vivo* by intraperitoneal injection of the mother with 14 or 56 mg/kg bw naphthalene on gestational day 2 were collected on gestational day 3.5. Their subsequent in-vitro growth was markedly reduced during 72 h of culture. The viability and implantation capacity were also significantly inhibited (Iyer *et al*., 1990).

In a study of the role of biotransformation on the rodent in-vitro preimplantation embryotoxicity of naphthalene, no toxic effects were observed in the absence of a rat S9 activation system in the culture medium. In the presence of the S9 system, naphthalene caused concentration-dependent embryolethality (approximate LC_{50}, 0.18 mM). This

result indicates that the embryotoxicity of naphthalene is dependent on activation to reactive metabolites (Iyer *et al*., 1991).

(*c*) *Reproductive toxicity in male rats*

Perturbation of glutathione levels in the testes, epididymides and liver following a single intraperitoneal dose of naphthalene (500 mg/kg bw) was studied in adult Sprague-Dawley rats. Naphthalene decreased hepatic and epididymal glutathione, but had little effect on the concentration in the testis. Chemical-induced lowering of glutathione levels in the male reproductive tract may be a mechanism for potentiation of chemically induced germ-cell mutations (Gandy *et al*., 1990).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 10 for references)

Naphthalene has consistently been found inactive in standard bacterial mutagenicity tests. However, when it was tested in the presence of nitrogen-containing reagents under photo-oxidizing or photolytic conditions, mutagenicity was observed, probably as a result of formation of nitronaphthalenes or hydroxynitronaphthalenes (Suzuki *et al*., 1982; Arey *et al*., 1992). Naphthalene also increased the mutagenicity of benzo[*a*]pyrene towards *Salmonella typhimurium* in the presence of an exogenous metabolic activation system (Hermann, 1981).

Naphthalene induced somatic mutations and recombination in the *Drosophila melanogaster* wing-spot test following larval feeding. It also induced sister chromatid exchange and, in the presence of exogenous metabolic activation, chromosomal aberrations in Chinese hamster ovary cells *in vitro*. Naphthalene did not induce gene mutations at the *TK* or *HPRT* locus in human MCL-5B-lymphoblastoid cells; however, an increase in the frequency of CREST-negative micronuclei, indicative of clastogenicity, was reported in this cell line. The naphthalene metabolites, 1,2-naphthoquinone and 1,4-naphthoquinone also caused an increase in sister chromatid exchange in dividing human lymphocytes, while naphthalene 1,2-oxide was inactive.

Oral exposure of mice and rats to naphthalene caused enhanced DNA fragmentation in brain and liver tissues, as judged from the presence of fragmented DNA in supernatants of homogenized tissue lysates. Mice were more sensitive to these effects, particularly p53-deficient mice. Micronuclei were not induced in bone-marrow erythrocytes of Swiss mice exposed to naphthalene *in vivo*. Adducts to haemoglobin, albumin and other proteins were found in liver, lung, kidney, brain tissue and blood cells of CFW and

Table 10. Genetic and related effects of naphthalene and its metabolites

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli K12 *envA*$^{-}$ *uvrB*$^{-}$, prophage induction	NT	–	500	Ho & Ho (1981)
Escherichia coli GY5027 *envA*$^{-}$ *uvrB*$^{-}$, GY40415 *amp*^{R}, prophage induction	NT	–	2000 µg/plate	Mamber *et al.* (1984)
Escherichia coli PQ37, SOS induction (chromotest)	–	NT	NR	Mersch-Sundermann *et al*. (1993)
Salmonella typhimurium TA1535/pSK1002, *umu* gene expression (SOS-inducing activity)	–	–	83 µg/mL	Nakamura *et al.* (1987)
Escherichia coli WP2/WP100 *uvr*A^{-} *rec*A^{-} assay, differential toxicity	NT	–	2000 µg/plate	Mamber *et al*. (1984)
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	NT	–	100 µg/plate	McCann *et al*. (1975)
Salmonella typhimurium TA100, TA98, reverse mutation	–	–	384 µg/plate	Florin *et al.* (1980)
Salmonella typhimurium TA100, TA98, UHT8413, UHT8414, reverse mutation	–	–	2000 µg/plate	Connor *et al*. (1985)
Salmonella typhimurium TA100, TA98, TA2637, reverse mutation	–	–	500 µg/plate[c]	Nohmi *et al.* (1985)
Salmonella typhimurium TA100, TA98, TA97, reverse mutation	–	–	50 µg/plate[d]	Sakai *et al.* (1985)
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	33 µg/plate[d]	Mortelmans *et al.* (1986)
Salmonella typhimurium TA1535, reverse mutation	NT	–	1000 µg/plate	Narbonne *et al.* (1987)
Salmonella typhimurium TA1537, reverse mutation	NT	–	100 µg/plate[d]	Gatehouse (1980)
Salmonella typhimurium TA1537, reverse mutation	NT	–	200 µg/plate	Seixas *et al*. (1982)
Salmonella typhimurium TA1538, reverse mutation	NT	–	500 µg/plate	Gatehouse (1980)
Salmonella typhimurium TA98, reverse mutation	NT	–	500 µg/plate	Ho *et al.* (1981)
Salmonella typhimurium TA98, reverse mutation	NT	–	100 µg/plate[d]	Narbonne *et al.* (1987)
Salmonella typhimurium TM677, reverse mutation	NT	–	256 µg/plate	Kaden *et al.* (1979)

Table 10 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Drosophila melanogaster, somatic mutation and recombination	+		640 (larval feed)	Delgado-Rodriguez *et al.* (1995)
DNA strand breaks, rat hepatocytes *in vitro*, alkaline elution	–	NT	38	Sina *et al.* (1983)
Micronucleus formation, newt larvae (*Pleurodeles waltl*) erythrocytes	(+)		0.25 ppm	Djomo *et al.* (1995)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	27	Galloway *et al.*, 1987; National Toxicology Program (2000)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	+	30	Galloway *et al.*, 1987; National Toxicology Program (2000)
DNA fragmentation, macrophage J774A.1 cells *in vitro*, centrifugation	+	NT	26	Bagchi *et al.* (1998a)
Gene mutation, human MCL-5B-lymphoblastoid cells, *TK* and *HPRT* loci, *in vitro*	–	NT	40	Sasaki *et al.* (1997)
Sister chromatid exchange, human lymphocytes *in vitro*	–	–	13	Tingle *et al.* (1993); Wilson *et al.* (1995)
Micronucleus formation ($CREST^-$), human MCL-5B-lymphoblastoid cells *in vitro*	+	NT	30	Sasaki *et al.* (1997)
Cell transformation, BALB/c 3T3 cells	–	NT	150	Rundell *et al.* (1983)
Cell transformation, RLV-infected Fischer rat embryo cells	–	NT	0.5	Freeman *et al.* (1973)
DNA fragmentation, female Sprague-Dawley rat liver and brain tissue *in vivo*	+		110 po × 30[e]	Bagchi *et al.* (1998b)
DNA fragmentation, female C57BL/6NTac mouse liver and brain tissue *in vivo*	+		220 po × 1[f]	Bagchi *et al.* (2000)
DNA fragmentation, female C57BL/6TSG-p53 mouse liver and brain tissue *in vivo*	+		22 po × 1[f]	Bagchi *et al.* (2000)

Table 10 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, male ICR Swiss mouse bone marrow erythrocytes *in vivo*	–		500 po × 1	Harper *et al.* (1984)
1,2-Naphthoquinone				
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	1.6	Wilson *et al.* (1996)
1,4-Naphthoquinone				
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	1.6	Wilson *et al.* (1996)
Naphthalene 1,2-oxide				
Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	15	Wilson *et al.* (1996)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; NR, not reported
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; po, oral; ip, intraperitoneal
[c] Toxicity in the absence of metabolic activation
[d] Toxicity at next higher dose
[e] Rats sacrificed on days 15, 30, 45, 60, 75, 90, 105 and 120; increased DNA fragmentation starting day 30 through day 120
[f] LED for liver, based on an oral LD_{50} = 2200 mg/kg; LED for brain is 1100 mg/kg bw.

$B6C3F_1$ mice given a single intraperitoneal injection of naphthalene (Cho *et al.*, 1994b; Tsuruda *et al.*, 1995).

4.5 Mechanistic considerations

Mechanistic studies conducted in experimental animals and tissues using a variety of approaches have attempted to determine the modes of action of naphthalene with respect to its toxicity and carcinogenicity. Such studies can provide insights into the relevance of the rodent tumours (lung tumours in female but not male mice, and nasal tumours in male and female rats) in predicting the carcinogenic response in humans.

In general, mice appear to be more susceptible to lung tumour induction by epoxides and epoxide-forming chemicals than rats (Melnick & Sills, 2001). Thus inhalation of ethylene oxide, 1,3-butadiene, isoprene and chloroprene induced lung tumours in mice but not in rats (Lynch *et al.*, 1984; National Toxicology Program, 1984; Snellings *et al*., 1984; National Toxicology Program, 1987; Owen *et al.*, 1987; Melnick *et al*., 1994; National Toxicology Program, 1998, 1999; Melnick & Sills, 2001). The determinants underlying the susceptibility of the mouse lung towards tumour formation may rely in part on toxicokinetic considerations, but toxicodynamic determinants probably also play a role. If naphthalene 1,2-oxide is responsible for the lung tumours observed in mice, species differences in response at this organ may be due to a combination of higher rates of naphthalene 1,2-oxide production in the Clara cells of the mouse lung, and, possibly, a greater susceptibility of the mouse lung to epoxide-induced carcinogenesis (National Toxicology Program, 2000).

4.5.1 *Interspecies differences in toxicokinetics and metabolism of naphthalene*

The initial step in naphthalene metabolism involves the formation of a 1,2-epoxide and this process is a key step in the generation of cytotoxic metabolites. Substantial differences in both the rates of epoxide formation and the stereochemistry of the epoxides formed are observed between target tissues (mouse lung and olfactory epithelium, rat olfactory epithelium) and non-target tissues (rat and hamster lung, hamster olfactory epithelium). The rates of metabolism in lung microsomes from humans and non-human primates are very similar and are 10–100-fold lower than in lung microsomes from rodents. CYP2F in mouse lung is important in the local metabolism of naphthalene and this is likely to be a critical determinant in naphthalene-induced cytotoxicity in the mouse.

4.5.2 *Interspecies differences in toxicodynamics and mode of action of naphthalene*

There is no evidence for mutagenic activity of naphthalene in the most widely used genotoxicity assays. For example, naphthalene was not mutagenic in the *Salmonella*

assay with or without metabolic activation or in metabolically competent human lymphoblastoid cells at either of two loci tested. In contrast, positive results were obtained in assays for micronucleus formation, chromosomal aberrations and chromosomal recombinations *in vitro*, consistent with a potential clastogenic mechanism of action. Some, but not all, of these tests required metabolic activation for induction of genotoxicity. It is not clear, however, which reactive naphthalene metabolite is responsible for the clastogenic, and presumably carcinogenic, effects, as evidence for the reactivity of both naphthalene 1,2-oxide and naphthoquinone exists.

Exposure to naphthalene causes cellular injury and increases cell replication rates, suggesting a cytotoxic mode of action. For example, intraperitoneal administration of naphthalene produces injury (swelling, vacuolation, exfoliation, necrosis) of the tracheobronchial epithelial Clara cells of mice but not of rats (Plopper *et al*., 1992a,b). In the same study, naphthalene was also cytotoxic to the olfactory epithelium of both rats and mice, but the effect was seen at much higher doses in mice, suggesting higher sensitivity of the rat nose. These site and species differences in toxicity correlate well with the higher rates of metabolism by mouse lung tissue and rat nasal tissue; metabolism *in vitro* in pulmonary tissue fractions from human and non-human primates is 1–2 orders of magnitude lower than that in rodents.

Overall, the proposed mechanism of action of naphthalene is that the higher rates of metabolism lead to cytotoxic metabolites in mouse lung, causing increased cell turnover and tumours. The absence of rat lung tumours is entirely consistent with this mechanism. Significantly, the maximal rates of metabolism in human lung microsomes are about two orders of magnitude lower than those in mice. The high rates of metabolism in rat nasal epithelium similarly lead to tissue damage and nasal tumours; however, the etiology of these nasal tumours, particularly the neuroblastomas, is not fully understood.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Naphthalene is a commercially important aromatic hydrocarbon which is produced from coal tar and petroleum. It is used mainly as an intermediate in the production of phthalic anhydride, naphthalene sulfonates and dyes and to a lesser extent as a moth-repellent. Human exposure to naphthalene can occur during its production, in creosote treatment of wood, in coal coking operations, during its use as an industrial intermediate, as a result of its use as a moth-repellent, and as a result of cigarette smoking.

5.2 Human carcinogenicity data

The only data available to the Working Group were two case series. No inference on the carcinogenicity of naphthalene could be drawn from these.

5.3 Animal carcinogenicity data

Naphthalene was tested for carcinogenicity by oral administration in one study in rats, by inhalation in one study in mice and one in rats and in one screening assay in mice, by intraperitoneal administration in newborn mice and in rats, and by subcutaneous administration in two studies in rats. Exposure of rats by inhalation was associated with induction of neuroblastomas of the olfactory epithelium and adenomas of the nasal respiratory epithelium in males and females. Both of these tumours were considered to be rare in untreated rats. In the screening assay study by inhalation using only female mice, there was an increase in lung adenomas per tumour-bearing mouse. In the inhalation study in mice, there was an increase in the incidence of bronchiolo-alveolar adenomas in female mice. An apparent increase in the incidence of these tumours in male mice was not statistically significant. The studies by oral administration in rats, intraperitoneal administration in mice and subcutaneous administration in rats were too limited for an evaluation of the carcinogenicity of naphthalene.

5.4 Other relevant data

Animal studies suggest that naphthalene is readily absorbed following oral or inhalation exposure. Although no data are available from human studies on absorption of naphthalene, the determination of metabolites in the urine of workers indicates that absorption does occur, and there is a good correlation between exposure to naphthalene and the amount of 1-naphthol excreted in the urine. A number of metabolites, including quinones, naphthols and conjugates (glucuronides, sulfates, glutathione) are derived from the 1,2-epoxide either directly or through multiple metabolic steps.

Naphthalene causes cataracts in humans, rats, rabbits and mice. Humans accidentally exposed to naphthalene by ingestion develop haemolytic anaemia, but there is no evidence of haemolytic anaemia in rodents. Cases of haemolytic anaemia have been reported in children and infants after oral or inhalation exposure to naphthalene or after maternal exposure during pregnancy.

Naphthalene causes lung toxicity in mice, but not rats, following either intraperitoneal injection or inhalation exposure. In mice, the injury is dose-dependent and Clara cell-specific. After repeated administration of naphthalene, mouse Clara cells become tolerant to the naphthalene-induced injury that occurs following a single dose of naphthalene. Acute and chronic exposure to naphthalene caused nasal toxicity in both mice and rats.

In isolated mouse Clara cells, 1,4-naphthoquinone and naphthalene 1,2-oxide were more toxic than naphthalene. Injury to Clara cells in perfused lungs occurred at lower concentrations of naphthalene 1,2-oxide compared with naphthalene or its other metabolites.

There is some evidence of developmental toxicity in rats and mice at dose levels that caused clear maternal toxicity. Clara cells of neonatal mice are more sensitive than those of adult mice to the cytotoxic effects of naphthalene.

There is little evidence for induction of gene mutations by naphthalene. In contrast, positive results were obtained in assays for micronucleus formation, chromosomal aberrations and chromosomal recombinations *in vitro*, which are consistent with a clastogenic potential.

Overall, the proposed mechanism of carcinogenic action is that the higher rates of metabolism of naphthalene in mice lead to cytotoxic metabolites in the lung, causing increased cell turnover and tumours. The absence of lung tumours in rats is entirely consistent with this mechanism. The maximal rates of metabolism measured in human lung microsomes are about 10–100 times lower than those in mice.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of naphthalene.

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

Overall evaluation

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

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